Quality issues in caring for older people

- Appropriateness of transition from long-term care facilities to acute hospital care
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Doctoral Thesis
Anna Renom Guiteras
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Quality issues in caring for older people:

- **Appropriateness of transition from long-term care facilities to acute hospital care**
- **Potentially inappropriate medication: development of a European list**

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Contents

Introduction

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Introduction

Research context

This doctoral thesis should be put in the context of the first three years of a 5-year stay in Germany (2010-2015), when I worked as research fellow in the research team of Professor Gabriele Meyer, nursing scientist, in the Institute of Nursing Science at the University of Witten/ Herdecke in the city of Witten. This experience took place after specializing in geriatrics in Barcelona (Parc de Salut Mar). Professor Ramón Miralles, geriatrician in the Parc de Salut Mar (Universitat Autònoma de Barcelona), agreed with the idea of supervising my doctoral thesis within this context and so did Professor Gabriele Meyer, who gave me the opportunity to work in her team.

The main project I was involved in was the European project "RightTimePlaceCare", a project which was carried out from January 2010 until September 2013 and in which eight European countries participated: England, Estonia, Finland, France, Germany, the Netherlands, Spain and Sweden (1, 2). The project was coordinated by the University of Witten/Herdecke in Germany, and led by Professor Gabriele Meyer. The aim of the *RightTimePlaceCare* project was to develop best practice recommendations for dementia care throughout Europe. The project included interviews with a European cohort of older people with dementia and their formal and informal caregivers. Several medical, nursing, and socio-economical aspects of dementia and dementia care were evaluated prospectively at two points of time, separated by 3 months (cross-sectional design).

As a research fellow, I participated in some design aspects of the study, in the selection of assessment tools, recruitment of participants, collection of data (interviews with participants), preparation of the statistical plan and database, and in the data analysis and interpretation. Several doctoral students were involved in the study and a publication plan was prepared in the early stages of the study. Together with my supervisors (Professor Ramón Miralles and Professor Gabriele Meyer) I decided to work on two research topics: hospital admission and use of potentially inappropriate medications. I had the opportunity to make suggestions on how to gather data on these two issues, in consensus with the *RightTimePlaceCare* Consortium members.

During this period of time, we planned two further research projects in the line of the mentioned research topics, which ended up constituting the core studies of my doctoral thesis: the preparation of a systematic review of the literature on assessment tools for determining the appropriateness of admission to acute care of persons transferred from long-term care (LTC) facilities and the development of a European list of potentially inappropriate medications for older people.

Background of the research topics

This doctoral thesis covers two issues concerning the frail older population: hospital admission and prescription of medications.

The ageing process of the population is a known challenge in our society. By 2050 it is estimated that 21% of the population in the western industrialised states will be aged 60 years and older, and developing countries will also experience this tendency (3). Older people tend to be frail, showing higher comorbidity, cognitive and functional impairment. It is estimated that between 5-7% of the people older than 60 are affected by dementia (4) and more than half of the population aged 75 and older suffer from comorbidities (5, 6). Every year, people aged 70 and older may experience an increase in the limitation of their activities of daily living of between 1% and 2.5% in (7). Furthermore, older people may experience changes in their social and living situation such as admission to an LTC facility. In Europe, the percentage of people receiving care in institutions ranges between 1% and 7% for those people aged 65 years and older, and between 2% and 20% for those aged 80 and older, depending on the country (8).

Frail older people have an increased rate of hospital referral and hospital admission. Up to a quarter of all emergency department visits are accounted for by patients aged 65 and older (9). In nursing homes, the incidence of emergency department visits has been estimated to be approximately 30 transfers per 100 beds per year (10).

Older people have also a higher risk of being prescribed a high number of medications (polypharmacy). Between 34% and 59% of people aged 75 and older are exposed to five or more drugs (11-13) and the prescription of ten or more drugs to older people in nursing homes can reach 24% (14). Further, older people are also at risk of being inappropriately prescribed; for example, they may be prescribed duplicated active substances, doses of drugs not adjusted to renal function or drugs considered as “potentially inappropriate medications” (PIM) for this age group (15).

Hospital admission and the prescription of medications are often necessary and beneficial for older people, but they may also be inappropriate and associated with adverse consequences. Thus, inappropriate prescribing and/or the prescription of PIM for older people can be associated with adverse drug events (16-18), hospitalisation (19, 20) and death (21). Similarly, the admission of a frail old person to an emergency department or hospital represents a risk of distress, hospital-acquired nosocomial events (22), and deterioration of mobility and cognition (23, 24). Some older people who died in hospital after having been transferred to acute care may have benefited more from a palliative care approach at home or in the LTC facility (25).

For many years, several authors have been developing assessment tools to measure the appropriateness of hospital admission and the appropriateness of prescribing to older people.

These tools have been used for describing the current practices regarding these two issues, identifying areas of improvement and evaluating the effectiveness of the interventions aimed at improving the clinical practice. Nevertheless, important knowledge gaps still exist in the evidence regarding these measurement tools, and there is a need for further research, as is acknowledged by several authors. This doctoral thesis addresses these needs.

Presentation of the articles

The first article of this doctoral thesis is entitled "**Assessment tools for determining appropriateness of admission to acute care of persons transferred from long-term care facilities: a systematic review**".

LTC facilities have high rates of hospital transfers and there is potential for the optimisation of working procedures. Therefore, a considerable number of studies have evaluated the appropriateness of hospital admission within this setting. International studies suggest that between 10% and 60% of hospital admissions among LTC residents may be inappropriate (26, 27). Variation may result from differences in the acute care settings, the nursing home populations, the facility characteristics, or the regional organisational aspects (e.g. incentives or procedures). However, part of the variation in the estimates of appropriate admissions can also be explained by the different assessment tools used.

So far, there is no agreement on which tool better evaluates the appropriateness of hospital admissions of older people transferred from LTC facilities. The terminology and definitions are not yet clarified, as claimed by some authors (28-31). Furthermore, there is no document available that provides an overview of the internationally existing assessment tools and that also describes them.

Systematic reviews are rigorous formats for synthesizing the evidence and play an important role in the disclosure of the knowledge available about a particular health issue. The performance of systematic reviews is characterized by stringency arising from a priori protocol development, transparency, comprehensive literature search, selection and appraisal of the evidence by independent reviewers, rigour in synthesis, and peer review at numerous stages during the conduction and reporting of the systematic review (32).

Thus, this article consists of a systematic review of the literature on the assessment tools for determining appropriateness of admission to acute care of persons transferred from LTC facilities. This systematic review has been published in BMC Geriatrics.

The second article of this doctoral thesis is entitled "**The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries**".

The term "potentially inappropriate medications (PIM) for older people" refers to those drugs which should not be prescribed for this population because the risk of adverse events outweighs the clinical benefit, particularly when there is evidence in favour of a safer or more effective alternative therapy for the same condition (33, 34). The prevalence of inappropriate prescribing and/or use of potentially inappropriate medications has been estimated as being between 20% and 79%. This variation can be explained by the differences in the populations studied, the settings and the specific tools used for the evaluation (19, 34-38).

A recently published systematic review identified 46 tools or criteria for assessing inappropriate prescribing (39), and a prior systematic review identified 14 criteria specific for individuals aged 65 and older (40). No single ideal tool has been identified so far, but each tool seems to have its strengths and weaknesses, and the choice of a tool may depend on the purpose of use (i.e. daily practice, research) and availability of data (39). However, to the best of our knowledge, no assessment tool covers the drug markets of several European countries and could thus enable the analysis of European databases.

This article was conceived when planning to analyse the prescription of PIM among the European cohort of people with dementia participating in the *RightTimePlaceCare* study. None of the existing criteria could be applied to our cohort, either because they were too country-specific or because they required too much clinical information which was not available. Thus, we planned to develop a European list of PIM for older people consented by experts from seven European countries, namely the European Union (EU)(7)-PIM list. We had the opportunity to work together with two researchers who had been previously involved in the development of the PRISCUS list (41), a PIM list for older people covering the German drug market. We planned the development of the EU(7)-PIM list in two main phases. The first phase was the preparation of a preliminary PIM list based on the German PRISCUS list (41), PIM from other international PIM lists (33, 42-44) and a comprehensive literature search. The second phase was the expansion of the preliminary list with further drugs and the assessment of its appropriateness by means of a two-round Delphi survey by a group of experts on geriatric prescribing from the same European countries who participated in the *RightTimePlaceCare* project.

The Delphi technique is a research method that aims at obtaining information via an expert consensus. This method has been widely used for the development of PIM lists (33, 41, 45, 46) due to the lack of good quality evidence on drug efficacy and safety in older people, which makes it difficult to develop assessment tools based on evidence only (47).

The EU(7)-PIM list has been published in the European Journal of Clinical Pharmacology.

Summary and discussion of the results

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Summary and discussion of the results

The first article of this thesis entitled **"Assessment tools for determining appropriateness of admission to acute care of persons transferred from long-term care facilities: a systematic review"** aimed at systematically reviewing and describing the internationally existing assessment tools used for determining appropriateness of hospital admission among long-term care (LTC) residents. Twenty-nine articles assessing this issue were included in the systematic review, and 16 different assessment tools were identified among them. Mean age of the study samples ranged from 81 to 86, and the proportion of women varied from 62% to 80%. Studies varied regarding their designs (e.g. prospective vs. retrospective, observational vs. interventional), the population under study (e.g. residents of LTC facilities only vs. also older persons living in the community; all older people vs. only older people with dementia) and the acute care setting (e.g. only admission to emergency department vs. only in-patient hospitalisation vs. either emergency department or in-patient hospitalisation). The proportion of admissions considered as inappropriate varied widely, ranging from 2% to 77%.

Sixteen assessment tools were identified. Considerable heterogeneity among the tools was found regarding the concepts studied (e.g. inappropriate vs. avoidable vs. preventable admissions), the format of use (e.g. tool applied by study authors vs. expert panel or nursing staff) and data sources used for their application (e.g. administrative databases vs. resident's hospital of LTC facility record vs. interview with residents or nursing staff). We agreed on a list of six aspects that were covered by the assessment tools' items: specific medical diagnoses, acuteness or severity of symptoms at time of transition , resident's characteristics prior to admission to hospital, resource availability/requirement, residents'/families' wishes, and information on the existence of a care plan. However, not all assessment tools covered all aspects: most tools covered less than four of these aspects, and six of the tools covered four or more aspects. For example, one assessment tool consisted of a list of medical conditions called "Avoidable Hospital Conditions" (48) which judged appropriateness based on the specific medical diagnoses only; another tool consisted of an "Appropriateness Evaluation Protocol" (26) that judged appropriateness based on the acute symptoms (e.g. persistent fever, abnormally high or low pulse rate) and the resources available/needed (e.g. prescription of parenteral medications, vital sign monitoring). Only six assessment tools included some items on the residents' characteristics prior to acute care admission, and only three assessment tools took the residents'/families' wishes or the information about the existence of a care plan into consideration. For example, the "Quality Improvement Review tool" part of the INTERACT-II tool (49, 50) judged appropriateness based on a balance of issues: information about the resident's characteristics, acute symptoms, and actions taken by staff before the transfer including presence of advanced care planning. The fact that many assessment tools did not include any items on any residents' individual aspects is remarkable, considering that residents in LTC facilities often differ in terms of comorbidity, cognitive and functional status, and stage of their diseases, and considering the present advocacy towards person-centred care (51).

The results of this study are in the line with the results of a non-systematic review on tools used to identify preventable hospitalisations (including community-dwelling older people) (31, 52). The authors of that review emphasized the need for comprehensive measures to account for aspects such as medical comorbidities, clinical complexity or differences in resources in the care settings.

This systematic review did not include the assessment of the risk of bias of the original studies included. The reason is that we were interested in the concepts and tools identified, rather than in the internal validity of the studies. However, we described the study designs and most studies were secondary or retrospective routine data analyses, suggesting that the quality of the studies is limited.

This article provides an overview of the tools internationally used to assess the appropriateness of hospital admissions among LTC residents, and the study contexts where they were used. It provides some evidence about the lack of consideration of individual aspects and the lack of comprehensiveness of some assessment tools. It may contribute to the clarification of the concept "appropriateness of admission of LTC residents to acute care" and may support authors choosing an assessment tool to measure appropriateness of hospital admission. It may also be a first step towards the development of an evidence-based, comprehensive and generalizable tool. Authors aiming at developing interventions to reduce inappropriate hospital admissions may also benefit from this systematic review because the development of complex interventions requires studies that help to refine the design, identify suitable measures, and predict long term outcomes (53).

Unfortunately, we could not evaluate the appropriateness of hospital admission within the European cohort of older people with dementia participating in the *RightTimePlaceCare* project, because the data available were insufficient. However, we are currently evaluating the frequency, reasons and factors associated with hospital admission.

The second article of this thesis entitled **"The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries"** aimed at developing a European list of PIM for older people, which can be used for the analysis and comparison of prescribing patterns across European countries and for clinical practice. The European Union (EU)(7)-potentially inappropriate medication (PIM) list was developed based on the German PRISCUS list (41) and additional drugs from the French (33), American (42, 43, 46) and Canadian (44) lists. A preliminary PIM list was developed, expanded and assessed in a two-round Delphi survey with the collaboration of thirty experts in geriatric prescribing from seven European countries and from different professions. The experts were asked to assess appropriateness by using a 1-5 point Likert scale, and they were asked to provide suggestions for dose adjustments and safer therapeutic alternatives for those drugs judged as inappropriate. We calculated the means, the corresponding 95% confidence intervals and the medians of all Likert scores given to each drug and, depending on the scores, each drug was classified into PIM, non-PIM or questionable PIM.

The preliminary PIM list contained 184 drugs. Experts suggested 75 additional drugs. The participation of experts was moderate to high: 62% of the invited experts participated in the expansion phase, 90% in the first Delphi round and 86% in the second Delphi round. A last brief survey was carried out consisting of 11 questions with multiple-choice answers and covering issues regarding 13 drugs. The questions covered mostly dose-related issues commented by the experts during the survey and which remained open, and inconsistencies in the results identified after checking the literature. Experts reached consensus that 282 chemical substances or drug classes from 34 therapeutic groups are PIM for older people. Some PIM are restricted to a certain dose or duration of use or both; for example, the use of ibuprofen is considered to be potentially inappropriate if the dose prescribed is higher than 400mg, three times per day, or if the length of use is longer than one week. The level of agreement between experts in the Delphi survey varied and is reported in this article. Table 1 of this article displays an abbreviated version of the EU(7)-PIM list, with the 72 PIM most frequently identified among the participants of the *RightTimePlaceCare* survey (1, 2). Appendix 1 shows the complete EU(7)-PIM list, and Appendix 2 and 3 present the full lists of questionable PIM and non-PIM, respectively.

The EU(7)-PIM list can be seen as a screening tool or as a tool to draw attention to PIM among older people's prescriptions. The main advantages of the EU(7)-PIM list are: 1) it can be applied both in the clinical practice and to databases where the amount of clinical information available is limited; 2) it covers the drug markets of seven different European countries; 3) it contains suggestions on dose adjustments and therapeutic alternatives.

The main limitations/considerations of use of the EU(7)-PIM list are: 1) the Delphi technique relies widely on the knowledge of the participating experts (54); 2) not all European countries were involved; 3) it cannot substitute the individual assessment of appropriateness of prescription, which should take into account other aspects such as the aims of the treatment, individual responses, and the older person's functional level, values and preferences (55).

To the best of our knowledge, the EU(7)-PIM list is the first list that requires only a small amount of clinical data for its application and that has been developed taking into account several existing PIM lists and European markets. This list may allow the comparison of data on PIM use between different European countries, which was limited until now because the majority of the tools were country-specific (40, 56). The EU(7)-PIM list could represent one step towards the development of prescribing quality indicators which are useful for the electronic monitoring of the quality of prescribing in older people in Europe (57).

The EU(7)-PIM list is ready for use and has been applied for the first time to the *RightTimePlaceCare* data on older people with dementia. The results of this first application show that the use of certain PIM according to the EU(7)-PIM list differs between European countries. Furthermore, results suggest that, among people with dementia and according to the EU(7)-PIM list, those who are older than 80 years, have lower functional status and live in nursing homes may be

prescribed PIMs more often. Results also suggest that the use of ≥2 PIM might be associated with an increased risk for hospitalisation and falls (58).

Both topics of this doctoral thesis are public health concerns with economic implications. Lower hospital admission rate has been used as an indicator of the quality of care in nursing homes (59). Beyond adverse clinical effects, hospital transfers account for a high proportion of total healthcare costs (60, 61). In the United States, for example, potentially avoidable hospitalisations of nursing home residents have become a major focus of the proposed Medicare Pay for Performance Demonstration (60). Also inappropriate prescribing and/or the prescription of PIM to older people have been found associated not only with adverse events but also with increased health costs (62, 63), and attempts are being undertaken to develop prescribing quality indicators which are useful for the electronic monitoring of the quality of prescribing in older people in Europe (57).

Thus, research focussing on the improvement of the measurement tools for the assessment of these issues seems necessary, and this doctoral thesis is a contribution to this body of knowledge. The development of measurement tools which are applicable to different settings, regions or countries should facilitate the analysis and comparison of data and help learning from each other. Furthermore, such tools can help evaluating the efficiency of interventions aimed at improving the clinical practice. Nevertheless, tools cannot substitute the individual judgement on appropriateness at patient level, and this is the reason why some authors working in these fields often use the term “potentially inappropriate” or “potentially avoidable”, as the final judgement should be done for each individual case.

Conclusions

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Conclusions

Article "**Assessment tools for determining appropriateness of admission to acute care of persons transferred from long-term care facilities: a systematic review**":

- Twenty-nine studies were identified that assessed the prevalence of the appropriateness of acute care admissions among older people living in long-term care (LTC) facilities. The prevalence of inappropriate admissions ranged from 2% to 77%. This systematic review provides information about the study designs, populations and types of facilities analysed in each study.

- Sixteen different assessment tools were applied in the studies. This systematic review provides detailed information on each tool regarding the concepts analysed, how they were developed, their psychometric properties, their format of use and the aspects covered by their items.

- Six aspects were covered by the items of the assessment tools: "specific medical diagnoses", "acuteness or severity of symptoms at time of transition", "resident's characteristics prior to admission to hospital", "resource availability/requirement", "residents'/families' wishes" and "information on the existence of a care plan".

- Five of the tools covered only one of the aspects, while six tools considered four or more. The aspects less covered were "resident's characteristics prior to admission to hospital", "residents'/families' wishes" and "information on the existence of a care plan". Thus, most assessment tools were not comprehensive and did not take into account individual aspects of the residents.

- This systematic review may be the basis for further research in this area which is needed to develop an evidence-based and comprehensive tool supported by quality assuring strategies to improve decisions on the appropriateness of hospital admissions among residents of LTC facilities.

Article "**The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries**":

- This article describes the development process of the European Union (EU)(7)-PIM list, a tool for the assessment of potentially inappropriate medications (PIM) for older people. The list was consented by experts from seven European countries within a two-round Delphi survey.

- This article presents the complete EU(7)-PIM list, which contains 282 chemical substances or drug classes from 34 therapeutic groups. It contains suggestions for dose adjustments and therapeutic alternatives.

- The EU(7)-PIM list is a screening tool for PIM that can be applied to databases and to individual patient data. It is the first list focussing on chemical substances and requiring only a small amount of clinical data for its application that has been developed taking into account several existing PIM lists and European markets, and that has been consented by experts from different European countries.

- This list allows the description and comparison of PIM prescription between different European countries and may be used as a guide in the clinical practice. Its application is a first step towards the identification of areas of improvement and towards the harmonisation of the prescription quality throughout Europe.

- The EU(7)-PIM list has been already applied to the data of the European cohort of people with dementia participating in the *RightTimePlaceCare* project (Renom-Guiteras, 8th IAGG-ER Conference, Dublin 2015). Further research is needed to investigate the feasibility, applicability and the clinical benefits of the newly developed list.

Overall conclusions:

- This doctoral thesis covers two topics which belong to the area *assessment tools for the evaluation of quality of medical care issues in older people*: appropriateness of hospital admission and appropriateness of prescribing.

- The first article provides an *overview of the available assessment tools* for determining appropriateness of hospital admission, and the second article describes the *development of a new assessment tool* for the identification of inappropriate prescriptions.

- Both articles aim at enhancing the unification of concepts and the extent of consensus between professionals in different settings and countries. They are part of a wider research process towards the improvement of the evidence-based care of older people.

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Articles

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ARTICLE 1

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RESEARCH ARTICLE Open Access

Assessment tools for determining appropriateness of admission to acute care of persons transferred from long-term care facilities: a systematic review

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Abstract

Background: Residents of long-term care facilities have a high risk of acute care admission. Estimates of the frequency of inappropriate transfers vary substantially throughout the studies and various assessment tools have been used. The purpose of this study is to systematically review and describe the internationally existing assessment tools used for determining appropriateness of hospital admissions among long-term care residents.

Method: Systematic review of the literature of two databases (PubMed and CINAHL®). The search covered seven languages and the period between January 2000 and December 2012. All quantitative studies were included if any assessment tool for appropriateness of hospital and/or emergency department admission of long-term care residents was used. Two pairs of independent researchers extracted the data.

Results: Twenty-nine articles were included, covering study periods between 1991 and 2009. The proportion of admissions considered as inappropriate ranged from 2% to 77%. Throughout the studies, 16 different assessment tools were used; all were based on expert opinion to some extent; six also took into account published literature or interpretation of patient data. Variation between tools depended on the concepts studied, format and application, and aspects evaluated. Overall, the assessment tools covered six aspects: specific medical diagnoses (assessed by n = 8 tools), acuteness/severity of symptoms (n = 7), residents' characteristics prior to admission (n = 6), residents' or families' wishes (n = 3), existence of a care plan (n = 1), and availability or requirement of resources (n = 10). Most tools judged appropriateness based on one fulfilled item; five tools judged appropriateness based on a balance of aspects. Five tools covered only one of these aspects and only six considered four or more aspects. Little information was available on the psychometric properties of the tools.

Conclusions: Most assessment tools are not comprehensive and do not take into account residents' individual aspects, such as characteristics of residents prior to admission and wishes of residents or families. The generalizability of the existing tools is unknown. Further research is needed to develop a tool that is evidence-based, comprehensive and generalizable to different regions or countries in order to assess the appropriateness of hospital admissions among long-term care residents.

Keywords: Nursing home, Patient transfer, Hospitalization, Systematic review

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Background

Residents of long-term care (LTC) facilities have a high risk of being admitted to hospital. Internationally, the incidence of visits to an emergency department has been estimated to be approximately 30 transfers per 100 LTC beds per year [1]. LTC residents are often sent to emergency departments (ED) when they are in a highly acute condition, and are likely to be admitted to the hospital [2]. Common underlying diagnoses are pneumonia, urinary tract infection, congestive heart failure, chronic obstructive pulmonary disease, fall-related injuries, and altered conscious state [3,4].

LTC residents are often frail and suffer from diseases in advanced stages, have several comorbidities, high levels of dependency and take multiple medications. The referral or admission to an ED or acute hospital – although often unavoidable and beneficial – represents an unfavourable discontinuity of care and encompasses threats to the residents including distress, risk of iatrogenic events [5], and deterioration of mobility and cognition [6,7]. Beyond adverse clinical effects, hospital transfers account for a high proportion of total healthcare costs [8].

Many authors have evaluated the appropriateness of ED visits or hospitalisation among LTC residents. There is an on-going debate on how to define appropriateness of admissions in order to reduce negative effects of inappropriate transfers without withholding residents from admission if acute care is needed. To distinguish between admissions to acute care that are inappropriate and those that are not is of great interest not only for the residents concerned but also for nursing home providers and policy makers alike. In international studies, between 10% and 60% of hospital admissions have been classified as inappropriate [9,10]. So far, the reason for this high variability is not clarified. Variations may result from different study objectives, including different concepts such as inappropriate, preventable, avoidable, or unnecessary hospitalisation. Differences in acute care destinations and nursing home populations included in the studies may also affect the rates of inappropriate admissions. Several studies suggest that facility characteristics may be as important as residents' clinical characteristics [11,12]. In addition, regional differences in terms of financial incentives may also have an influence [13]. Interestingly, considerable variations in inappropriate hospital admission rates were even found in studies including nursing homes in well-defined areas only [14].

It is also important to take into account that authors used different assessment tools to judge the appropriateness of acute care transfers. Up to now, there is no consensus on which tool to use for assessment of appropriateness of residents' hospital admission. Furthermore, there is no agreement on the aspects to be covered by such a tool. The terminology and definitions are not yet clarified, as claimed by some authors [11,15-17]. As a first step towards clarification, it seems to be justified to systematically review all assessment instruments applied for judgement of appropriateness of transfers, to analyse their development, their underlying concepts, the aspects included, their psychometric properties, and to critically review them in the context of the complexity of acute care admissions of frail and vulnerable LTC residents.

Thus, the aim of our systematic review is 1) to provide an overview of the studies dealing with tools for assessing appropriateness of hospital admissions in LTC residents and 2) to describe the published assessment tools in detail, including information about their development and the aspects covered by the tools.

Methods

Four researchers from Spain, Germany, Denmark and Austria, all experienced in geriatric care and research, established a working group and developed a research protocol (available from the authors on request). In January 2013, two reviewers conducted a literature search. The search covered the databases Medline via PubMed and CINAHL® and was limited to studies published between January 2000 and December 2012. The following search strategy was used for Pubmed: (("Residential Facilities"[MeSH]) OR (nursing homes) OR (homes for the aged) OR (aged care facilit*) OR (nursing facilit*) OR ("Long-Term Care"[MeSH])) AND (("Emergency Service, Hospital"[MeSH]) OR hospital OR (acute care) OR (emergency AND (medicine OR department* OR unit* OR ward* OR service* OR room*))) AND (appropriat* OR suitable OR avoidable OR preventable) AND (("Patient Transfer"[MeSH]) OR ("Hospitalization"[MeSH]) OR referral* OR admission* OR transition*) AND (English[lang] OR French[lang] OR German[lang] OR Spanish[lang] OR Catalan[lang] OR Danish[lang] OR Norwegian[lang]) AND ("2000/01/01"[PDat]: "2010"[PDat])). The corresponding search terms were used for CINAHL®. Articles published in English, German, French, Spanish, Catalan, Danish and Norwegian were considered for inclusion. Two reviewers independently checked titles and abstracts for relevance and, in a second step, eligible full-text articles for inclusion. Reference lists of the included articles were checked manually. In addition, we followed PubMed-indexed related citations of two included articles which have been published recently and which focus on different acute care destinations [10,15].

We included prospective and retrospective, experimental and non-experimental studies if they 1) investigated residents from any type of LTC setting who were transferred to hospital emergency departments or hospital wards, 2) provided or assessed diagnostic and/or therapeutic data on the process of transfer, 3) developed, administered or derived a tool for assessing appropriateness

of hospital admissions, including any list of aspects or any single question that could be used to distinguish between appropriate or inappropriate admissions. Studies using different terms (e.g. inappropriate, preventable, avoidable admissions) and operational definitions of appropriateness were considered for inclusion.

Two pairs of independent researchers extracted information on the study characteristics and the assessment tools using a piloted data extraction form. Publications cited in the reference list were retrieved if necessary. Results were discussed and, in the case of disagreement, a third author was consulted to reach consensus. In case of doubt, the authors of the primary study were contacted.

Data extraction covered information about the type of study, description of participants and settings, information on which assessment tool was used, how and by whom it was used, number and proportion of inappropriate admissions to acute care reported, period of time studied, and information on how the assessment tool was developed and which items were evaluated by the tool. Once data extraction was finished, the research team agreed on a list of aspects that were covered by the items found in the assessment tools.

We refrained from formal critical appraisal of the included studies, since we were interested in the concepts and tools used for assessing appropriateness of hospital admissions only, rather than the internal validity of the studies. Assessment of risk of bias would not have provided any substantial information with regard to the aim of this review.

Inter-rater reliability was not calculated because most information extracted was descriptive. All disagreements could be solved after checking for accuracy and discussion.

Results

Twenty-nine articles met the inclusion criteria [3,4,8-10,15,18-41]. Two articles reporting on the same study were considered as one source [21,38]. A list of studies excluded, along with the reason for exclusion, is available from the authors on request. Figure 1 displays the process of identification of studies for inclusion in the systematic review. (Additional file 1: Table S1) presents the characteristics of the included studies. The majority (n = 24) were retrospective. Five studies reported on an intervention or a strategy for reducing transfers to acute care (information not shown in the table) [21,23,26,27,30,38].

The majority of the studies (n = 24) investigated residents of LTC facilities only; five studies also included older persons living in the community [27,29,31,32,39]. Most studies (n = 25) considered the general population of LTC residents; four studies focused on specific groups: residents with long-term neurological conditions [32], residents with advanced cognitive impairment [37], and residents at the end-of-life [31,39]. Mean age of the study samples ranged from 81 [31,41] to 86 years [37], and the proportion of women varied from 62% [15] to 80% [23].

While types of LTC facilities seemed to be similar, the acute care destinations varied substantially: some studies focused either on ED visits or in-patient hospitalisation (n = 3), others included in-patient hospitalisation only, irrespective of a previous ED visit (n = 8), others included ED visits with consecutive in-patient hospitalisation (n = 2), ED visits with subsequent discharge to nursing homes (n = 1) or ED visits irrespective of subsequent in-patient hospitalisation (n = 6). Some studies investigated hospitalisation without any further specification (n = 9).

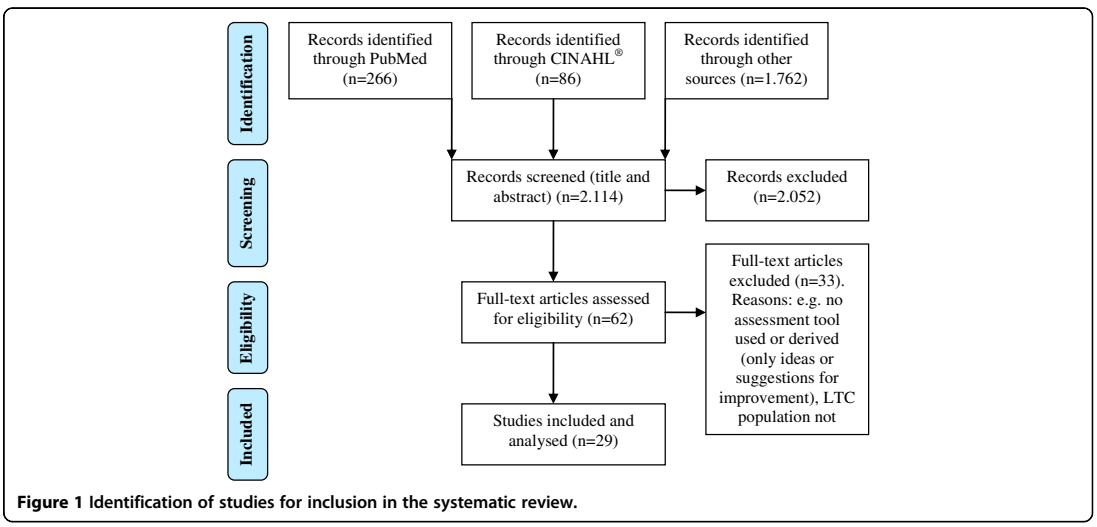

Figure 1 Identification of studies for inclusion in the systematic review.

In eighteen studies the assessment tool used for determining appropriateness was applied to administrative databases. In eleven studies hospital or LTC facility records, or interviews with residents or nursing staff were used as data sources.

Results regarding the rate of inappropriate hospital admissions varied substantially. Some studies reported low proportions of inappropriate admissions. For example, Bermejo et al. [35] and Finn et al. [3] reported on 1.6% and 13.1% of inappropriate emergency department visits, respectively; Becker et al. [33] reported on 18% of preventable hospitalisation. Other studies documented high proportions of inappropriate admissions. In the study by Saliba et al. [18], 36% of all ED visits were judged as inappropriate; Walker et al. [19] and Ouslander et al. [30] reported on 55% and 77% of potentially avoidable hospitalisation, respectively.

Sixteen assessment tools determining appropriateness of hospital admissions among residents of LTC facilities were identified throughout the included studies. Information on their names, development, psychometric properties, aim/concept studied, way of use, items included and aspects covered are displayed in (Additional file 2: Table S2). Those tools without an own name are given the name of the first author of the corresponding study (see column "Tool [corresponding studies]").

The terms used for indicating "inappropriate" hospitalisation varied throughout the different assessment tools: while most of them favoured the term "appropriate"/"inappropriate" (e.g., AEP), others used the terms "avoidable" or "preventable" (e.g., ACSC; additional tool by Finucane et al. [9]; AHC), and one study applied the term "potentially burdensome" (tool by Gonzalo et al. [37]).

Most tools aimed at measuring appropriateness of hospital transfer, i.e., from the LTC facility to either ED or hospital ward. Some of them focused on visits to ED (e.g., Modified AEP, tool by Jensen et al. [15]), while others focused on admissions to hospital (e.g., AEP), or on both ED visits and hospital stay (e.g. Quality Improvement Review tool (INTERACT-II)). A smaller number of tools aimed at determining those hospital transfers which could have been prevented by adequate ambulatory care (e.g., ACSC, AHC), focusing therefore on the period preceding the acute moment of transition.

All assessment tools were developed and based upon expert opinion to different extents: two tools were compiled using an expert consensus method, and six expert groups also took into account the results of a literature search or the interpretation of patient data. In all studies, tools were applied retrospectively, i.e., after hospital admission had already taken place.

Assessment tools were applied by the investigators themselves (n = 9), an external panel of experts (generally with experience in LTC) looking for consensus (n = 5), or professionals directly engaged in the care of residents transferred (n = 2).

As can be seen in Additional file 2: Table S2, some tools (e.g. AEP; ACSC) comprised a list of conditions or diseases (e.g. congestive heart failure, hypoglycaemia) while others consisted of a short definition or question (e.g. tool by Ong et al. [39], tool by Hammond et al. [32]).

The assessment tools differed widely regarding the aspects considered as criteria for judgement of appropriateness of acute care admissions. The six aspects are summarized in Table 1. Eight tools considered specific medical diagnoses as indicators for appropriate or inappropriate hospitalisation; seven tools considered the acuteness or severity of the symptoms at the moment of hospital transfer or admission; six tools took into account the resident's characteristics prior to admission; three tools considered the residents' or families' wishes; one tool assessed whether a nursing care plan had been defined and adhered to; ten tools considered resource availability or requirement.

While most tools judged appropriateness based on one fulfilled item of the above mentioned aspects, five tools determined appropriateness by considering a balance of issues, for example by asking the professionals applying the criteria to give their judgement on appropriateness after considering all the aspects.

Some tools focused on one or two of the aspects (e.g. ACSC; tool by Gonzalo et al. [37]), while others were more comprehensive, i.e. covered a higher number of aspects. Six tools covered four aspects or more (e.g. tool by Abel et al. [31]; tool by Jensen et al. [15]; Quality Improvement Review tool; SIR).

Most tools (n = 10) were developed or adapted in the context of the actual studies, providing no information about their use in other studies or generalizability. Other tools had been used previously, but with an aim other than assessing appropriateness of admission to hospital (e.g. AEP). Finally, some tools had been developed or used only in one country or context (e.g. ACSC, Quality Improvement Review tool (INTERACT-II)). Moderate to good levels of inter-rater reliability were found for six tools (SIR; AEP; tool by Abel et al. [31]; tool by Hammond et al. [32]; tool by Codde et al. [34].

Discussion

We reviewed 29 studies applying 16 assessment tools aimed at determining the appropriateness or preventability of ED or hospital admissions of LTC residents.

The rates of admissions considered as inappropriate differed substantially throughout the studies from 2% [9] to 77% [30]. The studies included in our review, most of them retrospective in nature and thus susceptible for bias, were distinctive in many aspects. They varied considerably in study designs and objectives. Outcomes were defined in

Table 1 Aspects covered by the assessment tools

Aspect	Examples of items included in the tools	Number of tools covering the aspect
Specific medical diagnoses	Suspected fracture, ACSC (asthma, congestive heart failure, angina, grand mal seizure disorder, hypoglycaemia, hypertension, etc.), death	8
Acuteness or severity of symptoms at time of transition	Sudden onset of unconsciousness, incapacitating pain, tachycardia, gastrointestinal bleeding symptoms, signs of being systemically unwell	7
Resident's characteristics prior to admission to hospital	Resident's baseline health status, level of functional ability, resident with advanced cognitive impairment, presence of a terminal illness	6
Resource availability/requirement	Requirement of intravenous antibiotics, laboratory, radiology, admission to hospital, physician and nurse availability and expertise	10
Residents'/families' wishes	Advance care directive in place, request of hospital admission or emergency department visit by family	3
Information on the existence of a care plan	Actions taken by staff before the transfer (including presence of advanced care planning)	1

different terms or even different concepts, e.g., inappropriate, avoidable, or preventable admissions. Besides, the acute care destinations varied, as well as the selection of the LTC population and LTC facility-level factors. Furthermore, studies took place in different regions and countries, implicating different reimbursement policies and financial incentives. The impact of these varying aspects on the rate of hospital admissions has been a matter of discussion for nearly 30 years. However, literature on this issue is scarce. In a previous review, case mix differences representing LTC population-level factors turned out to give only partial explanation for the variations in hospital admission [42]. This was confirmed by a study published by Wennberg et al., reporting that disparities in hospital admissions remained in similar geographic areas even after adjusting for case mix [43]. A recently published review of the literature confirmed that the propensity of being referred to acute care was rather associated with facility characteristics including nursing home ownership and bed-hold requirements than with patient characteristics [11].

Interestingly, to the best of our knowledge, the impact of assessment tools on the variability of inappropriate hospital admissions has not been studied so far.

In our review, we noticed considerable heterogeneity among the tools regarding the aims of use and the concepts studied (e.g. assessment of appropriateness of ED visits vs. in-patient hospitalisation; focus on preventable nature of the admissions vs. appropriateness of hospital transfer), format of use (tool applied by study authors vs. expert panel or nursing staff), data sources used (administrative databases vs. resident' hospital or LTC facility record vs. interview with residents or nursing staff), and aspects evaluated.

Our research team isolated six most prominent aspects considered by the assessment tools: specific medical diagnoses, acuteness or severity of symptoms at transition time point, resident's characteristics prior to admission to hospital, resource availability/requirement, residents'/families' wishes, information on the existence of a care plan. Most tools covered less than four aspects, and only six of them included four or more aspects and were therefore considered as more comprehensive. The individual aspects "residents' characteristics prior to admission to hospital" and "residents'/families' wishes" were evaluated only by six and three tools, respectively. Some tools (e.g. ACSC, Modified ACSC) only evaluated aspects like "specific medical diagnoses" or "acuteness or severity of symptoms at transition time point". Taking into consideration that residents in LTC facilities often differ in terms of comorbidity, cognitive and functional status, and stage of their diseases, it is surprising that residents' clinical characteristics prior to acute care admission were not acknowledged throughout as a necessary dimension of the judgement process. The same applies to residents' and relatives' preferences which otherwise play an important role regarding the present advocacy towards person-centred care [44]. It may also be seen as a weakness of the existing tools that they did not consistently include facility-level characteristics as an indicator of the appropriateness of admissions. In respect to the frequently quickly changing conditions of residents, the presence of skilled nursing staff and the availability of technical equipment including diagnostic and therapeutic procedures may greatly influence the decision on the appropriateness of acute care admission. Finally, only 5 tools judged appropriateness based on a balance of aspects.

All tools identified in this systematic review were developed based on expert opinion, at least to a great extent. Information on generalizability in other regions or countries is scarce.

Our findings are supported by a non-systematic review [17,45]. Ouslander and Maslow did not focus on LTC residents only, but also included community-dwelling older persons. The review on preventable hospitalisations focusses on

U.S. information sources and perspectives. The authors emphasize, as we do, the need for comprehensive measures to account for aspects such as medical comorbidities, clinical complexity or differences in resources in the care settings. They also criticize the lack of attention to how and where decisions about hospitalisation are made.

Our systematic review focussed on the assessment of appropriateness among LTC residents. The assessment of appropriateness of hospital admission among community-dwelling older persons may require the consideration of similar aspects, but adapted to the different setting. To the best of our knowledge, no systematic review covering international studies on this issue is available so far.

It may be seen as a limitation that we did not systematically assess the risk of bias of the original studies included in our systematic review. However, we were interested in the concepts and tools used for assessing appropriateness of hospital admissions, rather than in the internal validity of the studies. Nevertheless, even without formal validity assessment, it is obvious that the included studies suffer from methodological shortcomings, since many used secondary or retrospective routine data analysis and are therefore more prone to bias.

Our review, which is the first to overview the tools internationally used to assess the appropriateness of hospital admissions among LTC residents, may contribute to the clarification of the concept "appropriateness of admission of LTC residents to acute care". It also may present a first step towards the development of an evidence-based, comprehensive and generalizable tool. Such a tool may have a two-fold function: first as a quality indicator to assess the appropriateness of the decisions made when admitting individual residents to acute care, considering that the resources available were not modifiable at that time, and secondly to identify areas of improvement such as the need for training in palliative care or the need for more resources. The tool may attempt to assess appropriateness minimizing the effects of the different rater perspectives (i.e. nursing staff of the LTC facility, ED professionals, and researchers). It may also be used to assess the effectiveness of new interventions aimed at improving appropriateness of transition of LTC residents to acute care.

In the meanwhile, studies aiming at assessing appropriateness of admitting LTC residents to hospital are encouraged to use an assessment tool according to predefined aims and taking the different aspects into consideration. Studies should mention why a certain tool was chosen and the limitations of not using a more comprehensive tool should be clearly mentioned.

Conclusions

Our systematic review analysed 29 studies assessing the prevalence of the appropriateness of acute care admissions, which varied widely throughout the studies. We found 16 different assessment tools used in the studies. Only six tools covered more than four aspects as criteria to determine the appropriateness of acute care admissions. Most assessment tools did not take into account residents' individual aspects, such as characteristics of residents prior to admission and wishes of residents or families. Tools were based mostly on expert opinion, and information on their generalizability is not provided. Further research is warranted to develop an evidence-based and comprehensive tool supported by quality assuring strategies to improve decisions on the appropriateness of ED and hospital admissions among residents of LTC facilities.

Additional files

Additional file 1: Table S1. Studies dealing with assessment tools for determining appropriateness of hospital admissions among residents of LTC facilities.

Additional file 2: Table S2. Characteristics of the assessment tools to determine appropriateness of hospital admissions among residents of LTC facilities [46-52].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Review protocol: ARG, EM & GM. Literature search: ARG, EM, LU & GM. Data extraction: ARG, EM, LU & GM. Data interpretation: ARG, GM, EM, LU. Drafting of the manuscript: ARG. Critical revision of the manuscript with regard to important intellectual content: GM, EM & LU. Study supervision: EM & GM. All authors read and approved the final manuscript.

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ARTICLE 2

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries

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Abstract
Purpose The aim of the study was to develop a European list of potentially inappropriate medications (PIM) for older people, which can be used for the analysis and comparison of prescribing patterns across European countries and for clinical practice.
Methods A preliminary PIM list was developed, based on the German PRISCUS list of potentially inappropriate medications and other PIM lists from the USA, Canada and France. Thirty experts on geriatric prescribing from Estonia, Finland, France, the Netherlands, Spain and Sweden participated; eight experts performed a structured expansion of the list, suggesting further medications; twenty-seven experts participated in a two-round Delphi survey assessing the appropriateness of drugs and suggesting dose adjustments and therapeutic alternatives. Finally, twelve experts completed a brief final survey to decide upon issues requiring further consensus.
Results Experts reached a consensus that 282 chemical substances or drug classes from 34 therapeutic groups are PIM for older people; some PIM are restricted to a certain dose or duration of use. The PIM list contains suggestions for dose adjustments and therapeutic alternatives.
Conclusions The European Union (EU)(7)-PIM list is a screening tool, developed with participation of experts from seven European countries, that allows identification and comparison of PIM prescribing patterns for older people across European countries. It can also be used as a guide in clinical practice, although it does not substitute the decision-making process of individualised prescribing for older people. Further research is needed to investigate the feasibility and applicability and, finally, the clinical benefits of the newly developed list.

Keywords Potentially inappropriate medication · Inappropriate prescribing [MeSH term] · Aged [MeSH term] · Screening · Europe [MeSH term]

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Background

Appropriate prescribing for older people is a public health concern, and several assessment tools are available for its evaluation. Most of the tools focus on pharmacological appropriateness of prescribing [1]; they address various aspects of appropriateness, including overprescribing of medications that are clinically not indicated, omission of medications that are needed, and incorrect prescriptions of medications that may be indicated [2]. The term "potentially inappropriate medications (PIM) for older people" has been used to refer

to those drugs which should not be prescribed for this population because the risk of adverse events outweighs the clinical benefit, particularly when there is evidence in favour of a safer or more effective alternative therapy for the same condition [3, 4].

The prevalence of inappropriate prescribing and/or use of PIM has been analysed by several authors and ranges from 20 to 79 % depending on the population studied, the setting or country, and the specific tool used [5–10]. Inappropriate prescribing and use of PIM can be associated with adverse outcomes such as adverse drug events [11–13], hospitalisation [6, 14] and death [15].

A recently published systematic review identified 46 tools or criteria for assessing inappropriate prescribing [16]. A prior systematic review identified 14 criteria specific for individuals aged 65 and older [1]. Generally, the assessment tools have been developed based on expert opinion due to the lack of high-quality studies on the use of drugs in older people [17], although some tools have additionally used a literature search [18, 19]. Criteria have been classified into explicit or implicit or mixed approach [1]. Explicit criteria are generally lists of medications or criteria which can be applied with little or no clinical judgement but do not address individual differences between patients [2]. Implicit criteria are based on the judgement of a professional and are person-specific [20], requiring individual patient data for application, however, they are time-consuming and more dependent on the user [2]. No single ideal tool has been identified so far, but each tool seems to have its strengths and weaknesses, and the choice of a tool may depend on the purpose of use (i.e. daily practice, research) and availability of data [16].

Assessment tools are being used increasingly for the evaluation of prescribing quality in older people, but their application cannot substitute the individual assessment of prescribing appropriateness [16]. One of the limitations of the tools is the fact that the majority was developed following country-specific guidelines, national drug markets and prescribing habits, hence, limiting their transferability to other countries [1, 21]. For instance, the German PRISCUS list of potentially inappropriate medications, a purely explicit list, defines 83 PIM drugs, of which twelve are not on the drug market in France, the USA and Canada. However, there are 124 drugs on the PIM lists of these countries which are not part of the German PRISCUS list, because seventy of them are not on the German drug market and many others are almost never used [22]. To the best of our knowledge, no assessment tool covers the drug markets of several European countries and could thus enable the analysis of European databases.

The present study was conceived when planning to analyse the prescription of PIM among a European cohort of older people with dementia participating in the *RightTimePlaceCare* study [23]. The primary aim of our study was to develop an expert-consensus list of potentially inappropriate medications covering the drug markets of seven European countries, which can be used for the analysis of potentially inappropriate prescription patterns in and across several European countries. Additionally, the list should be applicable in clinical practice to alert health care professionals to the likelihood of inappropriate prescribing, possible dose adjustments required and therapeutic alternatives.

Methods

A research team consisting of a clinical pharmacologist, a pharmacist, a nursing scientist and a geriatrician planned and coordinated the development of the European Union (EU)(7)-PIM list. Two members of the research team were developers of the German PRISCUS list [22]. The study comprised five consecutive phases:

1. *Preparation of a preliminary PIM list*. We prepared a preliminary PIM list which contained 85 PIM (82 active substances plus one combination of active substances and two different preparations of one substance) from the German PRISCUS list [22] and 99 PIM from the French [3], American [24, 25] and Canadian [26] lists. These tools have been used in research to evaluate the prescription of PIM and factors associated with PIM use [5, 6, 14, 27–29]. The main reason for each drug being PIM was formulated using the information provided by the original lists. This process was supported by a comprehensive literature search. The anatomical therapeutic chemical (ATC) code classification system was used (2011) [30].
2. *Recruitment of experts on geriatric prescribing/pharmacotherapy*. We established a collaboration with the Seventh Framework European project *RightTimePlaceCare* [23], a project aiming to develop best practice recommendations for dementia care throughout Europe. The consortium partners of this project supported the recruitment of experts on geriatric prescribing or pharmacotherapy in their respective countries. Thirty-three experts from six European countries agreed to participate; they came from Finland (n=3), Estonia (n=9), the Netherlands (n=4), France (n=2), Spain (n=7) and Sweden (n=8). The following professions were represented as follows: geriatricians (n=14), pharmacists (n=3), clinical pharmacologists (n=7) and other medical specialists (n=9). Experts were sent information documents describing the aims, concepts and steps of the study and were asked whether they preferred to participate in the expansion phase (phase 3), in the Delphi survey (phase 4), or in both.
3. *Expansion of the preliminary PIM list*. We asked thirteen experts representing the six countries to expand the preliminary PIM list by adding drugs that they considered

should be PIM and which were not represented, paying special attention to those drugs available on their respective countries' markets. Expansion of the preliminary list was Internet-based and concluded in May 2012.

4. *Two-round Delphi survey.* A two-round Delphi survey was performed [31]. The first Delphi round took place between October and December 2012, and the second Delphi round between March and May 2013. In the first round, we asked 29 experts to assess each drug of the preliminary expanded list for appropriateness by using a 1–5 points Likert scale where "1" represented "I strongly agree that the drug is potentially inappropriate for older people"; "2", "I agree that the drug is potentially inappropriate for older people"; "3", "average/neutral/undecided"; "4", "I disagree that the drug is potentially inappropriate for older people"; "5", "I strongly disagree that the drug is potentially inappropriate for older people"; and "0", "no answer; I do not feel qualified to answer". Experts were asked to provide suggestions for dose adjustments and safer therapeutic alternatives for those drugs judged as inappropriate. Experts were free to insert additional comments and were invited to expand the list with any further drugs they considered to be PIM.

   In the second Delphi round, we asked 28 experts to assess the appropriateness of those drugs classified as questionable PIM during the first round (see "Expert agreement and statistics"), as well as the further suggestions for PIM made by the experts during the first Delphi round, and also eight drugs appearing in the recently published updated Beers list [18]. Some PIM concepts were adapted taking the experts' suggestions made during the first Delphi round into account. The additional suggestions for PIM were given a justification as to why they may be classified as PIM, taking published data into consideration when necessary. Again, experts assessed the appropriateness of these drugs and were asked to provide dose adjustments, therapeutic alternatives, and to insert additional comments if necessary. Drugs were classified into PIM, non-PIM and questionable PIM (see "Expert agreement and statistics").

5. *Preparation of the final PIM list.* Dose adjustments and drug alternatives suggested by the experts during the Delphi survey were compiled and included in the EU(7)-PIM list, prioritising in each case those made by the higher number of experts. Suggestions were complemented, if necessary, with information available from the other PIM lists and from Micromedex® [32], a commercially available database which contains comprehensive information on drug use. We identified those drugs for which some discussion issues raised by the experts still remained open and those drugs where inconsistency in the results was identified after checking the literature. In order to solve these problems, a reduced number of experts (n=12) was invited to participate in the last brief survey which took place in September 2013.

Expert agreement and statistics

Several approaches have been suggested in the literature to define expert agreement within Delphi surveys [31]. In this study, after the first and second Delphi rounds, we calculated the means, the corresponding 95 % confidence intervals (CI) and the medians of all Likert scores given to each drug; expert agreement was considered if the CI of the mean score for each drug did not cross over the value 3. Thus, each drug was classified into PIM (if both the mean value of the score and the upper limit of the CI were lower than 3), non-PIM (if both the mean value of the score and the lower limit of the CI exceeded 3) and questionable PIM (if the CI was on both sides of the value 3). Statistical calculations were performed with SPSS, version 21.0.

Results

The preliminary PIM list contained 184 drugs (including two combinations of two drugs) and preparations (e.g. sustained-release preparations of oxybutynine). Eight of the 13 invited experts (62 %) participated in the expansion phase and suggested 75 additional drugs and preparations. Twenty-six out of the 29 invited experts (90 %) participated in the first Delphi round, and 24 out of the 28 invited experts (86 %) participated in the second Delphi round. Two experts from Spain and three experts from Finland chose to collaborate together in two teams to provide their assessments in both Delphi rounds. All the 12 experts invited participated in the last brief survey.

Figure 1 shows the development process of the list. In the first Delphi round, experts assessed 259 drugs and preparations, of which the majority (n=234) were classified as PIM and only one drug as non-PIM. In the second Delphi round, experts assessed 79 drugs and preparations, comprising 23 questionable PIM, 47 further suggestions by experts, eight additional drugs from the updated Beers list [18] and one drug (naproxen) judged as PIM for which the main reason for PIM was adapted taking recent published data and experts' comments into consideration. Again, 31 drugs and preparations remained as questionable PIM and 46 drugs were classified as PIM. Overall, after the third brief survey, 282 drugs and preparations were classified as PIM, 29 as questionable PIM and three as non-PIM.

The level of agreement between experts varied in the assessment of appropriateness. For example, experts reached consensus for diazepam being PIM with a mean Likert score of 1.61, confidence interval between 1.32 and 1.89, and

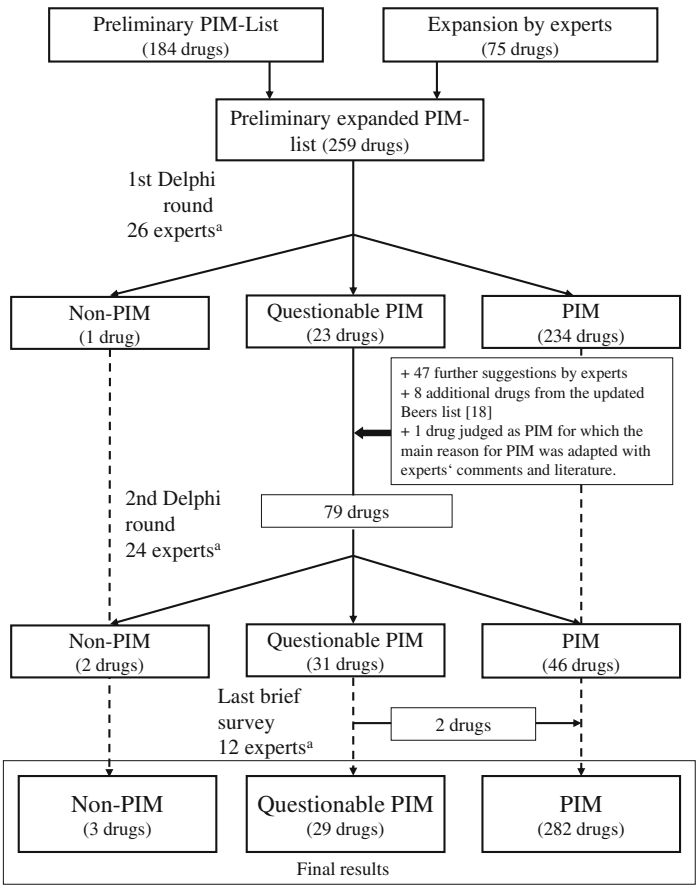

Fig. 1 The development process of the EU(7)-PIM list

[a]This number comprises two groups of 2 and 3 experts, respectively, doing joint assessments.

median of 2. Consensus was reached also for digoxin being PIM (mean Likert score 2.19; confidence interval 1.57–2.81; median 2), but in this case, the Likert scores ranged from 1 to 5. No consensus was reached on the appropriateness of some drugs such as metamizole, which was classified as questionable PIM. For this drug, the disparity seemed to be in part due to the experts' country of origin, since the majority of the Spanish experts considered metamizole to be appropriate when used in adequate doses, whereas the majority of Finnish experts considered this drug to be clearly inappropriate.

The last brief survey consisted of 11 questions with multiple-choice answers and covered issues regarding 13 drugs. The questions covered mostly dose-related issues commented by the experts during the survey which remained open (four drugs) and inconsistencies in the results identified after checking the literature (three drugs). Additionally, the research group asked the experts to provide their opinion on the use of three drugs. Finally, the research group did minimal corrections in the PIM which needed experts' approval (three drugs). All of the issues could be solved.

Table 1 displays an abbreviated version of the EU(7)-PIM list, with the 72 PIM most frequently identified among the participants of the *RightTimePlaceCare* survey [23], a European cohort of older people with dementia (data not shown).

Appendix 1 shows the complete EU(7)-PIM list, which comprises 275 chemical substances (i.e. 7-digit ATC codes; e.g. amitriptyline) including two combinations of two chemical substances, plus seven drug classes (i.e. 5-digit ATC codes; e.g. triptans), belonging to 55 therapeutic classes (i.e. 4-digit ATC codes; e.g. antidepressants) and 34 therapeutic groups (i.e. 3-digit ATC codes; e.g. the nervous system). Some PIM concepts are dose-related (e.g. zopiclone used at doses higher than 3.75 mg/day) or defined by length of use (e.g. proton-pump inhibitors used longer than 8 weeks) or drug regimen (e.g. insulin, sliding scale). Appendix 1 contains also information on the number of experts who assessed each PIM,

Table 1 PIM according to the EU(7)-PIM list[a]

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Drugs for peptic ulcer and gastro-oesophageal reflux			
Ranitidine	CNS adverse effects including confusion	CrCl <50 mL/min 150 mg q 24h (oral); 50 mg q 18–24 h (iv). E	When indication is appropriate, PPI (<8 weeks, low dose). E
PPI (>8 weeks) e.g. omeprazole, pantoprazole	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication		
Propulsives			
Metoclopramide	Antidopaminergic and anticholinergic effects, may worsen peripheral arterial blood flow and precipitate intermittent claudication	Short-term use and dose reduction; CrCl <40 mL/min 50 % of normal dose; maximum dose 20 mg/d; may be used in palliative care. E	Domperidone (<30 mg/d) if no contraindications. E
Laxatives			
Senna glycosides Sodium picosulfate	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel dysfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. E, P
Antipropulsives			
Loperamide (>2 days)	Risk of somnolence, constipation, nausea, abdominal pain and bloating. Rare adverse events include dizziness. May precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis	Start with a dose of 4 mg followed by 2 mg in each deposition until normalisation of bowel; do not exceed 16 mg/d; use no longer than 2 days; may be useful in palliative care for persisting non-infectious diarrhoea. E	Non-pharmacological measures, e.g. diet; phloroglucinol. E
Insulins and analogues			
Insulin, sliding scale	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels	Lower doses to avoid hypoglycemia. E	Basal insulin. E
Blood glucose lowering drugs, excluding insulins			
Glibenclamide	Risk of protracted hypoglycemia	Use conservative initial dose (1.25 mg/d for non-micronized glibenclamide; 0.75 mg/d for micronized glibenclamide) and maintenance dose; not recommended if CrCl <50 mL/min. M	Diet; metformin (<2×850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. E
Glimepiride	Risk of protracted hypoglycemia	Adjust according to renal function. E For patients with renal failure and for older people, use initial dose of 1 mg/d followed by a conservative titration scheme. Titrate dose in increments of 1 to 2 mg no more than every 1 to 2 weeks based on individual response. M	
Sitagliptine	Limited safety data available for adults aged ≥75 years old. Subjects aged 65 to 80 had higher plasma concentrations than younger subjects. Risk of hypoglycemia, dizziness, headache and peripheral oedema	Reduce dose to 50 mg/d in cases of renal failure (CrCl 30–50 mL/min); reduce dose to 25 mg/d in cases of severe renal insufficiency (CrCl <30 mL/min). E, M	
Antithrombotic agents			
Acenocoumarol	Risk of bleeding, especially in people with difficult control of INR value		
Dipyridamole	Less efficient than aspirin; risk of vasodilatation and orthostatic hypotension. Proven beneficial only for patients with artificial heart valves		Clopidogrel; aspirin (<325 mg)[b]. E, L

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Iron preparations			
Iron supplements / Ferrous sulfate (>325 mg/d)	Doses >325 mg/d do not considerably increase the amount absorbed but greatly increase the incidence of constipation		Intravenous iron. E
Cardiovascular system			
Cardiac glycosides			
Digitoxin	Elevated glycoside sensitivity in older people (women > men); risk of intoxication	Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. M	For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). E, P For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE inhibitors. E
Digoxin		Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. M For older people, use dose 0.0625–0.125 mcg/d; in cases of renal failure (CrCl 10–50 mL/min), administer 25–75 % of dose or every 36 h; in cases of renal failure (CrCl <10 ml/min), administer 10–25 % of dose or every 48 h. E	
Antiarrhythmics, classes I and III			
Amiodarone	Associated with QT interval problems and risk of provoking torsades de pointes	Start dose at the low end of the dosing range. M Use lower maintenance dose, e.g. 200 mg/48 h. E	Data suggest that for most older people rate control yields better balance of benefits and harms than rhythm control for most of older people. B
Other cardiac preparations			
Trimetazidine	Can cause or worsen parkinsonian symptoms (tremor, akinesia, hyperthonia); caution in cases of moderate renal failure and with older people (>75 years old); efficacy for the treatment of tinnitus or dizziness not proven	20 mg twice per day for patients with moderate renal insufficiency. E	
Antiadrenergic agents, centrally acting			
Rilmenidine	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Reduce dose in cases of renal failure (CrCl <15 mL/min). M, E	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). E
Antiadrenergic agents, peripherally acting			
Doxazosin	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Start with half of usual dose, taper in and out. P Start with 0.5 mg/d (immediate release) or 4–8 mg/d (extended release). E	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). E
Potassium-sparing agent			
Spironolactone (>25 mg/d)	Higher risk of hyperkalaemia and hyponatremia in older people, especially if doses >25 mg/d, requiring periodic controls	Reduce dose in cases of moderate renal insufficiency. E, M GFR ≥50 mL/min/1.73 m: initial dose 12.5–25 mg/d, increase up to 25 mg 1–2/d; GFR 30–49 mL/min/1.73 m: initial dose 12.5 mg/d, increase up to 12.5–25 mg/d; reduce dose if potassium levels increase or renal function worsens. GFR <10 mL/min: avoid. M	Consider alternatives depending on the indication; exclude PIMs

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Peripheral vasodilators			
Pentoxifylline	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators	Reduce dose to 400 mg twice daily in cases of moderate renal failure and to 400 mg once daily in cases of severe renal failure; close monitoring for toxicities. Avoid use if CrCl <30 mL/min. M	
Beta blocking agents			
Propranolol	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events	3 doses of 20 mg daily E start low—go slow for older people and patients with renal failure. M	Depending on the indication: cardioselective beta-blockers, ACE inhibitors, diuretics. E
Sotalol		Start at half or one third of the typical dose and increase slowly. P Reduce dose and dosing interval in cases of renal failure. M	Cardioselective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). E
Selective calcium channel blockers with mainly vascular effects			
Nifedipine (non-sustained-release)	Increased risk of hypotension; myocardial infarction; increased mortality	Lower initial dose, half of usual dose, taper in and out. P	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). E, L
Nifedipine (sustained-release)		Lower initial dose, half of usual dose, taper in and out. P Initial dose 30 mg/d; maintenance dose 30–60 mg/d. E	
Selective calcium channel blockers with direct cardiac effects			
Verapamil	May worsen constipation; risk of bradycardia	Immediate-release tablets: initial dose 40 mg three times daily; sustained release tablets initial dose 120 mg daily; oral controlled onset extended release initial dose 100 mg/d. M	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). E
Diltiazem		Reduce dose or increase dosing interval. M 60 mg three times daily. E	
Oestrogens			
Oestrogen	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women		Specific treatment for osteoporosis. E Local administration (i.e. vaginal application) considered safe and efficient. E, B
Other urologicals, including antispasmodics			
Oxybutynine (non-sustained-release)	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)	Start immediate-release oxybutynin chloride in frail older people with 2.5 mg orally 2 or 3 times daily. M	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). E
Oxybutynine (sustained-release)			
Tolterodine (non-sustained-release)		1 mg orally twice daily in cases of significantly impaired renal function. M	
Tolterodine (sustained-release)		Use 2 mg orally once daily in cases of severe renal failure (CrCl 10–30 mL/min); avoid use if CrCl <10 mL/min. M	
Solifenacin		Dose reduction may be needed. M	
Anti-inflammatory and antirheumatic products, non-steroid (NSAID)			
Diclofenac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	50 mg/d; start using low dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). E	Paracetamol; ibuprofen (≤3×400 mg/d or for a period shorter than one week); naproxen (≤2×250 mg/d or for a period shorter than one week). E Opiods with lower risk of delirium (e.g. tilidine/naloxone, morphine[b], oxycodone, buprenorphine, hydromorphone). E, P
Dexketoprofen		Start with lower dose, up to 50 mg/d in older people; in postoperative pain: 50 mg/d in case of renal or hepatic failure, maximum dose 50 mg/8 h; maximum length 48 h; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). E	

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Etoricoxib		Shortest possible duration of therapy. P Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). E	
Meloxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	11 mg/d; start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). E	
Ibuprofen (>3×400 mg/d or for a period longer than one week)	Risk of GI bleeding and increased risk of cardiovascular complications at higher doses (>1200 mg/d), especially in case of previous cardiovascular disease	The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). E	
Drugs affecting bone structure and mineralization			
Strontium ranelate	Higher risk of venous thromboembolism in persons who are temporarily or permanently immobilised. Evaluate the need for continued therapy for patients over 80 years old with increased risk of venous thromboembolism	Avoid in cases of severe renal failure (CrCl <30 mL/min). M	Bisphosphonates, vitamin D. E
Opioids			
Tramadol (sustained-release)	More adverse effects in older people; CNS side effects such as confusion, vertigo and nausea	Start low—go slow. Not to be used in cases of severe renal failure. E, M	Paracetamol; ibuprofen (≤3×400 mg/d or for a period shorter than one week); naproxen (≤2×250 mg/d or for a period shorter than one week). E Opioids with lower risk of delirium (e.g. tilidine/naloxone, morphine[b], oxycodone, buprenorphine, hydromorphone). E, P
Tramadol (non-sustained-release)		Start low—go slow; in persons older than 75 years, daily doses over 300 mg are not recommended. M Start with 12.5 mg/8 h and progressive increases of 12.5 mg/8 h; maximum 100 mg/8 h. E Reduce dose and extend the dosing interval for patients with severe renal failure. M	
Antiepileptics			
Clonazepam	Risk of falls, paradoxical reactions.	Start low—go slow; 0.5 mg/day. E	Levetiracetam[b]; gabapentin[b]; lamotrigine[b]; valproic acid[b]. E
Carbamazepine	Increased risk of SIADH-like syndrome; adverse events like carbamazepine-induced confusion and agitation, atrioventricular block and bradycardia	Adjust dose to the response and serum concentration. E	
Dopaminergic agents			
Ropinirole	Risk of orthostatic hypotension, hallucinations, confusion, somnolence, nausea	Start with three intakes of 0.25 mg per day, increase gradually by 0.25 mg per intake each week for four weeks, up to 3 mg/d. Afterwards the dose may be increased weekly by 1.5 mg/d up to 24 mg/d. E	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. E
Pramipexole	Side effects include orthostatic hypotension, GI tract symptoms, hallucinations, confusion, insomnia, peripheral oedema	Reduce dose in cases of moderate to severe renal failure. M Start with three intakes of 0.125 per day, increase gradually by 0.125 mg per intake every five to seven days, up to 1.5 to 4.5 mg. E	
Antipsychotics			
Chlorpromazine	Muscarinic-blocking drug; risk of orthostatic hypotension and falls; may lower seizure thresholds in patients with seizures or epilepsy	Start low—go slow; use one third to one half the normal adult dose for debilitated older people; use maintenance doses of 300 mg or less; doses greater than 1 g do not usually offer any benefit, but may be responsible for an increased incidence of adverse effects. M	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; < 5 mg/d); quetiapine[b]. E

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Levomepromazine	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Administer cautiously in cases of renal failure; start with doses of 5 to 10 mg in geriatric patients. M	
Haloperidol (>2 mg single dose; >5 mg/d)		Use oral doses of 0.75-1.5 mg; use for the shortest period possible. E	
Zuclopenthixol	Risk of hypotension, falls, extrapyramidal effects, QTc-prolongation	Use low oral doses of 2.5–5 mg/d. M	
Clozapine	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia; increased risk of agranulocytosis and myocarditis	Start with 12.5 mg/d. E Start low—go slow; reduce dose in cases of significant renal failure. M	
Risperidone (>6 weeks)	Problematic risk-benefit profile for the treatment of behavioural symptoms of dementia; increased mortality, with higher dose, in patients with dementia	Use the lowest dose required (0.5–1.5 mg/d) for the shortest time period necessary. E For geriatric patients or in cases of severe renal failure (CrCl <30 mL/min), start with 0.5 mg twice daily; increase doses by 0.5 mg twice daily; increases above 1.5 mg twice daily should be done at intervals of at least 1 week; slower titration may be necessary. For geriatric patients, if once-daily dosing desired, initiate and titrate on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter. M	
Anxiolytics			
Diazepam	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P, M Use initial oral dose of 2–2.5 mg once a day to twice a day. M	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[c]). E, P If used as hypnotics or sedatives: see alternatives proposed for "hypnotics and sedatives"
Lorazepam (>1 mg/d)		Reduce dose; use doses of 0.25–1 mg/d. E	
Bromazepam		Use the lowest possible dose, up to half of the usual dose, taper in and out according to individual response, shortest possible duration of treatment. P, M	
Alprazolam		Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P Starting dose 0.25 mg/12 h. E Immediate release tablets (including orally disintegrating tablets): start with 0.25 mg administered two to three times a day and titrate as tolerated; extended-release tablets: start with 0.5 mg once daily, gradually increase as needed and tolerated. M	
Hypnotics and sedatives			
Flunitrazepam	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P Reduce dose, e.g. 0.5 mg/d; start low—go slow. E, M For induction of anaesthesia in older, poor-risk people, titrate dose carefully; administer in small intravenous increments of 0.3 to 0.5 mg, at 30-s intervals. M	Non-pharmacological treatment; mirtazapine[b]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. E, P

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Lormetazepam (>0.5 mg/d)		Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P	
Temazepam		Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P Start with 7.5 mg/d and watch individual response. M	
Zopiclone (>3.75 mg/d) Zolpidem (>5 mg/d)		Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P	
Clomethiazole	Risk of respiratory depression	Reduce dose. E, M Use sedative dose 500–1000 mg at bedtime. M	
Antidepressants			
Amitriptyline	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly; reduce dose; start with 10 mg 3 times per day and 20 mg at bedtime. M, E, P Its use for treating neuropathic pain may be considered appropriate, with benefits overweighting the risks. E	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[c], mirtazapine[b], trazodone. E
Nortriptyline		Use 30–50 mg/d in divided doses. E, M Its use for treating neuropathic pain may be considered appropriate, with benefits overweighting the risks. E	
Fluoxetine	CNS side effects (nausea, insomnia, dizziness, confusion); hyponatremia	Reduce dose; start with 20 mg/d; maximum dose also 20 mg/d; avoid administration at bedtime. E, M	
Paroxetine	Higher risk of all-cause mortality, higher risk of seizures, falls and fractures. Anticholinergic adverse effects	For older people or for patients with renal failure, start immediate-release tablets with 10 mg/d (12.5 mg/d if controlled-release tablets), increased by 10 mg/d (12.5 mg/d if controlled-release tablets), up to 40 mg/d (50 mg/d if controlled-release tablets). E, M	
Venlafaxine	Higher risk of all-cause mortality, attempted suicide, stroke, seizures, upper gastrointestinal bleeding, falls and fracture	Start with 25–50 mg, two times per day and increase by 25 mg/dose; for extended-release formulation start with 37.5 mg once daily and increase by 37.5 mg every 4–7 days as tolerated. E Reduce the total daily dose by 25–50 % in cases of mild to moderate renal failure. M	
Psychostimulants, agents used for ADHD and nootropics			
Piracetam	No efficacy proven; unfavourable risk/benefit profile	Reduce dose for older people and for patients with renal failure. M	Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine. E
Anti-dementia drugs			
Ginkgo biloba	No efficacy proven; increased risk of orthostatic hypotension and fall		Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine. E

Table 1 (continued)

PIM	Main reason	Dose adjustment/special considerations of use	Alternative drugs and/or therapies
Other systemic drugs for airway diseases			
Theophylline	Higher risk of CNS stimulant effects	Start with a 25 % reduction compared to the doses for younger people. E Start with a maximum dose of 400 mg/d; monitor serum levels and reduce doses if needed; for healthy older people (>60 years), theophylline clearance is decreased by an average of 30 %. M	
Cough suppressants, excluding combinations with expectorants			
Codeine (>2 weeks)	Higher risk of adverse events (hypotension, sweating, constipation, vomiting, dizziness, sedation, respiratory depression). Avoid use for longer than 2 weeks for persons with chronic constipation without concurrent use of laxatives and for persons with renal impairment	Start treatment cautiously for older people (especially in cases of renal failure); start low—go slow; reduce dose to 75 % of the usual dose if GFR 10–50 mL/min and to 50 % if GFR <10 mL/min. M	If used for pain management consider alternative drugs proposed for "anti-inflammatory and antirheumatic products, non-steroid (NSAID)"
Antihistamines for systemic use			
Promethazine	Anticholinergic side effects (e.g. confusion, sedation)	Reduce dose; start low—go slow. M Reduce starting dose to 6.25–12.5 mg for iv injection. M	Non-sedating, non-anticholinergic antihistamines[d] like loratadine, cetirizine, but not terfenadine (which is PIM). E If used for insomnia see alternatives proposed for "hypnotics and sedatives"
Hydroxyzine	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance, confusion, sedation; electrocardiographic changes (prolonged QT)	Reduce dose to at least 50 % less than dose used for healthy younger people. E, M	Non-sedating, non-anticholinergic antihistamines[d] like loratadine, cetirizine, but not terfenadine (which is PIM). E Alternative therapies depending on indication. E

Note: if nothing is stated under "Dose adjustment/special considerations of use", this means that no suggestion was made either by the experts or in Micromedex®

E experts, *M* Micromedex® [32], *P* PRISCUS list [22], *L* Laroche et al. (2007) [3], *B* Beers list (2012) [18], *ACE* angiotensin-converting enzyme, *CNS* central nervous system, *ECG* electrocardiographic, *GI* gastrointestinal, *PIM* potentially inappropriate medication, *PPI* proton-pump inhibitors, *RTPC RightTimePlaceCare* [23], *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *ADHD* attention deficit hyperactivity disorder

Dosage abbreviations: *CrCl* creatinine clearance, *d* day, *GFR* glomerular filtration rate, *iv* intravenous, *mcg* micrograms, *mg* milligram, *min* minute, *mL* millilitre, *q* every

[a] Only the details on the drugs most commonly used in the RTPC database are presented—see also EU(7)-PIM long version in Appendix 1

[b] Caution: this drug was judged to be questionable PIM

[c] The following drugs belonging to this medication group were judged to be questionable PIM: citalopram, sertraline, and escitalopram

[d] In the group of non-sedating antihistamines, only loratadine was evaluated and judged to be questionable PIM; other drugs such as cetirizine were not evaluated

the mean, median and standard deviation of the scores given by experts to each drug (Likert scale), and the results of the compilation and selection of suggestions for dose adjustments and therapeutic alternatives. Furthermore, Appendix 1 shows two categories of those drugs (active substances characterised by their ATC code) on the EU-PIM list that are included also on other PIM lists. Category A means that precisely this active substance is named as a PIM which should be avoided in older people. Category B means that (i) this active substance is characterised as a PIM only in the case of certain clinical conditions or co-morbidities or (ii) this active substance is not specifically named but considered as a PIM drug class (e.g. anticholinergics or long-acting benzodiazepines). This information refers to six international PIM lists or criteria [3, 18, 19, 22, 26, 33] and shows that 24 drugs do not appear as PIM in any of the other lists, while the rest varies from appearing in one list only to appearing in all the lists.

The full lists of questionable PIM and non-PIM and the results of their assessments are presented in Appendix 2 and 3, respectively.

Discussion

We developed the EU(7)-PIM list in order to analyse the prescription patterns of potentially inappropriate medication (PIM) across several European countries, and more specifically among the people with dementia participating in the *RightTimePlaceCare* Seventh Framework European project [23]. We also aimed to develop a list that would be applicable in clinical practice. The development of the EU(7)-PIM list took several international PIM lists (i.e. the German PRISCUS list [22], the American Beers list [18, 24, 25], the Canadian list [26], and the French list [3]) into consideration, as well as further drugs suggested by experts on geriatric prescribing from seven European countries who belonged to different professions.

The EU(7)-PIM list can be seen as a screening tool for the identification of PIM for older people across many European countries. We have covered several regions of Europe including Finland and Sweden in Scandinavia, France and Spain in southern Europe, Germany and the Netherlands in central Europe, and Estonia in eastern Europe. As shown by Fialová et al. [5], the prevalence of PIM use in several European countries varies widely, depending on the PIM criteria set. Thus, the creation of a PIM list suitable for pharmacoepidemiological studies and clinical use in Europe seems to be mandatory. Attempts are being undertaken to develop prescribing quality indicators which are useful for the electronic monitoring of the quality of prescribing in older people in Europe [34], and the EU(7)-PIM list could represent a part of this.

We expect the EU(7)-PIM list to be a sensitive tool because of its inclusive development process. In contrast, other tools have been seen to be less sensitive, motivating some authors to use two or three assessment tools for the assessment of PIM use in their populations in order to increase the sensitivity [5, 6, 35, 36].

We aimed at developing a list which can be used even if the clinical information available is minimal. Therefore, we chose to develop explicit PIM criteria, restricted to drugs or drug classes, in some instances restricted to high doses or prolonged treatment duration. Thus, the EU(7)-PIM list is suitable for pharmacoepidemiological applications using administrative databases or surveys without any clinical information about the individuals concerned.

To the best of our knowledge, this is the first list focusing on chemical substances and requiring only a small amount of clinical data for its application that has been developed taking into account several existing PIM lists and European markets, and that has been consented by experts from different European countries. This is also one of the few lists including suggestions for dose adjustments and therapeutic alternatives. Furthermore, the list enables a distinction between different drugs belonging to the same pharmacological subgroup and provides different suggestions for each of them. The recently published screening tool of older person's prescriptions (STOPP)/screening tool to alert doctors to right treatment (START) criteria for potentially inappropriate prescribing for older people (version 2) were developed also with the participation of a European panel of experts [19]. However, these criteria often consider as PIM the use of pharmacological subgroups (e.g. thiazide diuretics) within specific clinical contexts (e.g. history of gout, or current significant hypokalaemia). Thus, the application of the START/STOPP criteria (both versions 1 and 2) [4, 19] requires clinical information, making these criteria more suitable in the clinical context for a comprehensive drug review of individual patients.

The development process of the EU(7)-PIM list resembles those of most other PIM lists, such as the French list [3], the German PRISCUS list [22], the Austrian PIM list [37], but also the most recent Beers list [18]. One major aspect of criticism of all PIM lists is that the classification of PIM is usually done without using evidence derived from randomised, controlled trials and relies on the expertise of the participants in the Delphi process [38]. However, this is partially justified by the lack of evidence on drug efficacy and safety in older people, due to their low enrolment in clinical trials [17]. In our study, we identified relevant literature and used it during the development process, but we did not systematically review and report it, which may be seen as a limitation.

The Delphi technique has also been criticised because of the lack of one standardised method, the difficulties in analysing the data, the difficulties in defining what an expert is, the often heterogeneous expert group, and the vague

concept of consensus [38]. In order to minimise the limitations of the Delphi technique, in the present study, the characteristics of the survey were predefined (e.g. steps, consensus concept), and researchers provided experts with all necessary information to favour their engagement and participation. Researchers compiled discussion issues raised by the experts and took them into consideration for the consecutive steps of the development process.

Only seven European countries participated in the development of the EU(7)-PIM list (Estonia, Finland, France, Germany, the Netherlands, Spain and Sweden). Furthermore, the number of experts participating from some countries was limited. Certain drugs may not have been assessed for appropriateness because they were neither included in the preliminary list nor were they suggested by the experts. Certain drugs were classified as PIM with a lower level of expert agreement than others; some disagreements seemed related to the experts' country of origin, which may show that there are international differences in prescription patterns or attitudes. Regular updates of the list should take into consideration the inclusion of other European markets, the changes in the drug markets, the prescribing tendencies, and above all, the new existing evidence.

The application of the EU(7)-PIM list cannot substitute the individual assessment of prescribing appropriateness, which should take into account other aspects such as the aims of the treatment, individual responses, and the older person's functional level, values and preferences, among others [39]. This limitation has been recognised in the literature with regard to most tools assessing appropriateness of prescription [16]. Despite its limitations, the concept of PIM suggests that their use should be associated with less favourable outcomes. Indeed, the use of PIM has been found associated with a higher rate of adverse drug reactions in several studies, as reported in a systematic review [40], with some variations depending on the settings studied. Other authors have suggested an association between PIM use and other adverse outcomes such as injuries [41] and hospitalisation [6, 14]. A limited number of studies on interventions involving the use of some of these tools have suggested benefits in terms or relevant outcomes [42–44]. However, according to a recent systematic review, it is unclear whether such interventions result in clinically significant improvements, although benefits in terms of reducing inappropriate prescribing may exist [45].

Future research should study whether the use of PIM according to the EU(7)-PIM list shows any association with clinically relevant outcomes for older people, and whether the application of the list is associated with any benefits, both in a population and on individual levels. The acceptability of the list among health professionals should also be investigated, including the usefulness of the suggestions for drug adjustments and therapeutic alternatives.

In conclusion, the EU(7)-PIM list is an expert-consensus list of potentially inappropriate medications for older people, which was developed taking into consideration the medications appearing in six country-specific PIM lists, as well as medications used in seven European countries. It is an explicit list of chemical substances and contains suggestions for dose adjustments and therapeutic alternatives. It can be applied as a screening tool to identify potentially inappropriate medications in databases where little clinical information is available and in individual data. It can also be used for international comparisons of the prescription patterns of PIMs and may be used as a guide in the clinical practice. The application of the EU(7)-PIM list is a first step towards the identification of areas of improvement in both individual and population levels and towards the harmonisation of the prescription quality throughout Europe.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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Annexes

6

ANNEX 1.1
Article 1

Additional file 1: Table S1: Studies dealing with assessment tools for determining appropriateness of hospital admissions among residents of LTC facilities.

Authors and publication year	Country	Studied period	Method	Sample[a]	Type of LTC facilities and number	Acute care destination and number of facilities	Outcome concept and number or % of inappropriate admissions	Assessment tool used and data source (administrative databases, resident hospital / LTC facility records, interview)
Saliba et al., 2000 [18]	USA	1994-1995	Retrospective, secondary data analysis	Residents admitted to hospital (n=458)	NH (n=8)	EDV or IH (n=10)	Inappropriate EDV: 36% of the admissions; Inappropriate IH: 40%	SIR (LTC facility and hospital records)
Finucane et al., 2000 [9]	Australia	1998	Prospective, observational study	Residents admitted to hospital (n=153), admissions (n=184)	NH, rest homes, hostels (NNM)	EDV and consecutive IH (n=1)	Inappropriate hospitalisation: all participants 2/184 (1%), NH residents 1/65 (2%). Potentially avoidable hospitalisation : all 19/184 (10%), NH 17/65 (26%)	AEP + additional question on avoidability (LTC facility and hospital records, interview)
Murtaugh, 2002 [22]	USA	1992-1994	Retrospective, secondary data analysis	Older persons, including home care patients (n=3.057)	LTC settings (NNM)	IH (NNM)	Avoidable hospitalisation: 2% of the IH (not specific data for NH participants reported)	AHC (administrative databases)
Kane et al., 2003 [23]	USA	1998-2000	Retrospective, routine data analysis	Residents: intervention group (n=1.936), control groups (n=2.868)	Control and intervention NH (n=44 pairs)	IH (excluding IH after EDV) (NNM)	Preventable hospitalisation per 100 residents (rate per month): intervention 0.3; control I 0.8 (p<0.001); control II 0.9 (<0.001)	ACSC (administrative databases)
Carter, 2003 [24]	USA	1991-1993	Retrospective, secondary data analysis	Residents admitted to hospital (n=72.319 person-quarter observations)	NH (n=527)	Hospitalisation[b] (NNM)	Preventable hospitalisation due to ACSC: n= 8.070 (11%)	Modified ACSC (administrative databases)

Intrator et al., 2004 [25]	USA	1997	Prospective, observational, cross-sectional	Residents (n=54.631)	NH (663)	Hospitalisation[b] (NNM)	Potentially preventable or avoidable hospitalisation: n=3.137 (37%) out of 8.450 hospitalised at least once	ACSC (administrative databases)
Kane et al., 2004 [26]	USA	1998-2000	Retrospective, routine data analysis	Residents: intervention group (n=1.936), control groups (n=2.868)	Control and intervention NH (n=44 pairs)	IH (excluding IH after EDV) (NNM)	Preventable hospitalisation per 100 residents (rate per month): intervention 0.4; control I 0.9 (p<0.001); control II 1.1 (<0.001)	ACSC (administrative databases)
Kane et al., 2005 [27]	USA	1997-2001	Retrospective, routine data analysis	Residents: intervention group (n=1.985), control groups (n=3.970)	Control NH (n=181-289), intervention NH (n=110-118) (3 studied periods)	EDV or IH (NNM)	Preventable hospitalisation per 100 residents (rate per month): intervention 0.4; control I 0.7; control II 0.6. Preventable EDV per 100 residents (rate per month): intervention 1.7; control I 2.6; control II 2.3	Modified ACSC (administrative databases)
Carter and Porell, 2005 [28]	USA	1991-1993	Retrospective, secondary data analysis	Residents with ADRD (n=19.802), residents without ADRD (n=19.958)	NH (n=525)	IH (NNM)	Avoidable hospitalisation or hospitalisation due to ACSC: 41% of the IH among residents with ADRD; 43% of the IH among those without ADRD	ACSC (administrative databases)
Finn et al., 2006 [3]	Australia	2002	Retrospective, routine data analysis	Admissions to hospital from residential care institutions (n=541)	NH, hostels (NNM)	EDV (n=1)	Inappropriate EDV: n=71 (13%)	Modified AEP (resident hospital records)
Carter et al., 2006 [29]	US	2000-2002	Retrospective, secondary data analysis	Admissions to hospital from NH (n=1.279)	NH (NNM)	EDV and consecutive IH (NNM)	Potentially avoidable EDV and consecutive ICH with ACSC[c]	Modified ACSC (administrative databases)
Grabowski et al., 2007 [8]	USA	1998-2004	Retrospective, routine data analysis	Residents: 1999 (n=167.452), 2000 (n=165.228), 2001 (n=162.946), 2002 (n=161.967), 2003 (n=161.726)	NH (n=690)	IH (n=253)	IH with ACSC in 1999: 34%; 2000: 33%; 2001: 32%; 2002: 32%; 2003: 30%; 2004: 29%	ACSC (administrative databases)

Jensen et al., 2009 [15]	Canada	2000	Retrospective, routine data analysis	Residents admitted to hospital (n=606)	LTC facilities (n=19)	EDV (n=3)	Inappropriate EDV: n=2 (4%)	In-house developed (resident hospital records)
Walker et al., 2009 [19]	Canada	1997-2002	Retrospective, routine data analysis	Residents (n=76.629); Residents admitted to hospital (n=8.885)	High intensity LTC facilities (n=150)	Hospitalisation[b] (NNM)	Potentially avoidable hospitalisation according to the original US ACSC list: 47% (n=4.177 out of 8.885); according to the revised Canadian list: 55% of hospitalisation (n=4.874 out of 8.885)	Modified ACSC (administrative databases)
Ouslander et al., 2009 [30]	USA	2005-2007	a) Retrospective, routine data analysis; b) prospective, interventional pilot single arm study. Comparison of both data sets	a) Residents admitted to hospital (n=30); b) Residents admitted to hospital (n=65)	NH (n=3)	Hospitalisation[b] (NNM)	Potentially avoidable hospitalisation: a) n=23 (77%); b) n=32 (49%)	Modified SIR (resident hospital and LTC facility records)
Abel et al., 2009 [31]	England	2006-2007	Retrospective, routine data analysis	Residents admitted to hospital from NH (n=77) and RH (n=59) (who died in this episode of care)	NH, RH (NNM)	IH (irrespective of EDV) (n=1)	Appropriateness of staying at the LTC facility yes/maybe (inappropriately transferred): NH n=53 (69%); RH n=27 (45%)	In-house developed (resident hospital records)
Hammond et al., 2009 [32]	UK	2006-2007	Prospective	Residents with LTNC admitted to hospital (n=25)	NH (NNM)	IH (n=2)	Inappropriateness of admission: 12% (3 out of 25)	In-house developed (resident hospital records and structured interviews with residents)
Gruneir et al., 2010 [4]	Canada	2005	Retrospective, secondary data analysis	Residents (n=64.589)	NH (NNM)	EDV (NNM)	Potentially avoidable EDV: 25% of all EDV	ACSC (administrative databases)
Ouslander et al., 2010 [10]	USA	2005-2006	Retrospective, routine data analysis	Residents admitted to hospital (n=200)	NH (n=20)	Hospitalisation[b] (NNM)	Probably or definitely avoidable hospitalisation: n=134 (67%)	Modified SIR (resident LTC facility records)

Becker et al., 2010 [33]	USA	2003-2006	Retrospective, routine data analysis	Residents (n=72.251); residents admitted to hospital (n= 8.382)	NH (n=647)	Hospitalisation[b] (NNM)	Preventable hospitalisation: 18% of all hospitalisation (n=10.091 out of 8.382)	ACSC (administrative databases)
Caffrey, 2010 [20]	USA	2004	Retrospective, secondary data analysis	Residents (n=14.017)	NH (n=1.500)	EDV (NNM)	Potentially preventable EDV: 40% among residents with an EDV	Adapted from INTERACT II and other sources (administrative databases)
Codde et al., 2010 [34]	Australia	2007	Retrospective, routine data analysis	Residents admitted to hospital and discharged to NH (n=235)	NH (NNM)	EDV and discharge to NH (n=1)	Potentially avoidable EDV: 161 (69%) of patients discharged to NH; 31% of the total transfers, including patients with IH	In-house developed (resident hospital records)
Bermejo et al., 2010 [35]	Spain	2008	Retrospective, routine data analysis	Residents admitted to hospital (n=45); admissions to hospital (n=62)	NH (n=1)	EDV (n=1)	Inappropriate or not suitable EDV: 2% of all EDV	In-house developed (resident hospital and LTC facility records)
Kada et al., 2011 [36]	Austria	2008	Retrospective, routine data analysis + qualitative interviews	Residents admitted to hospital (n=4.149); residents with EDV (n=423)	NH, RH (n=15)	EDV (n=1)	Inappropriate EDV: 22% of all EDV	Modified AEP (administrative databases)
Gonzalo et al., 2011 [37]	USA	2000-2007	Retrospective, routine data analysis	Residents with ACI admitted to hospital (n=474.829)	NH (NNM)	Hospitalisation[b] (NNM)	Potentially burdensome transition to acute care: 6% of the residents with ACI	In-house developed (administrative databases)
a) Ouslander et al., 2011 [38]**; b) Lamb et al., 2011** [21]	USA	2008-2009	a) Prospective, single arm intervention; comparison with retrospective data; b) prospective single arm intervention + one-hour conference calls	a) Residents per NH (average size n=166); b) Residents per NH (average size n=174)	a) NH (n=25); b) NH (n=26)	EDV, IH (NNM)	Avoidable or possibly avoidable hospitalisation: 24% of hospitalisation (b)	Quality Improvement Review tool (INTERACT-II) (resident LTC facility records, and written questions to nursing staff)
Ong et al., 2011 [39]	England	2005-2006	a) Retrospective, routine data analysis + b) prospective qualitative analysis	Residents admitted to hospital from RH (n=223) and NH (n=117)	a) NH, RH (NNM); b) NH, RH (n=8)	IH (n=1)	Potentially avoidable or inappropriate acute hospitalisation (likely to have been managed in care homes): 41% of hospitalisation	In-house developed (administrative databases)

Young et al., 2011 [40]	USA	2006-2007	Retrospective, routine data analysis and secondary data analysis	Residents (n=26.746)	NH (n=147)	Hospitalisation[b] (NNM)	Potentially preventable hospitalisation due to ACSC rate: 654 per 100.000 resident-days	ACSC (administrative databases)
Becker et al., 2012 [41]	USA	2002-2008	Retrospective, secondary data analysis	Residents (n=16.208); residents older than 65 years (n=7.991)	Assisted living facilities	Hospitalisation[b] (NNM)	Hospitalisation due to ACSC: 22% (among residents older than 65 years)	ACSC (administrative databases)

Note: ACI: Advanced Cognitive Impairment; ACSC: Ambulatory Care Sensitive Conditions; ADRD: Alzheimer's Disease and Related Dementias; AEP: Appropriateness Evaluation Protocol; AHC: Avoidable Hospital Conditions; EDV: Emergency Department Visit; IH: In-patient Hospitalisation; ISD: Intensive Service Days; LTC: Long Term Care; LTNC: Long Term Neurological Conditions; NH: Nursing Home; NNM: Number Not Mentioned; RH: Residential Home; SIR: Structured Implicit Review.
[a]Only data from LTC facilities are displayed, if available.
[b]Not specified if EDV or IH.
[c]Number of inappropriate admissions not provided.

ANNEX 1.2
Article 1

Additional file 2: Table S2: Characteristics of the assessment tools to determine appropriateness of hospital admissions among residents of LTC facilities.

Tool [corresponding studies]	Term(s), concept(s) and aim(s) of use	Development	Psychometric properties	Format of use in the included studies	Summary of the items evaluated (aspects covered[a])
SIR [10,18,30]	To measure agreement between reviewers on the appropriateness of decisions to transfer NH residents to EDs or hospital [18], frequency and reasons for potentially avoidable hospitalisations [10], and efficacy of strategies to reduce potentially avoidable hospitalisation [30]	Developed by Saliba et al., 2000 [18]. Based on medical literature and semi-structured interviews with professionals and experts (e.g. nursing facility administrators, geriatric nurse practitioners, emergency room physicians, family medicine physicians, and geriatricians). Modified by Ouslander et al., 2010 [10]	Reviewer agreement: 84% agreement for EDV (kappa 0.68) and 89% and for hospitalisation [18]	Implicit criteria: list of questions for trained reviewers (experienced in LTC). Afterwards, they had to answer the question "was the hospitalisation avoidable?" with: "definitively not", "probably not", "probably yes" or "definitively yes"	Balance of issues between: residents' baseline health status (C), advance directives (W), potential benefits of acute transfer (R), and the care provided in the NH when the residents' status changed (R).
AEP [9]	To measure appropriateness of admission to hospital	Mostly expert based. Original version by Gertman and Restuccia, 1981 (USA), used to assess potentially unnecessary hospital days of care (not specific between NH and acute care) [46]. Refined by Baggoley et al., 1994 [47]	Original AEP (German and Restuccia, 1981) Overall agreement: 92% to 94% ($p<0.0001$); specific agreement rates for the reviewer pairs: 73% to 79%	List of items applied to residents' data by the authors. Hospitalisations deemed appropriate if any criteria fulfilled.	Items indicating appropriateness: 1) Severity of illness (e.g. sudden onset of unconsciousness, abnormally high or low pulse rate, persistent fever, incapacitating pain, electrocardiogram abnormality) (A); 2) Intensity of service (e.g. parenteral medications and/or fluid replacement, vital sign monitoring) (R)
Modified AEP [3,36]	To measure appropriateness of EDV	Defined by an expert multidisciplinary clinical review panel. Modified by Finn et al., 2006 [3]	No data provided	List of criteria applied by a research study nurse to the medical records of participants. Records of patients not meeting the criteria reviewed by a clinical panel (consisting of different professionals from both acute care and LTC) to determine whether the episodes could	Items indicating appropriateness, e.g. procedure unable to be performed in a nursing home (R), history of trauma with suspected fracture (D), difficult indwelling catheter insertion (R), PEG tube insertion (R), suspicion of cerebral event with decreasing consciousness (A), requirement for intravenous antibiotics (R), admission to hospital (R)

				have been managed within the nursing homes.	
Additional tool[b] [9]	To identify potentially avoidable hospitalisation	Developed in the context of the study as additional tool to AEP [9]. Methods not specified.	No data provided	Additional question to AEP. Applied by authors. Case conference involving senior clinicians	Availability of specialised care (e.g. parenteral fluid, parenteral drugs, high level of medical and nursing supervision) within the residential care setting (R)
AHC [22]	To identify potentially avoidable hospital stays, defined as hospital admissions for conditions suggesting inadequate ambulatory care	Developed in the context of the study [22]. Literature review and expert opinion considered. Based on research from Weissman et al., 1992 [48]	No data provided	List of items applied to residents' data by the authors	Items indicating avoidability, e.g. heart failure, urinary tract infection (D)
ACSC [4,11,23-29,33,40,41]	To identify preventable EDV or potentially avoidable hospitalisation of NH residents	Developed in the context of Billings et al., 1993 [49]. Modified Delphi method including a medical advisory panel of six internists and paediatricians, including national and local experts. Originally developed for community-dwelling older adults. Several modifications exist [50,24]	No explicit data found	List of items applied by the authors to residents' data	Items indicating avoidability, e.g. asthma, congestive heart failure, angina, grand mal seizure disorder, hypoglycaemia, hypertension. Modifications, e.g. Carter (2003) excluded pneumonia and congestive heart failure [24]; Kane (2005) added accidents and poisonings to the preventable emergency services [27] (D)
Modified ACSC [19]	To identify potentially avoidable hospitalisation in LTC facilities and to identify opportunities for improvement in preventive care, provider continuity and chronic disease management	Developed in the context of the study [19]. Expert panel assessed applicability of the pre-existing ACSC to an older institutionalised population in Canada and developed consensus-based revisions appropriate for the setting	No data provided	List of items applied to residents' data by the authors	Two items added to ACSC: septicaemia and falls/fractures; four conditions deleted: immunization-preventable conditions, nutritional deficiency, severe ear, nose and throat infections, tuberculosis (D)
Tool[b] **by Jensen et al., 2009** [15]	To assess appropriateness of EDV of LTC residents	Developed in the context of the study [15]. Defined by a physician team experienced in LTC (a health researcher and family physicians)	No data provided	Physician team (experienced in LTC) independently reviewed resident cases and made clinical judgment on appropriateness of referral. Consensus meeting.	Appropriateness defined as a balance of issues: timeliness, availability of diagnostic and treatment resources (e.g., intravenous, pharmaceuticals) (R), timely test results (R), physician availability and expertise (R), nursing availability and expertise (R), advanced directives (W),

					respect for patient and family wishes (W), availability of history and medical information, premorbid health status (C)
Tool[b] by Abel et al., 2009 [31]	To measure the appropriateness of staying at home (or LTC facility). Specific for the end-of-life phase.	Developed by authors, based on a previously developed national strategy: "End of Life Strategy" (Department of Health 2008), which considers the best existing evidence [51]	Level of agreement between consultants: kappa range 0.59, 0.70	One author (consultant for palliative medicine) reviewed the cases notes and applied the tool. Another author independently reviewed a random sample (10%). Appropriateness coded as "no" if it was clear that the resident needed hospital admission, "yes" if it was clear that they could have stayed at home and "maybe" if there was a degree of uncertainty.	Three aspects, balance of issues: 1) Assumption that the patient could have been looked after at home, if the End of Life Strategy (includes recognising patients as being in the last year of life, advance planning concerning place of death and priorities for care, care available at short notice 24 hours per day, nursing care at home available for final stages of life) was implemented and services available (R); 2) The patient should have a terminal illness as described in the Gold Standards Framework Prognostic Indication Guidance (C); 3) The cause of admission should not require immediate inpatient medical attention (A)
Tool[b] by Hammond et al., 2009 [32]	To measure the appropriateness of admissions and IH for patients with LTNC. To identify management alternatives for inappropriate admissions	Developed in the context of the study [32]. Methods not specified, probably based on expert opinion	Inter-rater reliability referring to agreement in judging the appropriateness of admission: kappa range 0.42- 0.44, Intra-rater reliability referring to the agreement between individuals' baseline decision and overall panel decision: 79%- 90% of cases	Panel of experts (a neurological rehabilitation physician, an acute care physician and a general practitioner) reviewed the cases notes and used the working definition to decide on appropriateness. Consensus meeting.	Working definition: "admissions deemed appropriate when the level of care required can only be provided at the hospital e.g. access to specialist equipment required, treatment administration such as intravenous antibiotics, or urgent specialist input". Data on medical history (C), admitting problem (A), circumstances surrounding the admission (A/R), level of functional ability (C), dependence and cognitive status (C) used. Balance of issues.

Tool[b] by Caffrey, 2010 [20]	To measure potentially preventable EDV by NH residents	Authors took medical conditions included at the INTERACT II tool and added conditions from other studies	No data provided	List of items applied by the authors to the data	Items indicating preventability, e.g. general fever symptoms (A), general chest pain symptoms (A), heart disease symptoms (A), symptoms of mental status changes (A), gastrointestinal bleeding symptoms (A), urinary tract infection symptoms (A), metabolic disturbance diseases (D), pneumonia (D), diseases of the skin (D)
Tool[b] by Codde et al., 2010 [34]	To measure potentially avoidable EDV by applying indicators and exclusion criteria	Developed in the context of the study [34]. Combination of expert opinion and prior work from Finn et al., 2006 (Modified AEP) [3]	Inter-rater reliability: 0.41, (95% CI 0.28-0.56)	List of items applied by the authors to the data	Items indicating avoidability, e.g. assessment and simple wound dressing or closure required (R), uncomplicated UTI (D), replacement of gastrostomy tube (R), advance care directive in place (W); Exclusion criteria for potentially avoidable conditions, e.g. triaged as category one on arrival in ED (A), trauma with suspected long bone fracture (D), laboratory or radiology necessary (R), signs of being systemically unwell (A), significant neurological changes (A), intravenous medication required (R), family requested ED (W)
Quality Improvement Review tool (INTERACT-II) [21,38]	To measure avoidability of EDV or IH of NH residents according to the NH staff; to assist NH staff in understanding the reasons for the transfer, identify opportunities to improve identification and management of changes in resident status, and reduce acute care transfers	Part of INTERACT II tool, based on analyses of data on hospitalisations rated by experts as potentially avoidable and on expert recommendations on the feasibility and importance of a variety of interventions	No data provided	Questionnaire to be filled in by NH staff. Once they have evaluated all the items they are required to answer to the question: "In retrospect, does your team think this transfer might have been prevented?" with "no" or "yes" and to provide opportunities for improvement.	Balance of issues between: resident information (C), hospital transfer information, including symptoms or change in condition that precipitated the transfer (A), actions taken by staff before the transfer (including presence of advanced care planning) (R, P, W); analysis of factors that may have influenced the transfer decision.
Tool[b] by Bermejo et al., 2011 [35]	To measure the appropriateness or suitability of EDV	Developed by the authors using data from prior studies	No data provided	The authors reviewed the cases notes and applied the tool.	Appropriate EDV if one criteria fulfilled: 1) Patient admitted to a hospital ward or stayed in observation for more than 24 hours (R); 2) Specialist visit or diagnostic

					test required, not available in the LTC facility (R); 3) Requirement of a treatment not available in the LTC facility (R)
Tool[b] by Gonzalo et al., 2011 [37]	To measure potentially burdensome transitions among NH residents with advanced cognitive and functional impairment	Developed in the context of the study on the basis of a previously conducted narrative analysis with families of patients affected and expert opinion [52]	No data provided	The authors reviewed the cases notes and applied the tool.	Condition defining burdensome transition: any transfer to acute care hospital of a resident with advanced cognitive impairment (C) in the last 3 days of life (D)
Tool[b] by Ong et al., 2011 [39]	To measure avoidable or inappropriate acute hospitalisation of NH and RH residents	Method of development not specified	No data provided	The authors reviewed the cases notes and applied the tool.	Condition defining avoidability: patients dying within 3 days after hospital admission considered inappropriately transferred; patients dying (D) after 7 days considered appropriately transferred

Note: ACSC: Ambulatory Care Sensitive Conditions; AEP: Appropriateness Evaluation Protocol; AHC: Avoidable Hospital Conditions; CI: Confidence Interval; EDV: Emergency Department Visits; NH: Nursing Home; LTC: Long Term Care; LTNC: Long Term Neurological Conditions; PEG: Percutaneous Endoscopic Gastrostomy; RH: Residential Home; SIR: Structured Implicit Review; UTI: Urinary Tract Infection.

[a]Aspects covered: A: acuteness/severity of the symptoms; C: resident's characteristics prior to admission to hospital; D: specific medical diagnoses; P: existence of a care plan; R: resource availability; W: residents' or families' wishes.

[b]Tool without a specific name.

ANNEX 2.1
Article 2

Appendix 1: complete EU(7)-PIM list

ATC-Code (according to WHO ATC-code [30] (2011))	**Potentially inappropriate drugs** Lists or criteria which include the specific drug (following either category A or B)[a]: 1: Laroche (2007) [3] 2: McLeod (1997) [26] 3: Finnish (2013) [33] 4: PRISCUS (2010) [22] 5: Beers (2012) [18] 6: STOPP/START (2014) [19]	**Results of the Delphi survey** (number of experts' answers at decisive Delphi round[b]; Likert-scale mean value [95% CI]; median)	**Main reason for PIM**	**Dose adjustment/special considerations of use**	**Alternative drugs and/or therapies**
A	**Alimentary tract and metabolism**				
A02	***Drugs for acid-related disorders***				
A02A	***Antacids***				
A02AA04	Magnesium hydroxide In lists: 3 (A)	20; 2.50 [2.01-2.99]; 2.00	Risk of hypermagnesemia, which is higher in moderate to severe renal failure	Maximum dose: 5 ml/8h; reduce dose for moderate to severe renal failure. *E*	Used as laxative: osmotically active laxatives (macrogol, lactulose) *E* Used as antacid, when indication is appropriate: PPI (<8 weeks, low dose) *E*
A02AB, A02AD	Aluminium-containing antacids In lists: 3 (A); 6 (B)	23; 2.09 [1.72-2.45]; 2.00	Renal excretion of aluminium decreases in older individuals. Risk of CNS toxicity	Adjust dose in severe renal failure. *M* Use for short periods (3-4 days). *E*	When indication is appropriate: PPI (<8 weeks, low dose) *E*

Appendix 1: complete EU(7)-PIM list

A02B	***Drugs for peptic ulcer and gastro-oesophageal reflux disease***				
A02BA01	Cimetidine In lists: 1 (A); 2, 5 (B)	23; 1.43 [1.18-1.69]; 1.00	CNS adverse effects including confusion	200 mg four times daily or 300 mg twice daily, due to a decrease in renal and hepatic function in adults aged ≥65 years old. *M*	When indication is appropriate: PPI (<8 weeks, low dose) *E*
A02BA02	Ranitidine In lists: 5 (B)	23; 2.26 [1.84-2.68]; 2.00	CNS adverse effects including confusion	CrCl <50 ml/min: 150 mg c/24h (oral); 50 mg c/18-24 h (iv) *E*	When indication is appropriate: PPI (<8 weeks, low dose) *E*
A02BA03	Famotidine In lists: 5 (B)	23; 2.17 [1.84-2.51]; 2.00	CNS adverse effects including confusion	CrCl <50 ml/min: administer 50% of dose or increase the dosing interval to every 36-48 h. *E*	When indication is appropriate: PPI (<8 weeks, low dose) *E*
A02BC	Proton pump inhibitors (PPI) (>8 weeks) e.g. omeprazole, pantoprazole In lists: 6 (B)	21; 2.00 [1.57-2.43]; 2.00	Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication		When indication is appropriate: PPI (<8 weeks, low dose) *E*
A03	***Drugs for functional gastrointestinal disorders***				
A03A	***Drugs for functional bowel disorder***				
A03AA04	Mebeverine[c] In lists: does not appear as PIM	20; 1.60 [1.16-2.04]; 1.00	Side effects such as dizziness, insomnia, anorexia	Caution if marked renal insufficiency. *M* Use only for short periods. *E*	Non-pharmacological measures, e.g. diet. *E*

Appendix 1: complete EU(7)-PIM list

A03AA05	Trimebutine In lists: 1, 2, 6 (B)	19; 1.47 [1.07-1.88]; 1.00	Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy		Non-pharmacological measures, e.g. diet. *E*
A03AA08	Dihexyverine In lists: 1 (A); 2, 6 (B)	14; 1.57 [1.03-2.11]; 1.00	Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy		Phloroglucinol. *L* Non-pharmacological measures, e.g. diet. *E, McL*
A03AB06	Otilonium bromide In lists: 2, 6 (B)	18; 1.50 [1.07-1.93]; 1.00	Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy		Non-pharmacological measures, e.g. diet. *E*
A03AB17	Tiemonium (iodide) In lists: 1 (A); 2, 6 (B)	15; 1.60 [1.10-2.10]; 1.00	Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy		Phloroglucinol. *L* Non-pharmacological measures, e.g. diet. *E, McL*
A03AX04	Pinaverium[c] In lists: does not appear as PIM	18; 1.50 [1.07-1.93]; 1.00	Side effects such as dizziness or esophageal ulceration		Non-pharmacological measures, e.g. diet. *E*
A03B	***Belladonna and derivates, plain***				
A03BA03	Hyoscyamine In lists: 5 (A); 1, 2, 5, 6 (B)	20; 1.05 [0.95-1.29]; 1.00	Highly anticholinergic, substantial toxic effects in older adults and uncertain effectiveness / no proven efficacy		Butylscopolamine 20mg/6-12h for a short time, especially in palliative care. *E* Phloroglucinol *E* Non-pharmacological measures, e.g. diet. *E, McL*
A03BA04	Belladonna alkaloids In lists: 1, 5 (A); 2, 5, 6 (B)	22; 1.14 [0.98-1.29]; 1.00	Highly anticholinergic, substantial toxic effects in older adults and uncertain effectiveness / no proven efficacy		Butylscopolamine *E* Phloroglucinol *E, L* Non-pharmacological measures, e.g. diet. *E, McL*

Appendix 1: complete EU(7)-PIM list

A03C	***Antispasmodics in combination with psycholeptics***				
A03CA02	Clidinium-Chlordiazepoxide In lists: 1, 3, 5 (A); 2, 6 (B)	19; 1.21 [1.01-1.41]; 1.00	Long half-life in older adults (often several days), producing prolonged sedation and increasing the risk of falls and fractures	Do not exceed chlordiazepoxide 10 mg, clidinium 5 mg/d; increase gradually and limit to the smallest effective dose. *M*	Phloroglucinol *E, L* Non-pharmacological measures, e.g. diet. *E, McL*
A03D	***Antispasmodics in combination with analgesics***				
A03DA02	Pitofenone In lists: 3 (A); 1, 2, 6 (B)	18; 2.00 [1.55-2.45]; 2.00	Anticholinergic side effects		Non-pharmacological measures, e.g. diet. *E*
A03F	***Propulsives***				
A03FA01	Metoclopramide In lists: 3, 5 (A); 6 (B)	23; 2.43 [1.97-2.90]; 2.00	Antidopaminergic and anticholinergic effects; may worsen peripheral arterial blood flow and precipitate intermittent claudication	Short-term use and dose reduction; CrCl <40 ml/min: 50% of normal dose; maximum dose: 20 mg/d; may be used in palliative care. *E*	Domperidone (<30 mg/d) if no contraindications. *E*
A03FA03	Domperidone (>30 mg/d)[c] In lists: does not appear as PIM	18; 2.11 [1.70-2.53]; 2.00	Increased risk of serious ventricular arrhythmia or sudden cardiac death in older adults	Treatment should be initiated at the lowest possible dose and titrated cautiously. *E*	Domperidone (<30 mg/d) if no contraindications. *E*
A03FA05	Alizapride In lists: 1 (A)	19; 1.53 [1.23-1.82]; 1.00	No proven efficacy; muscarinic-blocking agents; side effects such as confusion and sedation	Adjustment may be recommended in cases of renal failure. *M*	

Appendix 1: complete EU(7)-PIM list

A04	***Antiemetics and antinauseants***				
A04A	***Antiemetics and antinauseants***				
A04AB02[g]	Dimenhydrinate In lists: 1, 4 (A); 5, 6 (B)	19; 1.68 [1.29-2.08]; 1.00	Anticholinergic side effects	Caution for patients with enlarged prostate. *E*	Domperidone (<30 mg/d) if no contraindications. *E*
A04AD01	Scopolamine In lists: 1, 3 (A); 5 (B)	22; 1.68 [1.36-2.00]; 2.00	Anticholinergic side effects; no proven efficacy	5 mg/4h; may be appropriate and useful in palliative care. *E*	Domperidone (<30 mg/d) if no contraindications. *E*
A04AD05	Metopimazine In lists: 1(A)	19; 1.68 [1.26-2.11]; 1.00	No proven efficacy; muscarinic blocking agent; side effects such as confusion and sedation		Domperidone (<30 mg/d) if no contraindications. *E*
A06	***Laxatives***				
A06A	***Laxatives***				
A06AA01	Viscous paraffin (=Liquid paraffin) In lists: 4, 5 (A)	21; 2.43 [1.88-2.98]; 2.00	Pulmonary side effects if aspirated		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AA02	Docusate sodium (oral) In lists: 1 (A)	19; 1.95 [1.57-2.32]; 2.00	Stool softener laxative. Adverse events include cramping, nausea, diarrhoea. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AB02	Bisacodyl (>3 days) In lists: 1, 3 (A); 5 (B)	21; 1.90 [1.59-2.22]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*

Appendix 1: complete EU(7)-PIM list

A06AB05	Castor oil (=Ricinus communis, =Neoloid) In lists: 1 (A), 5 (B)	21; 2.24 [1.70-2.77]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AB06	Senna glycosides In lists: 3 (A)	23; 2.35 [1.79-2.91]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AB07	Cascara sagrada In lists: 1 (A); 5 (B)	19; 2.32 [1.71-2.92]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AB08	Sodium picosulfate In lists: 1, 3 (A)	22; 2.32 [1.82-2.82]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel dysfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AB13[g]	Aloe In lists: 1 (A)	16; 2.13 [1.65-2.60]; 2.00	Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction		Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*
A06AX05[h]	Prucalopride In lists: does not appear as PIM	11; 2.09 [1.46-2.73]; 2.00	Adverse effects can include abdominal pain, diarrhoea, headache, dizziness	Reduce dose for older adults and in cases of severe renal failure (GFR<30 ml/min); starting dose for persons over 65 years old: 1 mg/d; maximum dose: 2 mg/d (1 mg/d if severe renal failure) *E, M*	Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P*

Appendix 1: complete EU(7)-PIM list

A07	***Antidiarrhoeal, intestinal anti-inflammatory / anti-infective agents***				
A07D	***Antipropulsives***				
A07DA01 (Diphenoxylate) A03BA01 (Atropine)	Diphenoxylate-Atropine In lists: 1 (A); 2, 5, 6 (B)	22; 1.73 [1.29-2.16]; 1.00	No proven efficacy; muscarinic blocking agent		Non-pharmacological measures, e.g. diet. *E* Phloroglucinol *L*
A07DA03	Loperamide (>2 days) In lists: does not appear as PIM	21; 1.81 [1.47-2.15]; 2.00	Risk of somnolence, constipation, nausea, abdominal pain and bloating. Rare adverse events include dizziness. May precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis	Start with a dose of 4 mg followed by 2 mg in each deposition until normalisation of bowel; do not exceed 16 mg/d; use no longer than 2 days; may be useful in palliative care for persisting non-infectious diarrhoea. *E*	Non-pharmacological measures, e.g. diet; phloroglucinol. *E*
A07X	***Other antidiarrheals***				
A07XA04	Racecadotril In lists: does not appear as PIM	16; 2.31 [1.68-2.95]; 2.00	No proven efficacy; selective inhibitor of enkephalinase enzyme responsible for the degradation of the enkephalins, endogenous opioids which act by decreasing the intestinal lumen secretion of water and electrolytes	Maximum dose 100 mg/8h; maximum duration 7 days. *E*	Non-pharmacological measures, e.g. diet. *E*
A10	***Drug used in Diabetes***				
A10A	***Insulins and analogues***				

Appendix 1: complete EU(7)-PIM list

no ATC, treatment concept PIM	Insulin, sliding scale In lists: 5 (A)	13; 2.00 [1.45-2.55]; 2.00	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels	Lower doses to avoid hypoglycemia. *E*	Basal insulin. *E*
A10B	***Blood glucose lowering drugs, excl. insulins***				
A10BB01	Glibenclamide In lists: 1, 5 (A); 6 (B)	23; 2.00 [1.55-2.45]; 2.00	Risk of protracted hypoglycemia	Use conservative initial dose (1.25 mg/d for nonmicronized glibenclamide and 0.75 mg/d for micronized glibenclamide) and maintenance dose; not recommended if CrCl <50 ml/min. *M*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BB02	Chlorpropamide In lists: 5 (A); 1, 6 (B)	20; 1.40 [1.12-1.68]; 1.00	Risk of protracted hypoglycemia	Use initial doses of 100 to 125 mg/d. *M* In cases of mild renal failure (GFR >50 ml/min), decrease dose by 50%. *M, E* In cases of moderate to severe renal failure (GFR <50 ml/min), avoid. *M*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BB06	Carbutamide In lists: 1 (A), 6 (B)	16; 2.06 [1.61-2.52]; 2.00	Risk of protracted hypoglycemia	Adjust dose to renal function. *E*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BB07	Glipizide In lists: 1 (A)	22; 2.45 [2.01-2.90]; 2.00	Risk of protracted hypoglycemia	Use conservative initial and maintenance doses. *M* Starting dose: 2.5 mg/d *E, M* Increase by 2.5-5 mg/d at 1 to 2 week intervals. *E*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*

Appendix 1: complete EU(7)-PIM list

A10BB12	Glimepiride In lists: 3 (A); 6 (B)	21; 2.05 [1.71-2.38]; 2.00	Risk of protracted hypoglycemia	Adjust according to renal function. *E* For patients with renal failure and for older adults, use initial dose of 1 mg/d followed by a conservative titration scheme. Titrate dose in increments of 1 to 2 mg no more than every 1 to 2 weeks based on individual glycemic response. *M*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BF01	Acarbose In lists: does not appear as PIM	23; 2.22 [1.68-2.75]; 2.00	No proven efficacy		Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BG03	Pioglitazone In lists: 5, 6 (B)	21; 1.71 [1.42-2.01]; 2.00	Age-related risks include bladder cancer, fractures and heart failure. Use for more than one year has been associated with an increased risk of bladder cancer. May increase the incidence of fractures of the upper arms, hands and feet in female diabetics (compared to other oral antidiabetic agents). Can cause fluid retention in older adults, which may exacerbate or precipitate heart failure		Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
A10BH01	Sitagliptine In lists: does not appear as PIM	17; 1.94 [1.44-2.44]; 2.00	Limited safety data is available for adults aged ≥75 years old. Subjects aged 65 to 80 years had higher plasma concentrations than younger subjects. Risk of hypoglycemia, dizziness, headache and peripheral oedema	Reduce dose to 50 mg/d in cases of renal failure (CrCl 30-50 ml/min); reduce dose to 25 mg/d in cases of severe renal insufficiency (CrCl <30 ml/min). *E, M*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*

Appendix 1: complete EU(7)-PIM list

A10BH02	Vildagliptine In lists: does not appear as PIM	15; 1.87 [1.21-2.52]; 2.00	Limited safety data available in older subjects. In healthy older adults (≥70 years) the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). Adverse events (general population) include risk of hypoglycemia, dizziness, headache and peripheral oedema	Reduce dose to 50 mg/d in cases of moderate or severe renal failure. *E, M*	Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E*
B	**Blood and blood forming organs**				
B01	***Antithrombotic agents***				
B01A	***Antithrombotic agents***				
B01AA07	Acenocoumarol In lists: 6 (B)	17; 2.35 [1.84-2.87]; 2.00	Risk of bleeding, especially in people with difficult control of INR value		
B01AC05	Ticlopidine In lists: 1, 4, 5, 6 (A); 6 (B)	20; 1.70 [1.36-2.04]; 2.00	Risk of altered blood counts	Dose reductions may be required in cases of renal failure. *M*	Clopidogrel; aspirin (<325mg)[d]. *E, L*
B01AC07	Dipyridamole In lists: 1, 2, 3, 5 (A); 6 (B)	22; 2.14 [1.70-2.58]; 2.00	Less efficient than aspirin; risk of vasodilatation and orthostatic hypotension Proven beneficial only for patients with artificial heart valves		Clopidogrel; aspirin (<325mg)[d]. *E, L*
B01AC22	Prasugrel In lists: 4 (A); 6 (B)	18; 2.00 [1.41-2.59]; 2.00	Unfavourable risk/benefit profile, especially for adults aged 75 and older		Clopidogrel; aspirin (<325mg)[d]. *E, L*

Appendix 1: complete EU(7)-PIM list

B01AE07	Dabigatran[c] In lists: 6 (B)	22; 2.45 [2.01-2.90]; 2.00	Limited information on use for older adults and on the risk of bleeding events in this population; no reversal agent is available in case of overdose	Reduce dose for adults aged >75 years old (150 mg/d) and CrCl 30-50 (110 mg twice per day); contraindicated if CrCl <30. *E*	
B01AF01[g, h]	Rivaroxaban[c] In lists: 6 (B)	19; 2.42 [2.02-2.82]; 2.00	Limited information on use for older adults; risk of bleeding events; no reversal agent available in case of overdose; risk of bleeding may be higher in cases of severe renal failure	Reduce dose for adults aged >65 years and avoid use for persons with CrCl <30 ml/min. *E, M*	
B01AF02[i]	Apixaban[c] In lists: 6 (B)	16; 2.25 [1.75-2.75]; 2.00	Limited information on use for older adults; risk of bleeding events; no reversal agent available in case of overdose	Reduce dose to 2.5 mg orally twice daily for patients with any 2 of the following *(M)* (1 of the following *(E)*): ≥80 years old, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Do not use if CrCl less than 15 mL/min or if undergoing dialysis; reduce dose to 2.5 mg twice per day in cases of severe renal failure (CrCl 15 mL/min to 29 mL/min); no dosage adjustment necessary in cases of mild (CrCl 51 to 80 mL/min) or moderate (CrCl 30 to 50 mL/min) renal failure. *M*	
B03	***Antianemic preparations***				
B03A	***Iron preparations***				
B03AA	Iron supplements / Ferrous sulfate (>325 mg/d) In lists: 6 (B)	23; 2.22 [1.68-2.75]; 2.00	Doses >325 mg/d do not considerably increase the amount absorbed but greatly increase the incidence of constipation		Intravenous iron *E*

Appendix 1: complete EU(7)-PIM list

C	**Cardiovascular system**				
C01	***Cardiac therapy***				
C01A	***Cardiac glycosides***				
C01AA02	Acetyldigoxin In lists: 4 (A)	14; 2.14 [1.47-2.82]; 2.00	Elevated glycoside sensitivity in older adults (women >men); risk of intoxication	Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M*	For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E*
C01AA04	Digitoxin In lists: does not appear as PIM	16; 2.19 [1.57-2.87]; 2.00	Elevated glycoside sensitivity in older adults (women >men); risk of intoxication	Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M*	For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E*
C01AA05	Digoxin In lists: 4, 5 (A); 1, 6 (B)	23; 2.35 [1.92-2.77]; 2.00	Elevated glycoside sensitivity in older adults (women >men); risk of intoxication	Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M* For older adults, use dose 0.0625-0.125mcg/d; in cases of renal failure (CrCl 10-50 ml/min), administer 25-75% of dose or every 36 hours; in cases of renal failure (CrCl <10 ml/min), administer 10-25% of dose or every 48 hours. *E*	For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E*

Appendix 1: complete EU(7)-PIM list

C01AA08	Metildigoxin In lists: 4 (A)	15; 2.20 [1.57-2.83]; 2.00	Elevated glycoside sensitivity (women >men); risk of intoxication	Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M* In old adults with heart failure and normal renal function, oral maintenance dose requirement of digoxin is 1.4 times higher than metildigoxin. *M*	For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E*
C01B	***Antiarrhythmics, Class I and III***				
C01BA01	Quinidine In lists: 3, 4, 5 (A)	23; 1.48 [1.22-1.73]; 1.00	CNS side effects; increased mortality. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*		Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*
C01BA02	Procainamide In lists: 5 (A)	21; 1.76 [1.41-2.11]; 2.00	High risk of drug interactions. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*	Adjust dose to the individual patient response. Lower doses or longer intervals between doses may be required. *M* CrCl 10-50 ml/min administer every 6-12 h; CrCl <10 ml/min administer every 8-24 h. *E*	Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*
C01BA03	Disopyramide In lists: 1, 2, 5 (A)	23; 1.43 [1.18-1.69]; 1.00	Potent negative inotrope; anticholinergic side effects; may induce heart failure; may cause sudden cardiac death. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*	Start dose at the lower end of the dosing range and titrate upward to maximum dose as required for antiarrhythmic effects and based on CrCl. *M*	Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*

Appendix 1: complete EU(7)-PIM list

C01BA51	Quinidine in combination with verapamil In lists: 4 (A)	22; 1.36 [1.15-1.58]; 1.00	CNS side effects and increased mortality. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*		Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*
C01BC03	Propafenone In lists: 3, 5 (A)	19; 1.89 [1.44-2.35]; 1.00	High risk of drug interactions. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*	Start dose at the lower end of the dosing range and increase gradually. *M* A single oral 600 mg loading dose may be effective for converting recent-onset atrial fibrillation to sinus rhythm in persons older than 60 years without signs or symptoms of heart failure. *M*	Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*
C01BC04	Flecainide In lists: 3, 4, 5 (A)	22; 2.14 [1.66-2.62]; 2.00	Higher rate of adverse effects, especially in older adults. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*	Adjust dose in cases of renal failure. *M*	Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*
C01BD01	Amiodarone In lists: 3, 5 (A); 6 (B)	23; 2.30 [1.81-2.80]; 2.00	Associated with QT interval problems and risk of provoking torsades de pointes. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*	Start dose at the low end of the dosing range. *M* Use lower maintenance dose, e.g. 200 mg/48h. *E*	

Appendix 1: complete EU(7)-PIM list

C01BD07	Dronedarone In lists: 3, 5 (A)	21; 1.57 [1.23-1.91]; 2.00	Frequent drug interactions; prolonged QT interval; not recommended in permanent atrial fibrillation; increased mortality due to cardiovascular causes. Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B*		
C01E	***Other cardiac preparations***				
C01EB15	Trimetazidine In lists: does not appear as PIM	13; 1.62 [1.22-2.01]; 2.00	Can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia); caution in cases of moderate renal failure and with older adults (>75 years old); efficacy for the treatment of tinnitus or dizziness not proven	20 mg twice per day for patients with moderate renal insufficiency. *E*	
C01EB17	Ivabradine In lists: does not appear as PIM	16; 2.13 [1.61-2.64]; 2.00	Common adverse events (1-10% of patients) may include first-degree AV block, ventricular extrasystoles, dizziness and blurred vision	Lower initial dose for older adults; starting dose 2 x 2.5 mg/d in >75 years. *M, E* Use with caution for patients with CrCl less than 15 mL/min. *M*	
C02	***Antihypertensives***				
C02A	***Antiadrenergic agents, centrally acting***				

Appendix 1: complete EU(7)-PIM list

C02AA02	Reserpine In lists: 1, 2, 4, 5 (A); 6 (B)	20; 1.25 [1.04-1.46]; 1.00	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Low initial dose, half of usual dose, taper in and out. *P* Lower doses (0.05 mg/d) to normal doses (0.25 mg/d) are recommended. *M* Avoid if CrCl <10 ml/min. *M, E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other mediation groups depending on comorbidity (exclude PIM). *E*
C02AB01	Methyldopa In lists: 1, 4, 5 (A); 6 (B)	21; 1.38 [1.11-1.65]; 1.00	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Low initial dose, half of usual dose, taper in and out. *P* Suggested initial daily dose is 250 mg of methyldopa with a maximal daily dose of 1000 mg. *M* CrCl >50 ml/min administer every 8 h; CrCl 10-50 ml/min administer every 8-12 h; CrCl <10 ml/min administer every 12-24 h. *E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other mediation groups depending on comorbidity (exclude PIM). *E*
C02AC01	Clonidine In lists: 1, 3, 4, 5 (A); 6 (B)	22; 1.36 [1.04-1.69]; 1.00	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Lower doses for initial treatment of hypertension; half of usual dose, taper in and out. *M, P*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*
C02AC02	Guanfacine In lists: 1, 5 (A); 6 (B)	19; 1.42 [1.13-1.71]; 1.00	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Cautious dosing when using guanfacine hydrochloride immediate-release; start dosing at the low end of the range. *M*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*
C02AC05	Moxonidine In lists: 1, 3 (A); 6 (B)	22; 1.77 [1.34-2.20]; 1.50	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Caution in cases of moderate renal insufficiency (CrCl 30-60 ml/min): maximum doses 0.4 mg/d; avoid if CrCl <30ml/min. *M, E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*

Appendix 1: complete EU(7)-PIM list

C02AC06	Rilmenidine In lists: 1 (A); 6 (B)	17; 1.53 [1.16-1.90]; 1.00	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)	Reduce dose in cases of renal failure (CrCl <15 ml/min), *M, E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*
C02C	***Antiadrenergic agents, peripherally acting***				
C02CA01	Prazosin In lists: 1, 3, 4, 5 (A); 6 (B)	20; 1.55 [1.27-1.83]; 1.50	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Lower dose for initial treatment of hypertension. *M* Start with half of usual dose, taper in and out. *P* First dose given at bedtime: initial 1-2 mg/d. *E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*
C02CA04	Doxazosin In lists: 4, 5 (A); 6 (B)	22; 1.95 [1.61-2.30]; 2.00	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Start with half of usual dose, taper in and out. *P* Start with 0.5mg/d (immediate release) or 4-8 mg/d (extended release). *E*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*
C02CA06	Urapidil In lists: 1 (A); 6 (B)	19; 1.68 [1.29-2.08]; 1.00	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Reduce dose for older adults and patients with renal insufficiency. *M*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E*

Appendix 1: complete EU(7)-PIM list

C02CC02	Guanethidine In lists: does not appear as PIM	19; 1.58 [1.25-1.91]; 1.00	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Start low–go slow; Increase dose interval in cases of renal failure. *M*	Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIMs). *E*
C02D	***Agents acting on Arteriolar Smooth muscle***				
C02DB02	Hydralazine In lists: 6 (B)	21; 2.33 [1.73-2.93]; 2.00	Risk of orthostatic hypotension	Start low–go slow; Increase dose interval in cases of renal failure. *M, E*	
C03	***Diuretics***				
C03D	***Potassium-sparing agent***				
C03DA01	Spironolactone (>25 mg/d)[c] In lists: 5 (A); 6 (B)	20; 2.50 [1.99-3.01]; 2.00	Higher risk of hyperkalaemia and hyponatremia in older adults, especially if doses >25 mg/d, requiring periodic controls	Reduce dose in cases of moderate renal insufficiency. *E, M* GFR ≥50 mL/min/1.73 m: initial dose 12.5-25 mg/d, increase up to 25 mg 1-2x/d; GFR 30-49 mL/min/1.73 m: initial dose 12.5 mg/d, increase up to 12.5-25 mg/d; reduce dose if potassium levels increase or renal function worsens. GFR <10 mL/min: avoid. *M*	Consider alternatives depending on the indication; exclude PIMs.
C04	***Peripheral vasodilators***				

Appendix 1: complete EU(7)-PIM list

C04A	***Peripheral vasodilators***				
C04AD03	Pentoxifylline In lists: 1, 2, 3, 4 (A); 6 (B)	21; 1.95[1.42-2.48]; 2.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators	Reduce dose to 400 mg twice daily in cases of moderate renal failure and to 400 mg once daily in cases of severe renal failure; close monitoring for toxicities. Avoid use if CrCl <30 ml/min. *M*	
C04AE02	Nicergoline In lists: 1, 4 (A); 6 (B)	19; 1.63 [1.12-2.15]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators	Reduce daily dose in cases of renal failure (serum creatinine >2 mg/dl). *M*	
C04AE04	Dihydroergocristine In lists: 1 (A), 6 (B)	19; 1.42 [1.05-1.79]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AE54	Raubasine-Dihydroergocristine In lists: 1 (A); 6 (B)	18; 1.33 [0.99-1.67]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AX01	Cyclandelate (=Cyclospasmol) In lists: 6 (B)	18; 1.33 [1.04-1.63]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AX07	Vincamine In lists: 1 (A); 6 (B)	17; 1.53 [1.12-1.94]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AX10	Moxisylyte In lists: 1 (A); 6 (B)	17; 1.53 [1.12-1.94]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		

Appendix 1: complete EU(7)-PIM list

C04AX17	Vinburnine In lists: 1 (A); 6 (B)	17; 1.53 [1.12-1.94]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AX20	Buflomedil In lists: 6 (B)	16; 1.69 [1.08-2.29]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C04AX21	Naftidrofuryl In lists: 1, 4 (A); 6 (B)	17; 1.59 [1.11-2.07]; 1.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		
C05	***Vasoprotectives***				
C05C	***Capillary stabilizing agents***				
C05CA05	Hidrosmin In lists: 6 (B)	17; 1.82 [1.41-2.24]; 2.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		Compression stocking . *E*
C05CA07[g]	Escin (=Aescin) In lists: 6 (B)	18; 1.83 [1.37-2.29]; 2.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		Compression stocking . *E*
C05CA51	Vincamine-Rutoside In lists: 1 (A); 6 (B)	16; 1.75 [1.34-2.16]; 2.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		Compression stocking . *E*
C05CA54	Troxerutin-Vincamine In lists: 1 (A); 6 (B)	16; 1.81 [1.33-2.30]; 2.00	No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators		Compression stocking . *E*

Appendix 1: complete EU(7)-PIM list

C07	***Beta-blocking agents***				
C07A	***Beta-blocking agents***				
C07AA02	Oxprenolol In lists: 2, 6 (B)	16; 2.25 [1.79-2.71]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events		Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E*
C07AA03	Pindolol In lists: 3 (A); 2, 6 (B)	20; 2.40 [1.91-2.89]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events		Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E*
C07AA05	Propranolol In lists: 3 (A); 6 (B)	21; 2.33 [1.94-2.72]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events	3 doses of 20 mg daily *E* Start low–go slow for older adults and patients with renal failure. *M*	Depending on the indication: cardio-selective beta-blockers, ACE inhibitors, diuretics. *E*
C07AA07	Sotalol In lists: 4, 5 (A); 2, 6 (B)	21; 1.86 [1.64-2.07]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events	Start at half or one third of the typical dose and increase slowly. *P* Reduce dose and dosing interval in cases of renal failure. *M*	Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E*
C07AA12	Nadolol In lists: 2, 6 (B)	16; 2.44 [1.89-2.99]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression	If CrCl 31-50 ml/min: administer every 24-36 h; if CrCl 10-30 ml/min: administer every 24-48h; if CrCl <10 ml/min: administer every 40-60 h. *E, M*	Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E*
C07AG01	Labetalol In lists: 2, 6 (B)	20; 2.30 [1.87-2.73]; 2.00	Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression	Start dose 100 mg once or twice per day. E Maintenance dose 100-200 mg once or twice per day. *M*	Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E*
C08	***Calcium channel blockers***				

Appendix 1: complete EU(7)-PIM list

C08C	***Selective calcium channel blockers with mainly vascular effects***				
C08CA04	Nicardipine In lists: 1 (A); 2, 6 (B)	19; 2.00 [1.38-2.62]; 1.00	Risk of orthostatic hypotension, myocardial infarction or stroke	Lower initial dose. *M*	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L*
C08CA05	Nifedipine (non-sustained-release) In lists: 1, 4, 5 (A); 2, 6 (B)	23; 1.74 [1.28-2.19]; 1.00	Increased risk of hypotension; myocardial infarction; increased mortality	Lower initial dose, half of usual dose, taper in and out. *P*	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L*
C08CA05	Nifedipine (sustained-release) In lists: 1 (A); 2, 6 (B)	21; 1.95 [1.51-2.40]; 2.00	Increased risk of hypotension; myocardial infarction; increased mortality	Lower initial dose, half of usual dose, taper in and out. *P* Initial dose: 30 mg/d; maitenance dose: 30-60 mg/d. *E*	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L*
C08D	***Selective calcium channel blockers with direct cardiac effects***				
C08DA01	Verapamil In lists: 3, 5 (A); 2, 6 (B)	23; 2.39 [1.98-2.80]; 2.00	May worsen constipation; risk of bradycardia	Immediate release tablets: initial dose 40 mg three times daily; sustained release tablets: initial dose 120 mg daily; oral controlled onset extended release: initial dose 100 mg/d. *M*	Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E*
C08DB01	Diltiazem In lists: 3, 5 (A); 2, 6	23; 2.57 [2.18-2.95]; 2.00	May worsen constipation; risk of bradycardia	Reduce dose or increase dosing interval. *M* 60 mg three times daily. *E*	

Appendix 1: complete EU(7)-PIM list

	(B)				
C10	***Lipid modifiying agents***				
C10A	***Lipid modifiying agents, plain***				
C10AD02	Niacin (=Nicotinic acid) In lists: 2 (A)	22; 1.77 [1.28-2.26]; 1.00	Moderate risk of side effects; ineffective for the treatment of dementia		
G	**Genito-urinary system and sex hormones**				
G03	***Sex hormones and modulator of the genital system***				
G03C	***Oestrogens***				
G03C	Oestrogen (oral) In lists: 5 (A); 6 (B)	21; 1.52 [1.21-1.83]; 1.00	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women		Specific treatment for osteoporosis. *E* Local administration (i.e. vaginal application) considered safe and efficient. *E, B*
G04	***Urologicals***				
G04B	***Other urologicals, incl. antispasmodics***				
G04BD02	Flavoxat	16; 1.75 [1.22-2.28]; 1.00	May decrease urinary flow, leading to urinary retention		Non-pharmacological treatment (pelvic floor exercises, physical

Appendix 1: complete EU(7)-PIM list

	In lists: 5, 6 (B)				and behavioural therapy). *E*
G04BD04	Oxybutynine (non-sustained-release) In lists: 1, 3, 4, 5 (A); 5, 6 (B)	23; 1.43 [1.78-1.69]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)	Start immediate-release oxybutynin chloride in frail older adults with 2.5 mg orally 2 or 3 times daily. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD04	Oxybutynine (sustained-release) In lists: 1, 3, 4, 5 (A); 5, 6 (B)	23; 1.57 [1.16-1.97]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)		Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD07	Tolterodine (non-sustained-release) In lists: 1, 3, 4, 5 (A); 5, 6 (B)	22; 1.59 [1.27-1.92]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)	1 mg orally twice daily in cases of significantly impaired renal function. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD07	Tolterodine (sustained-release) In lists: 1, 3, 5 (A); 5, 6 (B)	22; 1.77 [1.32-2.23]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)	Use 2 mg orally once daily in cases of severe renal failure (CrCl 10-30 mL/min); avoid use if CrCl <10 mL/min. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD08	Solifenacin In lists: 1, 3, 4, 5 (A); 5, 6 (B)	21; 1.81 [1.34-2.28]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT)	Dose reduction may be needed. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*

Appendix 1: complete EU(7)-PIM list

G04BD09	Trospium In lists: 5 (A); 5, 6 (B)	18; 1.94 [1.42-2.47]; 2.00	Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects)	CrCl <30 mL/min: 20 mg/d (immediate release); avoid the use of extended release trospium. *M* In adults aged ≥75 years old, the dose frequency of trospium immediate release may be reduced to 20 mg/d. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD10	Darifenacin In lists: 3, 5 (A); 5, 6 (B)	14; 1.79 [2.27-2.30]; 2.00	Higher incidence of antimuscarinic adverse events (e.g., dry mouth, constipation, dyspepsia, increased residual urine, dizziness) and urinary tract infection in persons aged 75 years and older compared with younger patients		Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04BD11	Fesoterodin In lists: 3, 5 (A); 5, 6 (B)	14; 1.71 [1.24-2.19]; 1.50	Higher incidence of antimuscarinic adverse events (e.g., dry mouth, constipation, dyspepsia, increased residual urine, dizziness) and urinary tract infection in persons aged 75 years and older compared with younger patients	CrCl <30 mL/min: maximum dose 4 mg/d. *M*	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E*
G04C	***Drug used in benign prostatic hypertrophy***				
G04CA03	Terazosin In lists: 4, 5 (A); 6 (B)	21; 1.52 [1.25-1.80]; 1.00	Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease	Low initial dose, half of usual dose, taper in and out. *P* Initial dose: 1 mg at bedtime; up to 10 mg/d may be required. *E*	If used as antihypertensive, other antihypertensive agents: ACE inhibitors, beta-blockers, calcium antagonists, diuretics (exclude PIM). *E*

Appendix 1: complete EU(7)-PIM list

J	**Antiinfectives for systematic use**				
J01	***Antibacterial for systemic use***				
J01M	***Quinolone antibacterials***				
J01MA01	Ofloxacin In lists: does not appear as PIM	22; 2.23 [1.70-2.76]; 2.00	Its half-life may be prolonged with elevated serum concentrations in older adults; increased risk of torsade de pointes and tendinitis or tendon rupture	Reduce dose and increase dosing interval if renal failure. *M*	Other antibiotics in accordance with sensitivity and resistance testing. *E*
J01X	***Other antibacterials***				
J01XE01	Nitrofurantoin (>1 week) In lists: 1, 4, 5 (A)	21; 2.00 [1.59-2.41]; 2.00	Unfavourable risk/benefit ratio, particularly with long-term use (pulmonary side effects, liver damage, etc.); contraindicated if severe renal failure due to decreased excretion and increased risk of toxicity	50-100 mg/8h; use shorter than one week. *E*	Other antibiotics in accordance with sensitivity and resistance testing. *E*
M	**Musculo-skeletal system**				
M01	***Anti-inflammatory and anti-rheumatic products***				
M01A	***Anti-inflammatory and anti-rheumatic products, non-steroid (NSAID)***				

Appendix 1: complete EU(7)-PIM list

M01AA01	Phenylbutazone In lists: 1, 2, 4 (A); 5, 6 (B)	19; 1.21 [1.01-1.41]; 1.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; risk of blood dyscrasia	Use for the shortest period possible. *P* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AB01	Indometacin In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B)	23; 1.39 [1.08-1.70]; 1.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; risk of CNS disturbances	Reduce dose reduction by 25%. *M* Use for the shortest period possible. *P* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AB05	Diclofenac In lists: 5 (A); 1, 2, 5, 6 (B)	23; 2.00 [1.59-2.41]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	50 mg/d; start using low dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

M01AB11	Acemetacin In lists: 4 (A); 1, 2, 4, 5, 6 (B)	16; 1.50 [1.22-1.78]; 1.50	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	Use for the shortest period possible. *P* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AB15	Ketorolac In lists: 5 (A); 1, 2, 5, 6 (B)	21; 1.76 [1.44-2.08]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	Contraindicated in cases of advanced renal failure; oral dose not indicated as initial dose; recommended continuation dose after intravenous or intramuscular dosing is 10 mg every 4-6 hours, maximum 40 mg/d and for 5 days. *M* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AB16	Aceclofenac In lists: 1, 2, 5, 6 (B)	20; 1.85 [1.50-2.20]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Start using low dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

M01AC01	Piroxicam In lists: 4, 5 (A); 1, 2, 5, 6 (B)	22; 1.55 [1.28-1.81]; 1.50	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	Doses >20 mg are associated with increased GI toxicity and ulceration, especially in older adults. *M* Use for the shortest period possible. *P* 10 mg/d; start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AC05	Lornoxicam In lists: 1, 2, 5, 6 (B)	19; 1.74 [1.35-2.13]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Use for the shortest period possible. *P* Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AC06	Meloxicam In lists: 4, 5 (A); 1, 2, 5, 6 (B)	23; 1.65 [1.34-1.96]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	11 mg/d; start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

M01AE01	Ibuprofen (>3 x 400 mg/d or for a period longer than one week)[c] In lists: 5 (A); 5, 6 (B)	21; 2.43 [1.98-2.87]; 2.00	Risk of GI bleeding and increased risk of cardiovascular complications at higher doses (>1200 mg/d), especially in cases of previous cardiovascular disease	The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AE02	Naproxen (>2 x 250 mg/d or for a period longer than one week)[c] In lists: 5 (A); 5, 6 (B)	23; 2.04 [1.62-2.47]; 2.00	Risk of GI bleeding	Reduce dose; start low–go slow in older adults; avoid if CrCl <30 mL/min. *M* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AE03	Ketoprofen In lists: 4, 5 (A); 1, 2, 5, 6 (B)	23; 1.87 [1.45-2.29]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal	Reduce dose if CrCl <20 mL/min; start with lower dose and use reduced maintenance dose in older adults. *M* Use for the shortest period possible. *P* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

M01AE09	Flurbiprofen In lists: 1, 2, 5, 6 (B)	19; 1.84 [1.41-2.28]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AE17	Dexketoprofen In lists: 1, 2, 5, 6 (B)	23; 1.91 [1.50-2.32]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Start with lower dose, up to 50 mg/d in older adults; in postoperative pain: 50 mg/d in case of renal or hepatic failure, maximum dose 50 mg/8h; maximum length 48 hours; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AG01	Mefenamic acid In lists: 5 (A); 1, 2, 5, 6 (B)	18; 1.72 [1.35-2.10]; 2.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

M01AH01	Celecoxib In lists: 1, 2, 5, 6 (B)	21; 1.67 [1.28-2.06]; 1.00	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AH05	Etoricoxib In lists: 4 (A); 1, 2, 5, 6 (B)	22; 1.73 [1.34-2.12]; 1.50	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Shortest possible duration of therapy. *P* Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M01AX01	Nabumetone In lists: 5 (A); 1, 2, 5, 6 (B)	20; 1.70 [1.33-2.08]; 1.50	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications	Adjust dose in cases of moderate or severe renal failure; maximum starting dose should not exceed 750 mg or 500 mg/d, to a maximum of 1500 mg and 1000 mg/d; older adults should receive single daily doses of 1000mg; dose reduction recommended, consider low starting dose. *M* The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
M03	***Muscle relaxants***				

Appendix 1: complete EU(7)-PIM list

M03B	***Muscle relaxants, centrally acting agents***				
M03BA02	Carisoprodol In lists: 5 (A); 5 (B)	13; 1.62 [1.15-2.08]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia		
M03BA03	Methocarbamol In lists: 1, 2, 5 (A)	13; 1.62 [1.15-2.08]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia		Rehabilitation; botulinum toxin. *E*
M03BC01	Orphenadrine In lists: 3, 5 (A); 5 (B)	16; 1.38 [1.11-1.64]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia		Rehabilitation; botulinum toxin. *E*
M03BX01	Baclofen In lists: 1, 3, 4 (A)	22; 2.14 [1.72-2.55]; 2.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Dose reductions may be required in cases of renal failure; start low–go slow in older adults. *M* Start with 5 mg 2-3 times daily and increase gradually as needed; maximum dose: 10 mg 3 times daily. *E*	Rehabilitation; botulinum toxin. *E*
M03BX02	Tizanidine In lists: 3 (A), 5 (B)	18; 1.94 [1.37-2.52]; 2.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Dose reductions may be required in cases of renal failure. *M*	Rehabilitation; botulinum toxin. *E*
M03BX07	Tetrazepam In lists: 1, 4 (A)	15; 1.80 [1.37-2.23]; 2.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Cautious dosing in cases of renal failure. *M* Conservative dosing for older adults. *M, E*	Rehabilitation; botulinum toxin. *E*

Appendix 1: complete EU(7)-PIM list

M03BX08	Cyclobenzaprine In lists: 2, 5 (A); 5 (B)	16; 1.69 [1.22-2.15]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Start low–go slow. *M*	
M04	***Antigout preparations***				
M04A	***Antigout preparations***				
M04AC01	Colchicin In lists: 6 (B)	18; 2.11 [1.66-2.56]; 2.00	Higher risk of toxicity in older adults, particularly in cases of existing renal, GI or cardiac disease	Reduce dose by 50% in older adults (>70 years old). *M* Reduce dose in cases of renal failure. *E, M*	Ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*
M05	***Drugs for treatment of bone diseases***				
M05B	***Drugs affecting bone structure and mineralization***				
M05BX03	Strontium ranelate In lists: does not appear as PIM	18; 1.72 [1.35-2.10]; 2.00	Higher risk of venous thromboembolism in persons who are temporarily or permanently immobilised. Evaluate the need for continued therapy for patients over 80 years old with increased risk of venous thromboembolism	Avoid in cases of severe renal failure (CrCl <30 mL/min). *M*	Bisphosphonates, Vitamin D. *E*
M09	***Other drugs for disorders of the musculo-skeletal system***				

Appendix 1: complete EU(7)-PIM list

M09A	***Other drugs for disorders of the musculo-skeletal system***				
M09AA	Quinine and derivatives In lists: does not appear as PIM	15; 2.13 [1.44-2.82]; 2.00	Risk of cardiac and idiosyncratic adverse effects	Adjust dose in cases of renal failure. *M*	
N	**Nervous system**				
N02	***Analgesics***				
N02A	***Opioids***				
N02AB02	Pethidine (=Meperidine) In lists: 4, 5 (A); 2, 6 (B)	22; 1.50 [1.24-1.77]; 1.00	Risk of falls, fractures, confusion, dependency and withdrawal syndrome	Start low–go slow. *M, P* Use for the shortest period possible. *P* 50 mg every 4-6 hours. *E* Use 75% of the normal dose at the usual intervals in cases of moderate renal failure (GFR 10-50 mL/min); use 50% of the normal dose at the usual intervals in cases of severe renal failure (GFR <10 mL/min). *M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
N02AD01	Pentazocine In lists: 5 (A); 2, 6 (B)	18; 1.28 [1.05-1.51]; 1.00	Risk of delirium and agitation	For patients with GFR between 10 and 50 mL/min the dose should be reduced by 25% and for patients with GFR less than 10 mL/min, the dose should be decreased by 50%. *M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone).

Appendix 1: complete EU(7)-PIM list

					E, P
N02AX02	Tramadol (sustained-release) In lists: 5, 6 (B)	23; 1.83 [1.44-2.21]; 2.00	More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea	Start low–go slow. Not to be used in cases of severe renal failure. *E, M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
N02AX02	Tramadol (non-sustained-release) In lists: 5, 6 (B)	21; 2.33 [1.77-2.90]; 2.00	More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea	Start low–go slow; in persons older than 75 years, daily doses over 300 mg are not recommended. *M* Start with 12.5 mg/8h and progressive increases of 12.5 mg/8h; maximum 100mg/8h. *E* Reduce dose and extend the dosing interval for patients with severe renal failure. *M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*

Appendix 1: complete EU(7)-PIM list

N07BC02	Methadone In lists: 6 (B)	22; 1.82 [1.47-2.17]; 2.00	Very long-acting especially in the elderly	Lowest possible dose. *E* Start low–go slow. Lower initial methadone dose with longer dosing intervals are recommended, along with a slower dose titration for patients with renal failure. *M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
N02B	***Other analgesics and antipyretics***				
N02BA01	Acetylsalicylic acid (>325 mg) In lists: 3, 5 (A); 2, 5, 6 (B)	23; 1.83 [1.33-2.33]; 1.00	May exacerbate existing GI ulcers or produce new GI ulcers; increased risk of bleeding due to prolongated clotting time, elevation of INR values or inhibition of platelet aggregation		Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
N02C	***Antimigraine preparations***				
N02CA02	Ergotamine In lists: 4 (A)	20; 1.55 [1.08-2.02]; 1.00	Unfavourable risk/benefit profile		Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week); non-pharmacological treatment (silence, rest, darkness). *E*

Appendix 1: complete EU(7)-PIM list

N02CC	Triptanes (e.g. Sumatriptan, Eletriptan, Naratriptan, Zolmitriptan) In lists: does not appear as PIM	23; 2.13 [1.78-2.48]; 2.00	Safety and efficacy in older adults have not been established Naratriptan and sumatriptan use for older adults has an increased risk of decreased hepatic function and reduced clearance due to renal dysfunction, higher risk for coronary artery disease, and increases in blood pressure *M*	Start low–go slow. *M* Eletriptan Hydrobromide: initial dose of 20 mg, may be repeated after 2 hours; usual dose of 20-40 mg; maximum dose: 40 mg for older adults. *M* Naratriptan: contraindicated in cases of severe renal failure (CrCl <15 mL/min). In cases of mild to moderate renal failure, a lower starting dose should be considered and the maximum dose is 2.5 mg/d. *M*	Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week); non-pharmacological treatment (silence, rest, darkness). *E*
N03	***Antiepileptics***				
N03A	***Antiepileptics***				
N03AA02	Phenobarbital In lists: 4, 5 (A); 5 (B)	22; 1.50 [1.24-1.77]; 1.00	Risk of sedation, paradoxical excitation	Use lowest possible dose. *E, M* Start at the lowest possible dose, taper down to half of the usual dose. *P* Administer every 12-16 hours in cases of severe renal failure (GFR <10 ml/min). Avoid longer acting barbiturates for long term use in cases of renal failure. Decrease doses significantly for short-term therapy. *M*	Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E*

Appendix 1: complete EU(7)-PIM list

N03AB02	Phenytoin In lists: 3 (A); 5 (B)	22; 2.18 [1.76-2.61]; 2.00	Narrow therapeutic window; increased risk of toxicity in older adults (e.g. CNS and hematologic toxicity)	Lower doses or less frequent dosing may be necessary for older adults due to reduced clearance, hypoalbuminemia or renal disease. *M* Start with 3 mg/kg/day, in divided doses, adjust the dosage according to serum hydantoin concentrations and patient response; use as a guide the plasma levels, increase the dose in increments of 50-100 mg/d every 5-7 days to achieve an effective dose; the usual maintenance dose is 300-500 mg/d or 4-7 mg / kg / d in 2 doses. *E*	Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E*
N03AE01	Clonazepam In lists: 3, 5 (A); 5 (B)	23; 1.70 [1.45-1.94]; 2.00	Risk of falls, paradoxical reactions	Start low–go slow; 0.5 mg/d. *E*	Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E*
N03AF01	Carbamazepine In lists: 5 (A); 5 (B)	23; 2.17 [1.71-2.64]; 2.00	Increased risk of SIADH-like syndrome; adverse events like carbamazepine-induced confusion and agitation, atrioventricular block and bradycardia	Adjust dose to the response and serum concentration. *E*	Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E*

Appendix 1: complete EU(7)-PIM list

N03AX11	Topiramate In lists: 5 (B)	19; 2.53 [2.12-2.93]; 2.00	Risk of cognitive-related dysfunction (e.g., confusion, psychomotor slowing)	Dosage adjustment may be indicated in older adults to the extent renal function is reduced. In cases of evident impaired renal function (CrCl <70 mL/min/1.73 m), use one-half the usual dose. *M* Use initial dose of 25 mg/d and increase 25 mg/d weekly up to 100-200 mg/d. *E*	Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E*
N04	***Antiparkinson drugs***				
N04A	***Anticholinergic agents***				
N04AA01	Trihexyphenidyl In lists: 1, 5 (A); 2, 5, 6 (B)	17; 1.53 [1.08-1.98]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Start low–go slow. *M*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04AA02	Biperiden In lists: 1, 3 (A); 2, 6 (B)	20; 1.50 [1.78-1.82]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04AA12	Tropatepin In lists: 1 (A); 2, 6 (B)	15; 1.40 [1.05-1.75]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*

Appendix 1: complete EU(7)-PIM list

N04AC01	Benzatropine In lists: 2, 6 (B)	14; 1.14 [0.93-1.35]; 1.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Start low–go slow. *M*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04B	***Dopaminergic agents***				
N04BB01	Amantadine In lists: does not appear as PIM	20; 1.70 [1.39-2.00]; 2.00	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia	Start with 100 mg/d in 2 divided daily doses. *E*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC01	Bromocriptine In lists: 3 (A); 6 (B)	22; 1.86 [1.38-2.34]; 1.50	Risk of CNS side effects		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC02	Pergolide In lists: 6 (B)	16; 1.88 [1.45-2.30]; 2.00	Adverse events include dyskinesia, dizziness, hallucinations, dystonia, confusion, somnolence, insomnia, anxiety, nausea		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC03	Dihydroergocryptine In lists: 1, 4 (A); 6 (B)	13; 2.15 [1.42-2.89]; 2.00	Unfavourable risk/benefit profile		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*

Appendix 1: complete EU(7)-PIM list

N04BC04	Ropinirole[c] In lists: 6 (B)	17; 2.47 [1.92-3.02]; 2.00	Risk of orthostatic hypotension, hallucinations, confusion, somnolence, nausea	Start with three intakes of 0.25 mg per day, increase gradually by 0.25 mg per intake each week for four weeks, up to 3 mg/d. Afterwards the dose may be increased weekly by 1.5 mg/d up to 24 mg/d. *E*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC05	Pramipexole[c] In lists: 6 (A)	19; 2.32 [1.86-2.77]; 2.00	Side effects include orthostatic hypotension, GI tract symptoms, hallucinations, confusion, insomnia, peripheral oedema	Reduce dose in cases of moderate to severe renal failure. *M* Start with three intakes of 0.125 per day, increase gradually by 0.125 mg per intake every five to seven days, up to 1.5 to 4.5 mg. *E*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC06	Cabergoline[c] In lists: 3 (A); 6 (B)	18; 1.78 [1.25-2.31]; 1.50	CNS side effects		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC08	Piribedil In lists: 1 (A); 6 (B)	11; 1.73 [1.29-2.16]; 2.00	Risk of orthostatic hypotension and falls		Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N04BC09	Rotigotine In lists: 6 (B)	15; 2.33 [1.68-2.98]; 2.00	Side effects include orthostatic hypotension, headache, nausea, fatigue, sleep disorder, sudden onset of sleep, somnolence	One patch per day, usually started at 2 mg/24h and titrated weekly by increasing the patch size in increments of 2 mg/24h, up to 6 mg/24h; do not stop the treatment abruptly: sudden withdrawal may produce a syndrome resembling neuroleptic malignant syndrome or akinetic crisis. *E*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*

Appendix 1: complete EU(7)-PIM list

N04BD01	Selegiline In lists: 3 (A)	21; 2.29 [1.78-2.79]; 2.00	Increased risk of orthostatic hypotension and dizziness	Do not use at doses >10 mg/d; 6mg/24h patch recommended; increase dose cautiously, paying attention to changes in orthostatic blood pressure. *E*	Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E*
N05	***Psycholeptics***				
N05A	***Antipsychotics***				
N05AA01	Chlorpromazine In lists: 1, 5 (A); 2, 5, 6 (B)	21; 1.38 [1.11-1.65]; 1.00	Muscarinic-blocking drug; risk of orthostatic hypotension and falls; may lower seizure thresholds in patients with seizures or epilepsy	Start low–go slow; use one-third to one-half the normal adult dose for debilitated older adults; use maintenance doses of 300 mg or less; doses greater than 1 gram do not usually offer any benefit, but may be responsible for an increased incidence of adverse effects. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AA02	Levomepromazine In lists: 1, 3, 4 (A); 5, 6 (B)	22; 1.36 [1.15-1.58]; 1.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Administer cautiously in cases of renal failure; start with doses of 5 to 10 mg in geriatric patients. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AA04 N05BA05	Clorazepate-Acepromazine In lists: 1 (A); 6 (B)	14; 1.57 [1.08-2.06]; 1.00	Protracted activity; risk of adverse effects such as drowsiness and falls		Non-pharmacological treatment; antidepressant with anxiolytic profile (SSRI[e]). *E*
N05AA06	Cyamemazine In lists: 1 (A); 5, 6 (B)	12; 1.58 [1.08-2.09]; 1.00	Muscarinic-blocking drug		Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*

Appendix 1: complete EU(7)-PIM list

N05AB02	Fluphenazine In lists: 1, 4, 5 (A); 5, 6 (B)	21; 1.43 [1.09-1.77]; 1.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Start with oral dose of 1-2.5 mg/day. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AB03	Perphenazine In lists: 1, 3, 4, 5 (A); 5, 6 (B)	20; 1.40 [1.05-1.75]; 1.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Start low–go slow; use one-third to one-half the usual adult dose. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AB04	Prochlorperazine In lists: 3, 5 (A); 5, 6 (B)	17; 1.47 [1.10-1.84]; 1.00	Risk of anticholinergic side effects, sedation, falls, QTc-prolongation	Reduce dose; start low–go slow. *E, M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AB06	Trifluoperazine In lists: 5 (A); 5, 6 (B)	15; 1.80 [1.37-2.23]; 2.00	Risk of hypotension and neuromuscular reactions	Start low go slow. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AC01	Propericiazine (=Periciazine) In lists: 1, 3 (A); 5, 6 (B)	14; 1.79 [1.32-2.25]; 2.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia		Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*

Appendix 1: complete EU(7)-PIM list

N05AC02	Thioridazine In lists: 4, 5 (A); 5, 6 (B)	19; 1.37 [1.08-1.65]; 1.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Reduce dose. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AC04	Pipotiazine In lists: 1 (A); 5, 6 (B)	14; 1.50 [1.06-1.94]; 1.00	Muscarinic-blocking drug	Reduce dose; start with doses of less than 25 mg. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AD01	Haloperidol (>2 mg single dose; >5mg/d) In lists: 4, 5 (A); 5, 6 (B)	22; 1.59 [1.33-1.85]; 2.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Use oral doses of 0.75-1.5 mg; use for the shortest period possible. *E*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AD08	Droperidol In lists: 5, 6 (B)	15; 1.73 [1.20-2.27]; 1.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia	Reduce dose in cases of renal failure and in older adults. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AE03	Sertindole In lists: 3 (A); 5, 6 (B)	16; 1.63 [1.20-2.05]; 1.00	Risk of hypotension, falls, QTc-prolongation	10 mg/d. *E*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*

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N05AE04	Ziprasidone In lists: 5, 6 (B)	16; 2.13 [1.51-2.74]; 2.00	Risk of QTc-prolongation, torsades de pointes, sedation, insomnia and orthostatic hypotension. Not approved for the treatment of dementia-related psychosis. Risk of increased mortality, increased with higher doses, when used for behavioural problems in dementia may be similar to the risk for risperidone	Starting dose 20 mg/d. *E*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AF01	Flupentixole In lists: 3 (A); 5, 6 (B)	17; 1.71 [1.27-2.14]; 2.00	Adverse effects like tiredness, dizziness, QTc-prolongation	Dose adjustment may be required. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AF03	Chlorprothixen In lists: 3 (A); 5, 6 (B)	15; 1.87 [1.24-2.49]; 2.00	Lower seizure threshold	Start low−go slow. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AF05	Zuclopenthixol In lists: 3 (A); 5, 6 (B)	12; 1.50 [1.07-1.93]; 1.00	Risk of hypotension, falls, extrapyramidal effects, QT-prolongation	Use low oral doses of 2.5-5 mg/d. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*

Appendix 1: complete EU(7)-PIM list

N05AG02	Pimozide In lists: 5, 6 (B)	14; 1.57 [1.27-1.87]; 2.00	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality and risk of cerebrovascular accident in persons with dementia. More rarely: neuroleptic malignant syndrome and QT-prolongation	Recommended initial dose of 1 mg/d. *E, M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AH02	Clozapine In lists: 3, 4, 5 (A); 5, 6 (B)	22; 1.55 [1.28-1.81]; 1.50	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia; increased risk of agranulocytosis and myocarditis	Start with 12.5 mg/d. *E* Start low–go slow; reduce dose in cases of significant renal failure. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AH03	Olanzapine (>10 mg/d) In lists: 4, 5 (A); 5, 6 (B)	22; 1.64 [1.29-1.99]; 1.50	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia		Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*

Appendix 1: complete EU(7)-PIM list

N05AN01	Lithium In lists: 3 (A); 5, 6 (B)	22; 2.27 [1.80-2.75]; 2.00	Narrow therapeutic window; cumulation in renal failure	300-600 mg/d. *E* Start low–go slow; it may be necessary to decrease dosage by as much as 50% in older adults to compensate for reduced clearance; dose reduction in cases of renal failure: GFR 10-50 ml/min, 50-75% of the usual dose; GFR <10 ml/min, 25-50% of the usual dose given at the normal dosage interval. *M, E*	Non-pharmacological treatment; SSRI[e], mirtazapine[d], trazodone. *E*
N05AX08	Risperidone (>6 weeks) In lists: 5 (A); 5, 6 (B)	20; 2.45 [1.96-2.94]; 2.00	Problematic risk-benefit profile for the treatment of behavioural symptoms of dementia; increased mortality, with higher dose, in patients with dementia	Use the lowest dose required (0.5-1.5 mg/d) for the shortest time period necessary. *E* For geriatric patients or in cases of severe renal failure (CrCl <30 mL/min), start with 0.5 mg twice daily; increase doses by 0.5 mg twice daily; increases above 1.5 mg twice daily should be done at intervals of at least 1 week; slower titration may be necessary. For geriatric patients, if once-daily dosing desired, initiate and titrate on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter. *M*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05AX12	Aripiprazole In lists: 5 (A); 5, 6 (B)	16; 2.60 [1.46-2.66]; 2.00	Risk of increased mortality when used for behavioural problems in dementia	Use the lowest dose required (7-12mg/d) for the shortest time period necessary. *E*	Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E*
N05B	***Anxiolytics***				

Appendix 1: complete EU(7)-PIM list

N05BA01	Diazepam In lists: 1, 4, 5 (A); 2, 5, 6 (B)	23; 1.61 [1.32-1.89]; 2.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P, M U*se initial oral dose of 2-2.5 mg once a day to twice a day. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA02	Chlordiazepoxide In lists: 1, 4, 5 (A); 5, 6 (B)	19; 1.37 [1.08-1.66]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Reduce dose; for older adults use daily oral dose of 5 mg two to four times a day; in cases of severe renal failure (CrCl <10 ml/min), decrease dose by 50%. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA03	Medazepam In lists: 4 (A); 2, 5, 6 (B)	14; 1.50 [1.12-1.88]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Reduce dose for older adults and for patients with renal failure. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.

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N05BA04	Oxazepam (>60 mg/d) In lists: 1, 4, 5 (A); 5, 6 (B)	22; 1.50 [1.20-1.80]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Use doses of 10-20 mg/d; maximum dose: 30 mg/d. *E*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA05	Dipotassium clorazepate In lists: 1, 4 (A); 2, 5, 6 (B)	15; 1.40 [0.99-1.81]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA06	Lorazepam (>1 mg/d) In lists: 1, 4, 5 (A); 5, 6 (B)	21; 1.67 [1.23-2.11]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Reduce dose; use doses of 0.25-1 mg/d. *E*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.

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N05BA08	Bromazepam In lists: 1, 4 (A); 5, 6 (B)	19; 1.63 [1.30-1.96]; 2.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA09	Clobazam In lists: 1, 3, 4 (A), 5, 6 (B)	17; 1.41 [1.09-1.73]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *E, P* Reduce dose; start with 5 mg/d orally and titrate no faster than every 7 days to 10-20 mg/d in 2 divided doses, depending on weight. If well tolerated, further titrate if necessary starting on day 21 to a maximum of 20-40 mg/d, depending on weight; older adults may receive half of the usual adult dose. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.

Appendix 1: complete EU(7)-PIM list

N05BA11	Prazepam In lists: 1, 4 (A); 2, 5 (B)	16; 1.31 [0.99-1.63]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Reduce dose; for older adults or debilitated patients, start with 10-15 mg/d orally (in divided doses). *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA12	Alprazolam In lists: 1, 3, 4, 5 (A); 5, 6 (B)	22; 1.91 [1.40-2.42]; 2.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Starting dose 0.25mg/12h. *E* Immediate release tablets (including orally disintegrating tablets): start with 0.25 mg administered two to three times a day, and titrate as tolerated; extended-release tablets: start with 0.5 mg once daily, gradually increase as needed and tolerated. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA13	Halazepam In lists: 6 (B)	9; 2.00 [1.33-2.67]; 2.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Reduce dose; start with 20 mg once or twice daily for patients 70 years or older; adjust dose according to response. *M, E*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.

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N05BA16	Nordazepam In lists: 1 (A); 2, 5, 6 (B)	12; 1.75 [1.20-2.30]; 1.50	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Reduce dose. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA18	(Ethyl-) Loflazepate In lists: 1 (A); 5, 6 (B)	12; 1.75 [1.20-2.30]; 1.50	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Reduce dose. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05BA21	Clotiazepam (>5 mg/d) In lists: 1 (A); 5, 6 (B)	16; 1.56 [1.17-1.95]; 1.00	Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression	Reduce dose. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.

Appendix 1: complete EU(7)-PIM list

N05BC01	Meprobamate In lists: 1, 5 (A)	18; 1.33 [1.09-1.57]; 1.00	Risk of drowsiness, confusion	Reduce dose; start low–go slow; increase dosage interval in cases of renal failure; administer every 6 hours in cases of mild renal failure (GFR>50 ml/min), every 9 to 12 hours in cases of moderate renal failure (10 to 50 ml/min) and every 12 to 18 hours in cases of severe renal failure. *M*	Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P* If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C.
N05C	***Hypnotics and sedatives***				
N05CC01	Chloralhydrate In lists: 4, 5 (A); 5 (B)	17; 1.53 [1.21-1.85]; 1.00	Risk of dizziness and electrocardiographic changes. Higher risk in cases of renal failure	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* For the management of insomnia in geriatric patients, use initial oral dose of 250 mg/d. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD01	Flurazepam In lists: 4, 5 (A); 5, 6 (B)	20; 1.25 [1.04-1.46]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Start with 15 mg/d. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*

Appendix 1: complete EU(7)-PIM list

N05CD02	Nitrazepam In lists: 1, 3, 4 (A); 2, 5, 6 (B)	20; 1.40 [1.12-1.68]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Use 2.5-5 mg/d at bedtime. *E, M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD03	Flunitrazepam In lists: 1, 4 (A); 5, 6 (B)	22; 1.32 [1.03-1.60]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P Reduce dose, e.g. 0.5 mg/d; start low–go slow. *E, M* For induction of anaesthesia in older, poor-risk adults, titrate dose carefully; administer in small intravenous increments of 0.3 to 0.5 mg, at 30-second intervals. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD04	Estazolam In lists: 1, 5 (A); 5, 6 (B)	12; 1.42 [0.99-1.84]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	For older adults who are debilitated or have a low weight, consider initial dose of 0.5 mg at bedtime. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*

Appendix 1: complete EU(7)-PIM list

N05CD05	Triazolam In lists: 1, 2, 3, 4, 5 (A); 5, 6 (B)	18; 1.67 [1.18-2.15]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Reduce dose: 0.125-0.25 mg/d at bedtime Start low–go slow. *E, M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD06	Lormetazepam (>0.5 mg/d) In lists: 1, 4 (A); 5, 6 (B)	17; 1.47 [1.15-1.79]; 1.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD07	Temazepam In lists: 1, 4, 5 (A); 5, 6 (B)	17; 1.88 [1.34-2.42]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Start with 7.5 mg/d and watch individual response. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD08	Midazolam In lists: 3 (A); 5, 6 (B)	22; 2.45 [1.93-2.98]; 2.50	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Reduce dose to 50% of the dose used in healthy younger adults; start with 0.5-1 mg/d. *E* In cases of severe renal failure (CrCl <10 ml/min), the dose should be decreased by 50%. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*

Appendix 1: complete EU(7)-PIM list

N05CD09	Brotizolam (>0.125 mg/d) In lists: 4 (A); 5, 6 (B)	15; 1.73 [1.29-2.18]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Reduce dose; start low–go slow. *E* Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD10	Quazepam In lists: 5 (A); 2, 5, 6 (B)	11; 1.82 [1.31-2.32]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Reduce dose; start low–go slow. *E*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CD11	Loprazolam (>0.5 mg/d)[c] In lists: 1 (A); 5, 6 (B)	16; 1.63 [1.24-2.01]; 1.50	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Reduce dose; start low–go slow. Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*; *E*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CF01	Zopiclone (>3.75 mg/d) In lists: 1, 4, 5, 6 (A); 5 (B)	22; 2.27 [1.82-2.73]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*

Appendix 1: complete EU(7)-PIM list

N05CF02	Zolpidem (>5 mg/d) In lists: 1, 4, 5, 6 (A); 5 (B)	22; 2.09 [1.66-2.52]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CF03	Zaleplone (>5 mg/d) In lists: 3, 4, 5, 6 (A); 5 (B)	17; 1.94 [1.56-2.33]; 2.00	Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression	Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CM02	Clomethiazole In lists: 5 (B)	13; 2.23 [1.53-2.94]; 2.00	Risk of respiratory depression	Reduce dose. *E, M* Use sedative dose 500-1000 mg at bedtime. *M*	Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N05CM06	Propiomazine In lists: 5, 6 (B)	10; 1.20 [0.90-1.50]; 1.00	Risk of antimuscarinic effects, sedation and hypotension, dry mouth and extrapyramidal reactions		Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*

Appendix 1: complete EU(7)-PIM list

No ATC	Aceprometazine In lists: 1 (A); 6 (B)	14; 1.64 [1.21-2.07]; 1.50	Muscarinic-blocking drug, risk of cognitve impairment		Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P*
N06	***Psychoanaleptics***				
N06A	***Antidepressants***				
N06AA01	Desipramine In lists: 2, 5, 6 (B)	14; 1.50 [1.12-1.88]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Use doses of 25-100 mg/d; maximum dose: 150 mg/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA02	Imipramine In lists: 1, 4, 5 (A); 2, 5, 6 (B)	20; 1.50 [1.14-1.86]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly; reduce dose. *P* Use doses of 25-50 mg/d at bedtime; maximum dose: 100 mg/d. *E*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*

Appendix 1: complete EU(7)-PIM list

N06AA04	Clomipramine In lists: 1, 3, 4, 5 (A); 1, 2, 5, 6 (B)	21; 1.48 [1.14-1.82]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start with half the usual daily dose, increase slowly; reduce dose. *E, M, P* Starting dose 10-20 mg/d, max. 250 mg/day. *E*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA06	Trimipramine In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B)	16; 1.44 [1.10-1.77]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly; reduce dose. *M, P* Start with 50 mg/d and do not exceed 100 mg/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA09	Amitriptyline In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B)	22; 1.68 [1.26-2.10]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly; reduce dose; start with 10 mg 3 times per day and 20 mg at bedtime. *M, E, P* Its use for treating neuropathic pain may be considered appropriate, with benefits overweighing the risks. *E*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*

Appendix 1: complete EU(7)-PIM list

N06AA10	Nortriptyline In lists: 3 (A); 2, 5, 6 (B)	21; 2.10 [2.52-2.67]; 2.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Use 30-50 mg/d in divided doses. *E, M* Its use for treating neuropathic pain may be considered appropriate, with benefits overweighing the risks. *E*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA12	Doxepin In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B)	20; 1.40 [1.05-1.75]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly. *P* 0.5 mg/d. *E* 3 mg/d, maximum dose: 6 mg/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA16	Dosulepin In lists: 1 (A); 2, 5, 6 (B)	17; 1.29 [1.05-1.54]; 1.00	Muscarinic-blocking agents with cardiotoxicity when overdosed	Start with 50-75 mg/d. *E, M* Reduce dose in cases of renal failure. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AA17	Amoxapine In lists: 1 (A); 2, 5, 6 (B)	14; 1.50 [1.12-1.88]; 1.00	Muscarinic-blocking agents with cardiotoxicity when overdosed	Start with 25 mg given two to three times per day; by the end of the first week, increase to 50 mg given two to three times per day. 2-3x/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*

Appendix 1: complete EU(7)-PIM list

N06AA21	Maprotiline In lists: 1, 4 (A); 2, 5, 6 (B)	21; 1.43 [1.09-1.77]; 1.00	Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling	Start at half the usual daily dose, increase slowly; reduce dose. *P, E* Start with 25 mg/d, increase by 25 mg increments up to 50-75 mg/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AB03	Fluoxetine In lists: 3, 4 (A); 2, 5, 6 (B)	22; 2.27 [1.80-2.75]; 2.00	CNS side effects (nausea, insomnia, dizziness, confusion); hyponatremia	Reduce dose; start with 20 mg/d; maximum dose also 20 mg/d; avoid administration at bedtime. *E, M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AB05	Paroxetine In lists: 2, 5, 6 (B)	21; 2.29 [1.99-2.58]; 2.00	Higher risk of all-cause mortality, higher risk of seizures, falls and fractures. Anticholinergic adverse effects	For older adults or for patients with renal failure, start immediate-release tablets with 10 mg/d (12.5 mg/d if controlled-release tablets), increased by 10 mg/d (12.5 mg/d if controlled-release tablets), up to 40 mg/d (50 mg/d if controlled-release tablets). *E, M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AB08	Fluvoxamine In lists: 2, 5, 6 (B)	20; 2.05 [1.69-2.41]; 2.00	Higher risk of all-cause mortality, self-harm, falls, fractures and hyponatraemia	Reduce dose for older adults and patients with renal failure; start with 50-100 mg/d; titrate slowly. *E, M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AF04	Tranylcypromine In lists: 4 (A)	15; 1.73 [1.06-2.41]; 1.00	Irreversible MAO inhibitor. Risk of hypertensive crises, cerebral hemorrhage and malignant hyperthermia	Reduce dose: 30 mg/d; maximum dose: 60 mg/d. *E*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AX12	Bupropion In lists: 5 (B)	20; 2.30 [1.77-2.83]; 2.00	May lower seizure threshold	Reduce dose and dosing frequency for older adults and patients with renal failure. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*

Appendix 1: complete EU(7)-PIM list

N06AX16	Venlafaxine In lists: does not appear as PIM	21; 2.43 [2.06-2.80]; 2.00	Higher risk of all-cause mortality, attempted suicide, stroke, seizures, upper gastrointestinal bleeding, falls and fracture	Start with 25-50 mg, two times per day and increase by 25 mg/dose; for extended-release formulation start with 37.5 mg once daily and increase by 37.5 mg every 4-7 days as tolerated. *E* Reduce the total daily dose by 25-50% in cases of mild to moderate renal failure. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06AX18	Reboxetine In lists: does not appear as PIM	15; 1.87 [1.46-2.28]; 2.00	Side effects (dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating and insomnia). Higher risk of conduction disturbances, tachycardia, occasional atrial and ventricular ectopy	Reduce dose in cases of renal failure; start with 2 mg two times per day in cases of renal failure; for older adults, reduce dose to 4-6 mg/d. *M*	Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E*
N06B	***Psychostimulants, agents used for ADHD and nootropics***				
N06BA04	Methylphenidat In lists: 2 (A); 5 (B)	19; 1.63 [1.14-2.12]; 1.00	May cause or worsen insomnia; concern due to CNS-altering effects; concern due to appetite-supressing effects		Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E*
N06BX03	Piracetam In lists: 1, 4 (A)	19; 2.05 [1.40-2.70]; 2.00	No efficacy proven; unfavorable risk/benefit profile	Reduce dose for older adults and for patients with renal failure. *M*	Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d] *E*
N06D	***Anti-dementia drugs***				

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N06DX02	Ginkgo biloba In lists: 1 (A)	20; 2.05 [1.42-2.68]; 1.50	No efficacy proven; increased risk of orthostatic hypotension and fall		Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E*
C04AE01	Ergoloid mesylate (dihydroergotoxine) In lists: 1, 4 (A); 6 (B)	21; 1.48 [1.03-1.92]; 1.00	No efficacy proven; unfavourable risk/benefit profile; increased risk of orthostatic hypotension and fall	1 mg three times daily. *M*	Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E*
N07	***Other nervous system drugs***				
N07A	***Parasympathomimetics***				
N07AB02	Bethanechol In lists: does not appear as PIM	14; 1.71 [1.24-2.19]; 1.50	Anticholinergic bladder relaxants may cause obstruction in persons with benign prostatic hyperplasia		
R	**Respiratory system**				
R01	***Nasal preparations***				
R01B	***Nasal decongestants for systemic use***				
R01BA01	Norephedrine (=Phenylpropanolamine) In lists: 3 (A)	21; 2.05 [1.56-2.54]; 2.00	Higher risk of elevation of blood pressure secondary to sympathomimetic activity		

Appendix 1: complete EU(7)-PIM list

R01BA02	Pseudoephedrine In lists: 5 (B)	21; 2.00 [1.52-2.48]; 2.00	Higher risk of elevation of blood pressure secondary to sympathomimetic activity	Adjust dose in cases of renal failure; 15-30 mg three times per day for the treatment of urinary incontinence in older adults. *M*	
R03	***Drugs for obstructive airway diseases***				
R03C	***Adrenergics for systemic use***				
R03CC03	Terbutaline (oral) In lists: does not appear as PIM	20; 1.75 [1.25-2.25]; 1.00	Higher risk of adverse effects as compared to the inhaled form	Use 50% of the usual dose for patients with moderate renal failure (GFR 10-50 ml/min); avoid in cases of severe renal failure (GFR <10 ml/min). *M*	Inhaled form. *E*
R03D	***Other systemic drugs for airway diseases***				
R03DA04	Theophylline In lists: 3 (A); 5, 6 (B)	22; 2.27 [1.76-2.79]; 2.00	Higher risk of CNS stimulant effects	Start with a 25% reduction compared to the doses for younger adults. *E* Start with a maximum dose of 400 mg/d; monitor serum levels and reduce doses if needed; for healthy older adults (>60 years), theophylline clearance is decreased by an average of 30%. *M*	
R05	***Cough and cold preparation***				

Appendix 1: complete EU(7)-PIM list

R05D	***Cough suppressants, excl. combinations with expectorants***				
R05DA01	Ethylmorphine In lists: 3 (A)	21; 1.90 [1.43-2.38]; 2.00	No clear evidence in the treatment of acute cough		
R05DA04	Codeine (>2 weeks) In lists: 6 (B)	21; 2.00 [1.68-2.32]; 2.00	Higher risk of adverse events (hypotension, sweating, constipation, vomiting, dizziness, sedation, respiratory depression). Avoid use for longer than 2 weeks for persons with chronic constipation without concurrent use of laxatives and for persons with renal failure	Start treatment cautiously for older adults (especially in cases of renal failure); start low–go slow; reduce dose to 75% of the usual dose if GFR 10-50 ml/min and to 50% if GFR <10 ml/min. *M*	If used for pain management consider alternative drugs proposed for analgesics: paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P*
R05DA09	Dextrometorphan In lists: 3 (A)	20; 2.10 [1.55-2.65]; 2.00	No clear evidence in the treatment of acute cough		
R06	***Antihistamines for systemic use***				
R06A	***Antihistamines for systemic use***				

Appendix 1: complete EU(7)-PIM list

R06AA02	Diphenhydramine In lists: 1, 4, 5 (A); 5, 6 (B)	21; 1.48 [1.20-1.75]; 1.00	Anticholinergic side effects, sedation, dizziness; electrocardiographic changes	Reduce dose for older adults; start low–go slow. *M* Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* Increase the dosing interval to every 6 hours in cases of mild renal failure (GFR >50 ml/min), every 6-12 hours in cases of moderate renal failure (GFR 10-50 ml/min), and every 12-18 hours in cases of severe renal failure (GFR <10 ml/min). *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E* Consider low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs)
R06AA04	Clemastine In lists: 4 (A); 5, 6 (B)	22; 1.77 [1.37-2.18]; 2.00	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT)	Reduce dose. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AA08	Carbinoxamine In lists: 1 (A); 5, 6 (B)	14; 1.64 [1.16-2.13]; 1.00	Muscarinic-blocking drug; higher risk of sedation, drowsiness	Start low–go slow. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*

Appendix 1: complete EU(7)-PIM list

R06AA09	Doxylamine In lists: 1, 4, 5 (A); 5, 6 (B)	16; 1.38 [1.05-1.70]; 1.00	Anticholinergic side effects, dizziness; electrocardiographic changes	Reduce dose. *M* Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E* Consider low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs)
R06AB01	Brompheniramine In lists: 1 (A); 5, 6 (B)	15; 1.60 [1.14-2.06]; 1.00	Muscarinic-blocking drug; higher risk of sedation, drowsiness		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AB02	Dexchlorpheniramine In lists: 1, 4, 5 (A); 5, 6 (B)	17; 1.47 [1.10-1.84]; 1.00	Anticholinergic side effects (e.g. confusion, sedation)	5 mg/d. *E*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AB03	Dimetindene In lists: 4 (A); 6 (B)	16; 1.56 [1.13-2.00]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*

Appendix 1: complete EU(7)-PIM list

R06AB04	Chlorpheniramine (=Chlorphenamine) In lists: 1, 4 (A); 5, 6 (B)	17; 1.41 [1.05-1.78]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AB05	Pheniramine In lists: 1 (A); 6 (B)	15; 1.40 [1.12-1.68]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AB52	Dexchlorpheniramine-Betamethason In lists: 1, 5 (A); 5, 6 (B)	16; 1.31 [0.99-1.63]; 1.00	Muscarinic-blocking drug; higher risk of sedation, drowsiness		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AC04	Tripelennamine In lists: 6 (B)	16; 1.75 [1.22-2.28]; 1.00	Anticholinergic side effects (e.g. confusion, sedation)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AD01	Alimemazine In lists: 1 (A); 6 (B)	13; 1.31 [1.02-1.60]; 1.00	Muscarinic-blocking drug; higher risk of sedation, drowsiness	Reduce dose; start low–go slow. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*

Appendix 1: complete EU(7)-PIM list

R06AD02	Promethazine In lists: 1, 5 (A); 5, 6 (B)	18; 1.44 [1.14-1.75]; 1.00	Anticholinergic side effects (e.g. confusion, sedation)	Reduce dose; start low–go slow. *M* Reduce starting dose to 6.25-12.5 mg for iv injection. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E* Consider low doses of short to intermediate benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs)
R06AD07	Mequitazine In lists: 1 (A); 6 (B)	12; 1.33 [0.92-1.75]; 1.00	Anticholinergic side effects (e.g. confusion, sedation)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AD08	Oxomemazine In lists: 1 (A); 6 (B)	11; 1.36 [0.91-1.82]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AE01	Buclizine In lists: 1 (A); 6 (B)	12; 1.33 [0.92-1.75]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AE03	Cyclizine In lists: 3 (A); 6 (B)	17; 1.53 [1.21-1.85]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*

Appendix 1: complete EU(7)-PIM list

R06AE05	Meclozine In lists: 1, 3 (A); 6 (B)	16; 1.44 [1.05-1.83]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AX02	Cyproheptadine In lists: 1, 5 (A); 5, 6 (B)	18; 1.28 [0.99-1.56]; 1.00	Anticholinergic side effects (e.g. confusion, sedation)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AX07	Triprolidine In lists: 1, 4, 5 (A); 5, 6 (B)	14; 1.43 [0.99-1.87]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT)		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AX12	Terfenadine In lists: does not appear as PIM	17; 1.88 [1.52-2.24]; 2.00	Adverse effects include prolonged QT interval, tachyarrhythmia, weakness, anxiety, agitation	Administer one tablet daily if CrCl <40 ml/min. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AX22	Ebastine In lists: does not appear as PIM	19; 2.26 [1.84-2.68]; 2.00	Adverse events include impaired psychomotor performance with 50 mg or greater, somnolence, tachycardia, fatigue	Avoid / reduce dose if severe renal failure. *M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
R06AX23	Pimethixene In lists: 1 (A); 6 (B)	11; 1.36 [0.91-1.82]; 1.00	No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation		Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*
N05BB01	Hydroxyzine In lists: 1, 3, 4, 5 (A); 5 (B)	20; 1.40 [1.12-1.68]; 1.00	Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance, confusion, sedation; electrocardiographic changes (prolonged QT)	Reduce dose to at least 50% less than dose used for healthy younger adults. *E, M*	Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* Alternative therapies depending on indication. *E*

Appendix 1: complete EU(7)-PIM list

[a]Category A (A): precisely this active substance is named as a PIM. Category B (B): i) this active substance is characterized as a PIM only in the case of certain clinical conditions or comorbidities or ii) this active substance is not specifically named but considered as a PIM drug class (e.g. anticholinergics or long-acting benzodiazepines). [b]Decisive Delphi round: Delphi round in which consensus was reached (1st Delphi round: 26 experts participated; 2nd Delphi round: 24 experts participated; these numbers comprise two groups of 2 and 3 experts, respectively, doing joint assessments). [c]Drug reevaluated during the last brief survey. [d]Caution, this drug was judged to be questionable PIM. [e]The following drugs belonging to this medication group were judged to be questionable PIM: citalopram, sertraline, escitalopram. [f]In the group of non-sedating antihistamines, only loratadine was evaluated and judged to be questionable PIM; other drugs such as cetirizine were not evaluated. [g]ATC according to WIDO (2013) [46]; [h]ATC according to WHO ATC-code website 2013; [i]ATC according to WHO ATC-code website 2014.
E: Experts; *M*: Micromedex® [32]; *P*: PRISCUS list [22]; *L*: Laroche et al (2007) [3]; *McL*: McLeod et al (1997) [26]; *B*: Beers list (2012) [18]. ACE: Angiotensin-Converting-Enzyme; ADHD: Attention Deficit Hyperactivity Disorder; CNS: Central Nervous System; ECG: Electrocardiographic; GI: Gastrointestinal; PIM: Potentially Inappropriate Medication; PPI: Proton-Pump Inhibitors; SIADH: Syndrome of Inappropriate Antidiuretic Hormone secretion. Dosing abbreviations: CrCl: Creatinine Clearance; d: day; GFR: Glomerular Filtration Rate; iv: intravenous; mcg: micrograms; mg: milligram; min: minute; mL: millilitre; q: every.
Note: if nothing is stated under "Dose adjustment / special considerations of use", this means that no suggestion was made either by the experts or in Micromedex®.

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ANNEX 2.2
Article 2

Appendix 2: Questionable Potentially Inappropriate Medications (Questionable PIM): results of the Delphi survey.

Drug ATC[a]	Questionable PIM (number of experts' answers at decisive Delphi round[b])	Results of the 5-point Likert scale	
		Median	Mean [95% confidence interval]
A	**Alimentary tract and metabolism**		
A06	***Laxatives***		
A06A	***Laxatives***		
A06AC01	Plantago ovate (=Ispaghula, =Psylla seed) (17)	3	2.82 [2.27 - 3.38]
A10	***Drug used in Diabetes***		
A10B	***Blood glucose lowering drugs, excl. insulins***		
A10BA02	Metformin (>2 x 850 mg/d) (21)	2	2.57 [2.10 - 3.04]
B	**Blood and blood forming organs**		
B01	***Antithrombotic agents***		
B01A	***Antithrombotic agents***		
B01AC06	Aspirin low dose in primary prevention of cardiovascular disease (21)	2	2.71 [2.23 - 3.19]
C	**Cardiovascular system**		
C07	***Beta-blocking agents***		
C07A	***Beta-blocking agents***		
C07AG02	Carvedilol (21)	3	3.00 [2.50 - 3.50]
C08	***Calcium channel blockers***		
C08C	***Selective calcium channel blockers with mainly vascular effects***		
C08CA01	Amlodipine (21)	3	3.33 [2.85 - 3.82]
C08CA02	Felodipine (18)	3	2.78 [2.22 - 3.33]
G	**Genito urinary system and sex hormones**		
G04	***Urologicals***		
G04C	***Drug used in benign prostatic hypertrophy***		
G04CA02	Tamsulosin (19)	3	3.00 [2.55 - 3.45]
J	**Anti-infectives for systematic use**		
J01	***Antibacterial for systemic use***		
J01M	***Quinolone antibacterials***		
J01MA02	Ciprofloxacin (21)	3	3.29 [2.83 - 3.74]

J01MA12	Levofloxacin (20)	3.5	3.20 [2.73 - 3.67]
N	**Nervous system**		
N02	***Analgesics***		
N02A	***Opioids***		
N02AA01	Morphine sulfate (non-sustained-release) (21)	3	3.33 [2.89 - 3.77]
N02B	***Other analgesics and antipyretics***		
N02BB02	Metamizole (16)	1.5	2.25 [1.14 - 3.09]
N03	***Antiepileptics***		
N03A	***Antiepileptics***		
N03AF02	Oxcarbazepine (20)	2	2.65 [2.12 - 3.18]
N03AG01	Valproic acid (20)	2.5	2.95 [2.48 - 3.42]
N03AX09	Lamotrigine (19)	3	2.84 [2.35 - 3.33]
N03AX12	Gabapentin (21)	3	2.95 [2.53 - 3.37]
N03AX14	Levetiracetam (18)	4	3.17 [2.59 - 3.74]
N03AX15	Zonisamide (11)	2	1.82 [1.16 - 2.48]
N03AX16	Pregabalin (21)	2	2.81 [2.36 - 3.26]
N04	***Antiparkinson drugs***		
N04B	***Dopaminergic agents***		
N04BX01	Tolcapone (15)	2	2.60 [1.94 - 3.26]
N04BX02	Entacapone (16)	2.5	2.81 [2.22 - 3.40]
N05	***Psycholeptics***		
N05A	***Antipsychotics***		
N05AH04	Quetiapine (18)	2	2.67 [2.10 - 3.23]
N06	***Psychoanaleptics***		
N06A	***Antidepressants***		
N06AB04	Citalopram (21)	3	2.95 [2.51 - 3.40]
N06AB06	Sertraline (21)	3	2.95 [2.53 - 3.37]
N06AB10	Escitalopram (21)	3	2.86 [2.42 - 3.30]
N06AX11	Mirtazapine (21)	2	2.62 [2.20 - 3.04]
N06D	***Anti-dementia drugs***		
N06DX01	Memantine (20)	3	3.15 [2.54 - 3.76]
R	**Respiratory system**		
R03	***Drugs for obstructive airway diseases***		
R03B	***Other drugs for obstructive airway diseases, inhalants***		

R03BB01	Ipratropium bromide (inhaled) (21)	3	2.81 [2.34 - 3.28]
R03BB04	Tiotropium bromide (inhaled) (20)	2	2.70 [2.17 - 3.23]
R06	***Antihistamines for systemic use***		
R06A	***Antihistamines for systemic use***		
R06AX13	Loratadine (19)	3	2.74 [2.32 - 3.16]

[a]According to WHO ATC-code list 2011 [30]; [b]Decisive Delphi round: Delphi round in which the results presented were obtained (1st Delphi round: 26 experts participated; 2nd Delphi round: 24 experts participated; these numbers comprise two groups of 2 and 3 experts, respectively, doing joint assessments).

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ANNEX 2.3
Article 2

Appendix 3: Non Potentially Inappropriate Medications (Non-PIM): results of the Delphi survey.

Drug ATC[a]	**Non-potentially inappropriate drugs** (number of experts' answers at decisive Delphi round[b])	**Results of the 5-point Likert scale**	
		Median	**Mean [95% confidence interval]**
A	**Alimentary tract and metabolism**		
A06	***Laxatives***		
A06A	***Laxatives***		
A06AD15	Macrogol (2)	3.5	3.45 [3.03 - 3.87]
A06AD11	Lactulose (21)	4	3.71 [3.36 - 4.07]
B	**Blood and blood forming organs**		
B01	***Antithrombotic agents***		
B01A	***Antithrombotic agents***		
B01AC04	Clopidogrel (23)	4	3.74 [3.23 - 4.25]

[a]According to WHO ATC-code list 2011 [30]; [b]Decisive Delphi round: Delphi round in which the results presented were obtained (1st Delphi round: 26 experts participated; 2nd Delphi round: 24 experts participated; these numbers comprise two groups of 2 and 3 experts, respectively, doing joint assessments).

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