UNIVERSITY OF NAPLES FEDERICO II

DEPARTMENT OF PHARMACY

PhD Thesis in Pharmaceutical Sciences

Drug utilization studies as a strategy for the quality assessment of medication use

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ABSTRACT

Drug prescribing is a vital part of the whole healthcare system.

However, the processes involved in choosing an appropriate drug treatment are complex and lots of drugs are often prescribed and used in inappropriate ways, especially in the older people. The immediate consequences of inappropriate prescribing are diverse and include: an increment in negative drug events, hospitalization and mortality rates, healthcare resource wastage, and additional healthcare costs.

The present thesis describes the results of the first phase of the ongoing national collaborative project (EDU.RE.DRUG Project) founded by the Italian Medicine Agency (AIFA).

The EDU.RE.DRUG Project (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients) aims to deeply investigate the prescribing practice among general practitioners (GPs) and the appropriate drug use by their patients in two Italian regions.

In accordance with the first phase of the EDU.RE.DRUG Project, the main objectives of this thesis are: (i) to develop indicators of inappropriate prescribing suitable to the Italian context; (ii) to retrospectively assess the prevalence of drug use of selected drug classes, with a particular focus on older patients; (iii) to compare two different geographical areas in Italy; (iv) to investigate the influence of socioeconomic and sociodemographic variables on prevalence of drug use for each of the selected drug categories.

Within the framework of the present research project, a set of explicit indicators was defined so to identify potential inappropriate prescription and drug use. The set of indicators was adapted to the Italian drug market, providing, in this manner, a tool specifically tailored to the characteristics of the Italian healthcare system.

Besides providing specifically tailored indicators, an analysis of quality prescribing has been performed by employing data coming from two different Italian regions. In this

context, we also retrospectively assessed geographical variations in drug prescription across selected drug classes (those specifically targeting aged people).

Many differences arise between the two regions involved in the study. In general, compared to Lombardy LHUs (in the North of Italy), patients belonging to the Campania LHUs (in the South of Italy) are exposed to higher prevalence rate for all selected drug categories.

Particularly, the drug category that showed the highest geographical variability was antibiotics.

It is interesting to note that such geographical variability has been found not only among different Italian regions, but also among areas within the same region.

In most of the southern municipalities of Campania (e.g. Benevento and Salerno), prevalence rates and antibiotic consumption were lower than in coastal areas around Naples and eastern Avellino (from 15,2% in Omignano, Sa-LHU, to 61,9% in Moschiano, Av-LHU).

Furthermore, our study showed that socio-economic and socio-demographic factors can influence the appropriateness of drug use.

The intraregional variability observed in our study can also be explained by different prescribing patterns among physicians and different local health policies.

These results show the pressing need for an intervention aimed at improving the quality of prescribing and drug use. In this regard, the strategies necessary to the optimization of drug prescribing could benefit from the analysis provided by the present work.

PUBLICATIONS IN THIS THESIS AND AUTHOR'S CONTRIBUTION STATEMENT

The thesis is based on the following original papers.

I. Manuela Casula, Enrica Menditto, Federica Galimberti, Veronica Russo, Elena Olmastroni, Lorenza Scotti, Valentina Orlando, Giovanni Corrao, Alberico L Catapano, Elena Tragni, on behalf of EDU.RE.DRUG Group. A PRAGMATIC CONTROLLED TRIAL TO IMPROVE THE APPROPRIATE PRESCRIPTION OF DRUGS IN ADULT OUTPATIENTS: DESIGN AND RATIONALE OF THE EDU.RE.DRUG STUDY. This paper is under review by the journal Primary Health Care Research & Development.

II. Veronica Russo, Valentina Orlando, Valeria Marina Monetti, Federica Galimberti, Manuela Casula, Elena Olmastroni, Elena Tragni, Enrica Menditto, on behalf of EDU.RE.DRUG Group. GEOGRAPHICAL VARIATION IN THE PRESCRIBING OF MEDICATIONS: A MULTIREGIONAL DRUG UTILIZATION STUDY. This paper is under review by the journal Frontiers in Pharmacology.

III. Veronica Russo, Valeria Marina Monetti, Francesca Guerriero, Ugo Trama, Antonella Guida, Enrica Menditto, Valentina Orlando. PREVALENCE OF ANTIBIOTIC PRESCRIPTION IN SOUTHERN ITALIAN OUTPATIENTS: REAL-WORLD DATA ANALYSIS OF SOCIOECONOMIC AND SOCIODEMOGRAPHIC VARIABLES AT A MUNICIPALITY LEVEL. Clinicoeconomic and Outcomes Research 2018 May 3;10:251-258. doi: 10.2147/CEOR.S161299.

IV. Valentina Orlando, Valeria Marina Monetti, Aida Moreno Juste, Veronica Russo, Sara Mucherino, Ugo Trama, Antonella Guida, Enrica Menditto. DRUG UTILIZATION PATTERN OF ANTIBIOTICS: THE ROLE OF AGE, SEX AND MUNICIPALITIES IN DETERMINING VARIATION. Accepted by the journal Risk Management and Healthcare Policy on the 31 of December 2019.

LIST OF ABBREVIATIONS

ACB: Anticholinergic Cognitive Burden

ACOVE: Assessing Care Of the Vulnerable Elderly

ADR: Adverse Drug Reaction

AIC: Marketing Authorization Code

AIFA: Italian Medicine Agency

AL: Anticholinergic Load

API: Application Programming Interference

APIs: Appropriate Prescribing Indicators

ATC: Anatomical Therapeutic Chemical

AV-LHU: Avellino Local Health Unit

Bn-LHU: Benevento Local Health Unit

Ce-LHU: Caserta Local Health Unit

CI: Confidence Interval

CME: Continuous Medical Education

DALY: Disability-Adjusted Life Years

DDI: Drug-Drug Interaction

DDD: Defined Daily Doses

DRG: Diagnosis Related Group

DUR: Drug Utilization Research

ESAC: European Surveillance of Antimicrobial Consumption

EU: European Union

GP: General Practitioner

HTA: Health Technology Assessment

ICD: International Classification of Disease

LHU: Local Health Unit

MAI: Medication Appropriateness Index

Na 1-LHU: Naples 1 Local Health Unit

Na 2-LHU: Naples 2 Local Health Unit

Na 3-LHU: Naples 3 Local Health Unit

NHS: National Health System

NIC: Net Ingredient Cost

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

OECD: Organization for Economic Cooperation and Development

OPAT: Outpatient Parenteral Therapy

OR: Odds Ratio

OsMed: Italian National Observatory on Drug Prescription

OTC: Over-The-Counter

PDC: Proportion of Days Covered

PDD: Prescribed Daily Dose

pDDI: potential Drug-Drug Interaction

PIM: Potential Inappropriate Medication

PPI: Potential Inappropriate Prescription

PRs: Prevalence Rations

RCTs: Randomized Clinical Trials

RHS: Rational Health System

RWD: Real World Data

Sa-LHU: Salerno Local Health Unit

SL: Sedative Load

START: Screening Tool to Alert doctors to Right Treatment

STD: Standard Deviation

STOPP: Screening Tool of Older Person's Prescriptions

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TD: Therapeutic Duplication

US: United States

UK: United Kingdom

WHO: World Health Organization

Chapter 1

Appropriateness of Prescribing

1.1 Definition of Appropriateness

The Greek physician Herophilus, who lived in Alexandria during the IV century BC, is understood to have been the first to have spoken of the appropriate use of medicines. He allegedly said that "medicines are nothing in themselves but are the very hands of god if employed with reason and prudence" [1].

In the healthcare field, since then, and in particular during the last few decades, many different and sophisticated definitions of appropriateness have been suggested, though none of them provide a solidly and unequivocal conceptualization of the notion of appropriate healthcare [2].

The definition provided by Harvey et al., in a study published in 1991, states that we can deem as appropriate care "*that strategy of action which maximizes the potential health benefits valued by informed individuals or populations after considering the likely outcomes, their probabilities and their costs, for each of the separate components of the strategy, and that health care professionals are willing to provide*" [3].

In other words, he understands appropriate care as being the result of a pondered evaluation of both the available choices and resources.

Instead, the HSUS study defines appropriateness by explicitly focusing on the comparison between health benefits and costs, and it does so by drawing on the well-known Donabedian's definition of quality of care [4]. It therefore states that health care can be deemed as appropriate when: "*for an average group of patients presenting to an average U.S. physician.., the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing.., excluding considerations of monetary cost"* [5].

In more concise words, if the risks outweigh the benefits, the procedure is seen as inappropriate.

Although this definition was one of the most widely used, it has been criticized because it has several limitations. For example, it lacks situational specificity and it takes in account neither the healthcare resources available nor the patients' choices.

Some years later, probably as response to the shortcomings of studies such as the HSUS one, a Working Group for the National Health Service Executive defined appropriate healthcare as "*the intervention that is most likely to produce the outcomes desired by the individual patient*". In addition to such definition, they also specified certain criteria that must be met for an intervention to be deemed as appropriate [6].

This new definition has the merit to respect the individuality of patients, but it still does not take in account cost-effectiveness.

1.1.1 Definition of Rationality and Appropriateness in Prescribing Medication

Rational use of medicines plays an essential role in health promotion by ensuring help, curing diseases, relieving symptoms and alleviating patient suffering. Nonetheless, making a correct diagnosis and, consequently, defining an appropriate treatment for the given patient is not always a simple and direct process.

In 1985, the Conference of Experts on the Rational Use of Drugs, convened by the World Health Organization (WHO), defined rational use of medicines as a situation in which "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" [7].

This suggests that rational prescribing can be characterized as a process—that can be either rational or irrational. It is rational when prescribers correctly employ the information available to them and make prescribing decision accordingly. Conversely, it is irrational when it proceeds from the erroneous processing of the available information.

In addition, conditions may arise in which a prescription is rational and yet inappropriate. For example, this can happen when the reasoning that led to the prescription was correct, but it had, nonetheless, poor clinical results due to information deficits. Furthermore, a prescription may be irrational, but appropriate as result of mere luck.

Even though irrational use of medicines is mainly an outcome of an irrational prescribing process, many interrelated factors such as health system, prescriber, dispenser, patient and community can often influence the prescribing process and contribute to irrational use in a variety of ways [8].

This means, as Ofori et al. have shown, that the inappropriate use of medicines can begin at any of the four main stages of the medicines use cycle. These four stages are diagnosis, prescribing, dispensing, and patient adherence (Figure 1) [9]. The diagnosis stage involves identifying and defining the problem(s). In this stage, if the wrong problem (e.g. disease condition) is outlined for intervention, it is possible to prescribe the wrong treatment incurring in a form of inappropriate prescribing. Following the establishment of a diagnosis, which usually results in the prescription of a treatment, patients are supplied with said prescribed treatment, and are then expected to take the medications as directed (adherence) [9].

Unfortunately, ever since the accessibility of modern medicine increased, we have also witnessed to a proportional increment in the number of incidents concerning its misuse which might occur in the form of overprescribing, multi-drug prescribing, use of unnecessary drugs and self-medication.

In addition to the WHO's definition mentioned above, which is formulated proceeding from the medical therapeutic point of view, rational drug use can also be viewed from the consumers' perspectives. In fact, what is rational for a prescriber may not be understood as rational by a patient [10].

This specific issue may emerge, for example, when there are informational deficits or major differences in the perceptions or cognitive styles of both doctor and patient. Furthermore, it has been shown that doctor-patient communication about prescribing can be associated with continuing problem of non-adherence to treatment. Therefore, good communication between prescribers and patients is clearly an important factor. At this regard, Britten et al. have shown that the occurrence of misunderstandings between doctor and patient during the prescription phase can greatly influence the correct intake of drugs. In the cases considered by Britten et al., misunderstanding arises as consequence of: (i) lack of shared relevant information involving both sides, (ii) conflicting information, (iii) the patient failure to understand the doctor's diagnostic or therapeutic decision, and (iv) actions undertaken to preserve the doctor-patient relationship [11]. Consequently, it can be stated that good doctor-patient communication allows both

patient's health, and medical care to improve and, additionally, it tends to increase patient involvement and adherence to recommended therapy.

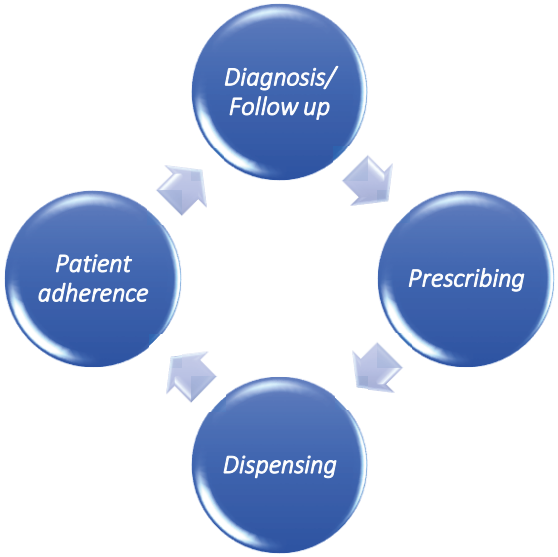

Figure 1. The cycle of medicine use [9].

1.2 The Prescribing Process

Nowadays, irrational use of medicines is a serious global problem whose main characteristics appear to be its inefficiency and harmfulness. Both in developing and transitional countries, when it comes to primary care, less than 40% of patients in the public sector and 30% of patients in the private sector are treated in accordance with standard treatment guidelines [12].

As prescribing appropriately is a really demanding challenge and requires to find the right balance among pharmacological rationality, the need of individual patients, and financial considerations, it could be said that prescribing appropriately is both a science and art [2].

At this regard, the systematic approach advocated by the WHO can help minimize poor quality and erroneous prescribing [13]. Its six-step approach to prescribing suggests that the physician should:

1. *Evaluate and define the patient's problem (diagnosis);*

   A correct diagnosis is indispensable to start the appropriate treatment. This step can be facilitated by a good doctor/patient communication, implemented in order to gather the right information from the patient.

2. *Specify the therapeutic aim(s);*

   Often, the prescribing process begins with the establishing of the therapeutic goal(s) (e.g. alleviating pain, curing an infection, or even improving appetite, etc.). Such therapeutic goals can sometimes be influenced by patient expectations and preferences, in the measure in which they can contribute to the determination of what are the goals to set or not to set. Subsequent to the determination of goals, a treatment is then selected [14].

3. *Select the appropriate drug therapy;*

   The final pharmacological choice should be defined by a series of variables such as a benefit-risk analysis based on medicine, patient factors, and other issues such as availability and cost. In particular, patient factors (physiological and pathological status) can influence medicine's selection. Similarly, the characteristics of drugs themselves can also influence the final pharmacological choice, that is to say drugs are evaluated and therefore selected on the ground of their safety, efficacy, and pharmacokinetic and pharmacodynamic properties [9].

4. *Writing prescriptions, updating medication and consider non-pharmacologic therapies;*

   Once the therapy has been defined, it is important that the patient reports any problem(s) inherent to the new treatment. In this manner, the doctor will be able to modify it or, if possible, consider a non-pharmacological treatment.

5. *Give information, instructions, and warnings;*

   Prescribers should educate patients about the use, the outcomes, and the potential adverse events for each medication. Furthermore, in order to avoid interactions, physicians must describe how the medication should or should not be administrated, including any important information regarding the potential interactions with food, other drugs, and time of day [15].

6. *Evaluate therapy regularly (e.g. monitoring treatment results and considering discontinuation of the drug);*

   The monitoring of the assigned treatment allows the doctor to understand if the treatment has been effective and, therefore, actually appropriate. If the problem has been resolved, the therapy will be suspended. In addition, monitoring can also be a way to assess patient adherence to treatment.

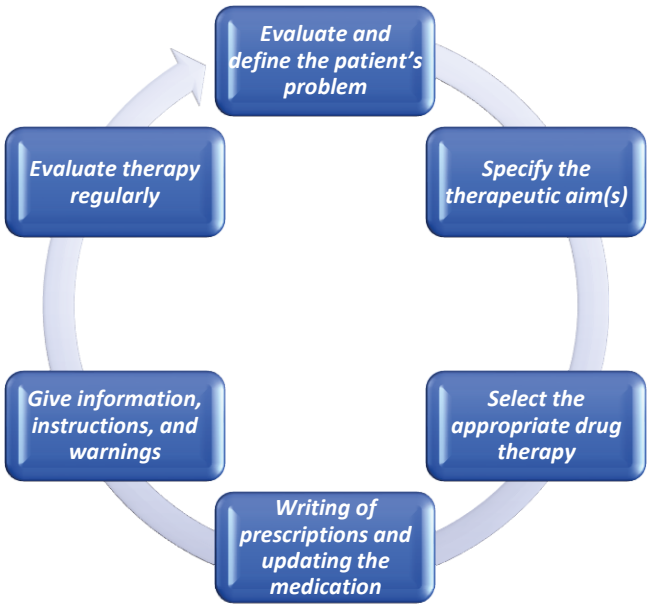

Figure2. Appropriate prescribing process.

1.2.1 What Constitutes Good Prescribing?

Over the years, the notion of what amounts to a good prescription has been much discussed in the literature. Many have tried to provide the correct definition. One of the most commonly quoted definition, sometimes identified as the five rights, "states that a good prescriber should give the right drug, in the right dose, by the right route of administration, at the right time, to the right patient" [16]. According to Aronson, "safe prescribing is a process that recommends a medicine appropriate to the patient's condition and ideally optimizes the balance of benefit to harm" [17]. This definition finds

a meeting point with the definition elaborated by Barber [18], who states that good prescribing is the one that meets four aims:

- Maximizing Effectiveness

  It is virtually undisputable that maximizing effectiveness should be an aim of good prescribing. At this aim and by means of a therapy, medicines are employed to try to re-establish, modify or improve certain physiological functions. The prescriber can verify if the therapy works by testing and measuring the relative parameters. The ultimate aim of this process is to achieve the standard values as quickly and completely as possible.

- Minimizing Risks

  It is not possible to eliminate any conceivable risks, yet a good prescribing practice should try to achieve what is considered as an "acceptable level of risk" both within a certain context, and in relation to an individual patient. Thus, the goal of good prescribing is to reduce the frequency and severity of the adverse drug reaction (ADR) by taking into consideration all unexpected reactions, even minor side effects.

- Minimizing Costs

  The financial concerns regarding drug treatment have undergone a sudden growth to the extent that it has brought into the scientific language a new term: "Pharmacoeconomics". Health expenditure has a significant impact on the economy of several countries, and this means that good prescribing involves also the reduction of costs. Such reduction can be achieved, in the first place, by quickly identifying and reducing the waste of resources and, then, by increasing the effectiveness of therapies. In fact, a correct prescription often leads to a more rapid healing, conversely an inappropriate prescription can lead to the prolongation and worsening of the disease causing also a waste of financial resources. Furthermore, the lower incidence of adverse effects deriving from effective therapies would avoid further drug prescriptions, favoring, indirectly, also the adherence to therapy by the patients. As the NHS is founded with public money, costs should be taken in account when assessing good prescribing, and

this because by reducing costs, it would be possible to free money to re-invest in the health care system. This last aspect would also provide moral justification for engaging in cost minimization. The assessing of the benefits of drug treatment in purely financial terms is more difficult and questionable, and for this reason it should be avoided by prescribers until methodological issues are better refined.

- Respecting Patient Choices

  Many are the ethical and practical reasons why patients' choices, particularly informed choices, should be taken into account when considering good prescribing. An effective communication between physicians and patients is essential, and for this reason physicians should make sure to both listen to their patients and inform them about any relevant aspects of the therapy. Might any objections arise, the prescriber should understand whether it is possible or even necessary to prescribe alternative and more suitable therapies. This kind of successful interaction leads to the establishment of a trust relationship between patient and prescriber which, in turn, makes the patient more satisfied and predisposed to treatment. Unfortunately, this fundamental dynamic is often absent. Obviously, valuing patients' choices does not mean that it is always possible to shape the necessary therapy according to them.

1.2.2 Different Types of Inappropriate Prescribing

According to the WHO's definition, irrational use of medicines includes all the practices that leaves appropriate medicine prescribing unfulfilled. In other words, irrational prescribing has been defined as the prescribing of medications that has more potential risks than potential benefits, or as the kind of prescribing that does not meet accepted medical standards [19].

Hence, irrational prescribing refers to prescribing that fails to conform to good standards of treatment. An inappropriate prescription can lead, in some cases, to therapeutic failure, in others, it can involve serious negative physical consequences for the patient (e.g. ADR, hospitalization, co-morbidity and mortality). In addition to the physical damage that the patient can report, inappropriate prescriptions can also bring about an increment in costs for the patients and the health service.

The listed occurrences of inappropriate prescriptions can manifest themselves in different ways: under-prescribing, over-prescribing, incorrect prescribing, extravagant prescribing, multiple prescribing, prescription cascade, and drug interactions.

- Under-Prescribing

  It indicates the omission, or an insufficient dosage of potentially useful drugs within a patient's medication regimen [20]. Under-prescribing is often overlooked when considering medication issues that contribute to polypharmacy, poor outcomes, and significant cost to the healthcare system. However, one study found that 8.8% (95% CI, 4.6–14.9) of drug-related hospital admissions were attributable to sub-therapeutic dosing, 16.2% (95% CI, 10.4–23.5) were due to noncompliance, and 8.1% were due to an untreated indication [21]. This does not mean that under-prescribing is always to be considered as irrational; on the contrary, it is indeed rational when the physician makes a deliberate decision not to prescribe a recommended drug [22].

- Over-Prescribing

  It refers to instances where a drug is prescribed even when non indicated or, if indicated, the duration of treatment is too long, or the quantity of medicine given to patients exceeds the amount required for the therapy. This form of inappropriate prescription is associated with an increased risk of adverse effects, for example, antibiotic over-prescribing has been shown to increase patient re-attendance as it medicalizes conditions which are self-limiting [23].

- Incorrect Prescribing

  It is a kind of irrational prescribing that manifests when a medicine is given as consequence of a wrong diagnosis, or when, given the right diagnosis, an incorrect drug or an incorrect dose is, nonetheless, prescribed. A study concluded that 11.4% of medication prescribing errors are associated with the use of an incorrect drug name, dosage form or abbreviation [24].

- Extravagant Prescribing

  It takes place when expensive drug is used instead of another one which is less expensive and yet equivalent. This prescription has no therapeutic reasons as it

does not provide any additional therapeutic advantage when compared to cheaper drugs. In other words, this kind of irrational prescribing occurs when a patented drug is preferred to an available generic.

- Therapeutic Duplication

  Therapeutic duplication (TD) is the practice according to which two or more drugs belonging to the same therapeutic category are prescribed at the same time. In this way, the combined daily dose exposes the patient to an increased ADR risk while bringing no further therapeutic benefits. On the contrary, TD may lead to a reduction in safety terms and to excessive healthcare costs. The risk of TD increases when patients receive more drugs from multiple health institutions or different prescribers, as it often happens with the older people.

- Prescribing Cascade

  It is the definition of a process that begins when a drug is prescribed to treat an adverse drug event which has been misinterpreted as a new medical condition. Prescribing cascades most commonly happen when multiple drug therapies are used on a chronic condition impacting the health and wellbeing of older patients. The identification and interruption of prescribing cascades is important to improve medication safety and use [25].

- Drug Interaction

  It is a phenomenon triggered by the interaction of the prescribed medicine either with a drug (drug-drug interaction), or with food (drug-food interaction), or with a pathology (drug-pathology interaction). All these different kinds of interactions end up by causing some adverse events such that the profile risk/benefit changes. A DDI (drug-drug interaction) occurs when the pharmacological or clinical effects, following the prescription of two or more drugs, is different from the expected one. In other words, DDI happens when a drug effect gets modified by the interaction with another drug [26]. Usually, combined therapies are used to obtain better therapeutic results, yet, in the older people DDI can occur more easily because they are usually more exposed to multiple medications and because there are age-related physiological changes in pharmacokinetic and

pharmacodynamic characteristics to be taken in account which can lead to potentially lethal adverse reactions or to therapeutic failure [27].

There are many factors that contribute to irrational prescribing. These factors can be classified into those emanating from patients, prescribers, workplace (health system), supply system (including industry influences), regulation, drug information or misinformation, or a combination of all said factors. The influence of patients in the prescription of certain drugs, such as antibiotics, has been widely documented. Specifically, Macfarlane et al., investigated the impact of patients' pressure on antibiotic prescribing in the management of acute lower respiratory tract illness in the UK. Their results indicated that, of the patients evaluated, 74% were prescribed antibiotics, and that non-clinical factors influenced prescribing 44% of those receiving antibiotics; of the 44%, more than half were due to patient pressure [28].

Other factors that might contribute to irrational prescribing are the lack of adequate training, or the use of obsolete practices. Furthermore, while analyzing the reasons for irrational prescribing, another factor worth considering is the health system as a whole. It is, in fact, very important that the healthcare facilities are easily accessible as an inadequate access to medical facilities and care is identified as a reason for poor compliance [29].

1.3 Economic Impact of the Irrational Use of Medicines

Prescribing is the most important tool used by physicians to cure illness, relieve symptoms and prevent future disease. It is also a complex intellectual task that requires the formulation of an appropriate treatment regimen which takes into account, among the other things, also the infinite variation in patients' characteristics encountered by prescribers. Unfortunately, suboptimal or inappropriate prescribing is significantly prevalent especially in older people, and it is associated with an increased risk of Adverse Drug Reactions (ADRs), increased morbidity and mortality. Moreover, it represents a significant burden in terms of healthcare costs and other adverse outcomes in the older people.

Data provided by the WHO show that more than 50% of all drugs are inappropriately prescribed or dispensed, with 50% of patients using them improperly [30]. According to

the WHO, the economic burden of futile services (those that do not provide benefit to patients) represents between 20% and 40% of all health expenditure [31]. In two cohort studies in Italy, 18% of older people outpatients had one or more potentially inappropriate medical prescriptions [32] and a substantial proportion of subjects was exposed to prescriptions at risk of potential drug-drug interaction (pDDI) [33]. The cost implications of ADRs can be considerable. In Germany, for example [34], ADRs are estimated to cost more than €430 million per year, while, in the United Kingdom, the cost of emergency admissions after ADRs has been estimated at £2 billion per year [35].

This irrational use of medicines alters the balance between risk and benefit, leading to ineffective and useless therapy, and to an increased risk for avoidable side effects. Therefore, effectively dealing with this rather urgent issue not only would increase the quality of healthcare in general, but it would also have as positive corollary the rationalization of pharmaceutical expenditure. In this scenario, the savings deriving from a correct use of financial resources could allow the reinvestment of such resources in the areas where they are needed the most.

1.4 Population Most Affected by Irrational Prescribing: Older People

According to the 1999 United Nations initiative, all nations should prepare their health, social and economic systems for the recent and future demographic aging of their populations [36]. The global population is aging, with the number of people aged over 65 years expected to reach 71 million by 2030, compared to 35 million in 2000 [37].

The population group constituted by the older people is constantly on the rise both in developed and in developing countries, and, for this group, there is a high prevalence rate of degenerative diseases and multiple chronic coexisting diseases, also known as multimorbidity.

Given the fact that older patients have complex clinical problems which often require multiple treatments (polypharmacy), they are particularly susceptible to medication errors. They may, of course, have a genuine need for more medications, however, numerous situations of multimorbidity often involve a multiple prescription of drugs which increases the possibility for irrational prescribing. Proper medications must be prescribed according to the history of disease, drug resistance, physical and mental

health, physical ability, memory, and family support. Moreover, in the case of the older people, additional factors must be taken in account as the risk of problems arising from irrational drug prescribing may increase in relation to physiological age-related changes [38]. In fact, inattention to different metabolic changes of medications such as their absorption, distribution, and excretion in older people's body compared to middle-aged people is regarded as an important factor in incidence of unwanted side effects in the older people.

Evidence suggests that suboptimal or inappropriate prescribing is highly prevalent in older people and is associated with an increased risk of adverse drug events (ADEs), increased morbidity, mortality and healthcare utilization. ADEs are defined as any injury resulting from drug therapy, from appropriate care, or unsuitable or suboptimal care [39]. ADEs include adverse reactions during normal use of a medicine, and any harm due to medication error whether of omission or commission. It could be difficult to interpret in aged people ADEs, especially if they have multimorbidity condition, because often present with no-specific symptoms or geriatric syndromes [40].

Furthermore, many studies have shown that care-home residents-the majority of whom have multimorbidity--are at a particularly high risk of prescribing errors. A large-scale US study reported that 93% of nursing-home residents had three or more conditions and, on average, were prescribed 8 medications daily [41]. Another study found that medication errors occurred in two-thirds of residents, and prescribing errors, as defined by Dean et al, occurred in 39.1% [42].

1.5 Measuring the Appropriateness of Prescribing

Given the set of serious problems arising with the inappropriate prescription of drugs, over the years, a series of reliable indicators have been developed to identify the appropriate, effective, safe and economic use of the medicines.

According to the Organization for Economic Cooperation and Development (OECD), an indicator is "a quantitative or qualitative factor or variable that provides a simple and reliable means of measuring results, reflecting changes related to an intervention or helping to evaluate the performance of a development actor" [43]. In line with such definition, a prescription indicator is a tool that measures prescription drug performance

in clinical practice [44]. Thanks to these characteristics, the indicators provide help for clinicians, planners and organizations that aim to improve health care and processes through which patient care is provided [45]. Measurement and monitoring of indicators have many purposes, but the main goals are to both increase the standard of care in order to get the best practices in term of results and rationalize healthcare pharmaceutical spending.

According to Mainz, an ideal indicator would have the following key characteristics:" *(i) valid and reliable; (ii) highly or optimally specific and sensitive, i.e. it detects few false positives and false negatives; (iii) based on agreed definitions, and described exhaustively and exclusively; (iv) able to discriminates in an effective manner; (v) be related to clearly identifiable events for the relevant user (e.g. if meant for clinical providers, it must be relevant to clinical practice); (vi) suitable for comparisons; and (vii) evidence-based"*. Each indicator must be defined in detail, with explicit data specifications in order to be specific and sensitive. Finally, a valid indicator must be reproducible, consistent and reliable. Reliability is important when using an indicator aimed at making comparisons among groups or within groups over time.

1.5.1 Quality Prescribing Indicators

As previously said, the irrational drug use can have a series of negative effects which can, in turn, impact on different areas of healthcare On the one hand, it compromises the quality of medical care and negatively influences the results of treatments; on the other, it leads to a consequent increment in health care costs.

This is particularly true for older people whose frailty makes the choice of the correct drug prescription even more difficult, especially in case of polypharmacy. Polypharmacy and inappropriate prescribing are well-known risk factors for ADRs, which commonly cause negative clinical outcomes in the aged people [46].

Fortunately, over the years, various tools have been developed and verified to identify potentially inappropriate prescriptions within the older population. Such tools are based on three main measures:

- Explicit Measures (based on pre-established criteria);
- Implicit Measures (based on the evaluation of the clinical case);

- Or Mixed Measures.

Explicit measures are disease or drug oriented and can be applied on big databases even when clinical assessment and/or awareness of clinical characteristics of the patient are absent. These measures do not take into account factors which pertain to quality care. Conversely, implicit measures focus on the assessment of patients rather than on the one of drugs and diseases, and they are less standardizable. Finally, there are mixed criteria which are based on both pre-established lists of drugs and the clinical assessment of the single patient.

1.5.2 Implicit Tools

The best-known implicit prescribing criteria set is the Medication Appropriateness Index (MAI), which was first published in 1992 [47]. Hanlon et al, who devised the MAI, proposed that it could be used to assist in recognizing prescribing errors and improving overall prescribing quality in older people. The MAI addresses ten aspects of each drug prescription, and, in so doing, it aims at identifying a variety of potential prescribing errors. The issues addressed are [48]:

Table 1. Ten aspects address by MAI

Medication Appropriateness Index
Is there an indication for the drug?
Is the medication effective for the condition?
Is the dosage correct?
Are the directions correct?
Are the directions practical?
Are there clinically significant drug-drug interactions?
Are there clinically significant drug-disease interactions?
Is there unnecessary duplication with other drugs?
Is the duration of therapy acceptable?
Is this drug the least expensive alternative compared to others of equal utility?

Each prescription is classified on the base of a final score: the appropriate prescription has a score of 1, a marginally appropriate one has a score of 2 and an inappropriate prescription is characterized by a score of 3. Several research studies over the last 20 years have shown that the MAI frequently detects potential prescribing errors and predicts adverse health outcomes [49]. However, MAI is time-consuming, such that its

use has, for the most part, remained confined to the realm of research rather than used routinely in the clinical practice.

1.5.3 Explicit Tools

Over the years, several authors have tried to provide lists of drugs whose use proved to be inappropriate in the older people. Examples of such lists are the Beers criteria, which was recently updated by the American Geriatrics Society, and the STOPP (Screening Tool of Older Person's Prescriptions) / START (Screening Tool to Alert doctors to Right Treatment) [50].

The characteristics of these kind of explicit criteria can be summarized in few points: (i) they are generally drug- or disease oriented, (ii) usually consist of lists of drugs or drug classes, dosages, drug–drug combinations and drug–disease combinations that are known to cause harmful effects and should therefore be avoided, (iii) can be applied to prescriptions even in the absence of clinical interpretation and judgment, (iv) are quick and easy to apply and generally exhibit a good level of reliability, (v) do not take in account the presence of co-morbidity, (vi) and are in need of constant updating.

1.5.4 Beers Criteria

The Beers criteria are the first set of explicit indicators of inappropriate (PIMs) in aged patients. They were first elaborated in 1991 in the USA [51] by a group of experts who have adopted the standard Delphi consensus methodology for their implementation This set of criteria have been frequently updated and reviewed in 1997 [52], in [53], in 2012 [54], in 2015 [55], and in 2019 [56] in order to include all settings of geriatric care.

The most recent Beers criteria revision incudes five lists:

1. Drugs or pharmacological classes potentially harmful to the older population, regardless of the patient's clinical conditions (see Appendix I);
2. Potentially dangerous drugs in certain clinical conditions (see Appendix II);
3. Drugs or classes of drugs that should be used with caution in older patients (see Appendix III);
4. Drugs or combinations of drugs that could lead to serious interactions (see Appendix IV);

5. Drugs that should be avoided or whose dosage should be re-modulated in patients with severe renal failure (see Appendix V).

The criteria need to be regularly updated as new drugs come into the market, as new evidence emerges in relation to the use of these medications, and as new methods to assess the evidence develop.

Beside the fact that Beers Criteria have shown themselves to be a useful clinical tool, they can have also a pedagogical side. The use of Beer Criteria can, in fact, increase awareness of polypharmacy and, therefore, aid decision making when choosing drugs to avoid in the older adults. The major problem with Beers' criteria is their limited transferability to markets other than the United States, where they were first introduced [57].

1.5.5 STOPP/START Criteria

An alternative method, which was elaborated by a team of eighteen Irish experts, suggests two sets of criteria: the first, called STOPP (Screening Tool of Older Person's Prescriptions) concerns drugs which should not be prescribed in the older patients; the second, which has been named START (Screening Tool to Alert doctors to Right Treatment), identifies the appropriate drugs to be prescribed to the patient given certain conditions and pathologies.

The studies were initially published in 2008 [58] and then revised in 2014 [59]. The 2014 version was developed following an extensive literature review and two rounds of Delphi consensus validation with 19 panelists across 13 European countries, each with recognized expertise in geriatric pharmacotherapy. STOPP final version consists of 80 inappropriate medicine use criteria which are capable of outlining clinical circumstances where specific commonly encountered medications or medication classes are considered as potentially inappropriate in older people (see Appendix VI). START, which comprises 34 criteria, is designed to seek for potentially inappropriate under-prescribing and it is intended to be used concomitantly with STOPP (see Appendix VII) [60].

A recent single-centre trial examined the effect of routine application of the STOPP/START criteria in older people. The study showed that the proportion of patients taking potentially inappropriate drugs at discharge was approximately halved in

comparison to the control patients receiving standard pharmaceutical care (19.3% vs 39.7%) [61].

1.5.6 EU (7) - PIM list

The European Union (EU) (7) - PIM list is a list of potentially inappropriate drugs in the older people compiled in Europe and developed with the participation of experts from seven European countries. It can be used as a tool to analyze and compare prescribing patterns in the older people across European countries. It can also be used as support in the clinical practice.

The EU(7)-PIM list has been carried out with the German PRISCUS list in mind [62], and by revising and integrating other American list [52, 53], Canadian McLeod's list [63] and French Laroche's lists [64]. Thirty geriatric experts from Estonia, Finland, France, the Netherlands, Spain and Sweden participated in the creation of this list. These experts have compiled a list of 282 chemicals that can be classified into 34 potentially inappropriate therapeutic groups when it comes to the care of older people. The EU(7)-PIM list also contains suggestions on possible dose adjustments and/or therapeutic alternatives to potentially inappropriate drugs [65].

1.5.7 Mixed Criteria

ACOVE tool (Assessing Care Of the Vulnerable Elderly) was created in 2001 in USA. It was elaborated on the ground of criteria which are both implicit and explicit. It takes into account drug-drug interactions, drug-disease interactions, and all a series of factors which are essential to ensure an attentive management of the older patient. It consists of 22 medical conditions which are deemed as critical in the older patient. Three of these conditions concern the hospitalized patient, the therapeutic reconciliation and the preventive medicine, one pertains to the medications area, while the remaining 18 include specific pathologies (e.g. hypertension, osteoporosis and pneumonia). For each of the 22 conditions, a minimum of six specific indicators have been established, for a total of 236 indicators.

Such indicators, besides being specifically designed in relation to the designed clinical condition, are also interrelated. This tool has been designed in order to identify the vulnerable older people and the clinical conditions associated with them [66].

1.5.8 Anticholinergic Load

Drugs with anticholinergic properties are commonly used in older people despite their high risk of central and peripheral adverse events. These effects can include constipation, dry mouth, dry eyes, blurred vision and increased heart rate (peripheral adverse effects). In addition, dizziness, sedation, confusion, delirium and even cognitive impairment have been reported as central adverse effects of anticholinergic drugs [67].

Anticholinergic risk scales are proposed to give physicians a practical tool to anticipate anticholinergic-related adverse effects in an old population. Among these proposed scales these is Anticholinergic Cognitive Burden (ACB) [68].

The ACB scale was generated through a combination of laboratory data, literature review, and expert opinion and was updated in 2012 (see Appendix VIII) [69].

According to this scale the drugs are rated from 0 to 3, with 0 signifying no known anticholinergic activity and 3 signifying marked activity.

- ACB score of 1: Drugs with serum anticholinergic activity or affinity in vitro with muscarinic receptors, but without clinically relevant known negative cognitive effects.
- ACB score of 2: Medicines with established and clinically relevant anticholinergic effects.
- ACB score of 3: drugs with an initial score of 2, when reported in associations also with delirium are assigned a score of 3 (decidedly anticholinergic).

All other drugs are given a score of 0 [70].

1.5.9 Sedative Load

Sedative drugs, as with the case of anticholinergic drugs, are more frequent among older people and similarly to anticholinergic drugs, also medication with sedative properties can increase the risk of falls and negatively impact activities of daily living, bringing about, in this manner, potential hospitalization and death. In order to try and avoid these problems, a Sedative Load (SL) model was developed.

This SL model was developed by reviewing the summary of product characteristics for all drugs available in Finland from 1998 to 2001 [71]. The model was developed to represent a comprehensive classification of all drugs on market and to include also drugs for somatic disorders. All said drugs were classified into 4 groups based on their sedative

potential (see Appendix IX). Group 1 included only psychotropics (primary sedatives, 40 drugs); Group 2 included drugs with sedation as a prominent side effect or preparations with a sedating component (80 drugs); Group 3 included drugs with sedation as a potential adverse effect; Group 4 included all the other medicines (drugs with no known sedation) [72].

1.6 PIP and their Limits

When it comes to PIP criteria it is important to not overlook an issue, that is to say the relation between PIP criteria themselves and their effect on patient outcomes. It is, in fact, important to investigate the nature of this connection, because, by establishing a causal relation between criteria and outcomes, we ensure the validity of the criteria themselves and justify their use.

Unfortunately, said investigation is seldom or insufficiently carried out. That is to say, even when this kind of studies have been undertaken, they overlooked the issue of causality and focused on others such as temporal relation and dose response. [73,74,75]

Beside the issue of causality, other methodological issues might weaken the evidence we have so far discovered in the field of PIP. [73,74,75]

For instance, the majority of the elderly still live in their communities, and yet many of the studies which focus on inappropriate prescribing have been carried out in hospital settings. This very fact makes those studies inapt for generalization. In this regard, a prospective study by Hamilton et al., which assessed the PIP by using both STOPP and the Beers criteria based on medications at the point of hospitalisation, found no significant association with the Beers criteria and, in addition to this, STOPP identified significantly more medications involved in ADEs, avoidable ADEs, and avoidable ADEs that contributed to hospital admission than Beers. [76]

Results in line with Hamilton work were found by a similar prospective study which focused on 715 acutely ill older adults admitted to hospital and whose medication were assessed on admission. Said study found that PIP according to STOPP caused or contributed to 11.5% of hospitalisations due to an ADE, while Beers criteria were implicated solely in 6%. This is a difference which cannot be ignored and that must be

added to further limitations, as for instance, the fact that the adult patients considered are not representative of the acutely ill population. Despite these limitations, the prospective designs of these studies are still an element of strength.[77]

Regarding the relationship between criteria of prescribing quality and clinical outcomes, the fact that studies assessing both STOPP and START have been carried out in hospital settings without also including primary care-based research on the general population of the elderly is a serious limitation which should be promptly addressed.

Still, concerning the indicator of inappropriate drug prescription, another element worth considering is that those, as well as other PIP criteria, have been developed in countries which have their own specific characteristics, which renders them not immediately applicable to other countries, at least, not before they undergo the necessary transformations and/or adaptation.

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Chapter 2

Automated Databases: Sources of Data for Drug Utilization Research

2.1 Drug Utilization Research: Objectives

Drug Utilization Research (DUR), known in Italy as "*farmacoutilizzazione"*, is a scientific discipline established, in the mid-1960s, in some University departments of Northern Europe and in the United Kingdom. In 1977, the World Health Organization [1] defined it as the discipline which studies "marketing, distribution, prescription and use of medicines, with special emphasis on the resulting medical and social and economic consequences". For DUR investigates the appropriateness of both drug prescribing and use, it requires a multidisciplinary approach which entails the collaboration of clinicians, pharmacologists and epidemiologists. Moreover, it can be divided into two big branches: one pertains to the research about the appropriateness of drug use, the other regards drug use statistics.

The main aim of drug utilization research is to improve the rational use of drugs in real world settings. The method DUR employs in order to pursue such aim can be exemplified by the following five questions:

1. Why are drugs prescribed?
2. Who are the prescribes?
3. Who do prescribers prescribe for?
4. Do patients comply with prescribers' instructions?
5. What are the costs and benefits of the prescribed drugs?

Proper interpretation of drug use data concerning a given pharmacological treatment requires a detailed analysis of many aspects. First of all, it is necessary to investigate the characteristics of the involved users (patients) and of the dispensed drugs. Knowledge regarding both the relevant markets and the consumed drugs is necessary too, and this with a particular focus on their medical and socio-economic consequences [2].

2.2 Drug Utilization Research: Types of Studies

Drugs Utilization Studies can be categorized in two distinct types. It is, in fact, possible to discriminate between descriptive and quantitative types.

Descriptive studies identify the issues which are in need of further and more detailed analysis. Instead, quantitative studies attempt to correlate data concerning drug

consumption with data about, respectively, morbidity, treatment outcomes and quality of care. The ultimate goal of such correlations is to assess whether the drug therapy is rational or not.

Furthermore, both types of studies can focus on the drug (e.g. dose-effect relationship), on the prescriber (e.g. quality indices of prescription), or on the patient (e.g. the selection of drug and dose in relation to disease conditions, age and physiological changes) [1,2].

Drugs Utilization Research is engaged in the furthering of knowledge concerning the following aspects [1,2]:

- Pattern of use: refers to the profiles and trends in medicine use, and to costs over time.
- Quality of use: verifies the conformity between current practice in drug utilization and national or regional prescription guidelines (local drug formularies may be also considered). The applied indices of quality regarding drug use can include (i) the choice of the drug (based, for instance, on patient adherence to pharmacological treatment), (ii) drug cost (in conformity with the available budget), (iii) drug dosage (which needs to take in account inter-individual variations in dose requirements and age-dependence), (iv) awareness of drug interactions and adverse drug reactions, and (v) the percentage of patients who are aware or unaware of their treatment cost-benefit analysis.
- Determinants of use: takes into account the characteristics of users (such as their sociodemographic parameters and attitudes towards drugs), prescriber characteristics (for instance, specialty, education and factors influencing therapeutic decisions,) and drug characteristics such as therapeutic properties and affordability [1,2].
- Outcomes of use: regards the consequences on the health of patients both in terms of benefits and adverse effects. In addition, this aspect of Drug Utilization deals also with outcomes of financial nature.

2.3 Drug Utilization Research: Types of Information

Depending on the different problem under investigation, it is necessary to employ different types of information regarding drug use. In some cases, for example, it is possible to employ data respectively about global drug use, the use of individual drugs, or specific groups of drugs. In other cases, what is relevant is the information about the type of treatment, the patient in general and the physician. Great importance is also given to data concerning drug costs [1,2].

In relation to the different types of information, it is possible provide a brief grid [1,2]:

- Drug-based approach: it can be useful to acquire information about trends in global drug use. However, more detailed data are often required both about drug use (at various levels) and on therapeutic indications (i.e. doses and dosage regimens).
- Problem-based approach: sometimes, instead of analyzing the hows of drug use, identifying the better manner to deal with a specific problem (e.g. hypertension or gastric ulcer) can be useful.
- Patient-based approach: demographic information, as well as information regarding other characteristics of the patients can be often useful. For example, this type of information is important in order to evaluate the likelihood of severe adverse effects correlated to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), or whether the drug is being used in patients belonging to a age group different from that in which the clinical trials were performed. Moreover, it can help tracing back the co-morbidities of the group of patients taken in account in order to determine treatments (e.g. ACE-inhibitors are the preferred treatment in patients with heart failure) and predict possible adverse effects (e.g. beta-blockers should not be used to treat patients presenting with asthma).
- Prescriber-based approach: prescribers are a key factor within the process that leads to the assessment of drug use. Therefore, the evaluation of all those factors which determine different prescribing behaviors is often essential to shed some light on how and why drugs are prescribed.

2.4 Sources of Drug Utilization Data

The constantly growing interest concerning the proper use of healthcare resources has led to the creation of databases designed to be used specifically within the field of Drug Utilization Research. Such databases are made up of two types of sources: administrative and clinic diagnostic.

These specifically conceived databases are called "automated databases" and are currently widely used as they cover large sizes of population, and the data they contain is readily available and easy to access.

Though, the sources of drug utilization data vary from country to country depending on the level of sophistication of record keeping, data collection, analysis and reporting and the operational considerations of the health care system. Moreover, databases may be international, national or local in scope [2].

2.4.1 Administrative Health Related Database

Health registers were created to meet administrative needs; however, such registers have demonstrated to have the necessary requirements to share and integrate the data they collect. Through the patient identification code is, in fact, possible to device the connections needed to create a population database. This, in turn, allows the formation, for each patient, of analytical and chronological profiles containing data about the employed treatments, the consumed resources, and the manner in which patients have used the allocated resourced.

These databases, which are set up and constantly updated by regional or local health authorities, include [1,2]:

- Demographic Databases: this is an inhabitant registry where the GP chosen by each subject is recorded. It stores information on residents who receive NHS assistance, including birth date, sex, district of residence, and GP code and information on GPs, such as their birth date, sex, and number of patients.
- Pharmacy Databases: this kind of archive collects all the information concerning data on drug prescriptions reimbursed by the NHS, including patient's anonymous unique code, prescriber's anonymous unique code, prescription date,

dispensation date, Anatomical Therapeutic Chemical (ATC) classification, marketing authorization code (AIC), number of Defined Daily Doses (DDD), number of boxes, and cost for NHS.

- Hospital Discharge Database. This kind of archive is conceived to collect all the hospitalization records and therefore is made up of all hospital discharge diagnoses (codified according to International Classification of Disease (ICD9 or ICD10)). Such kind of database contains also some other administrative and clinical information including patients' personal identification code, admission and discharge date, main diagnosis, co-morbidity data, outpatient status (i.e. discharged, transferred or deceased), length of hospital stay, assigned Diagnosis-Related Group (DRG), and costs.

When a patient goes to a pharmacy and gets a drug dispensed or if a patient goes to a hospital or to a physician for medical care, information about the type of service provided and the associated cost are registered for reimbursement by National Health System/insurance. The presence of unique patient and prescriber identifiers allows to link pharmaceutical data to information on patients and GPs (e.g. age, sex, number of patients) which are originally stored in separate databases. These more extensive data on patients and prescribers are necessary to analyze drug utilization patterns and to assess the appropriateness of drug use and prescribing. (Figure 3).

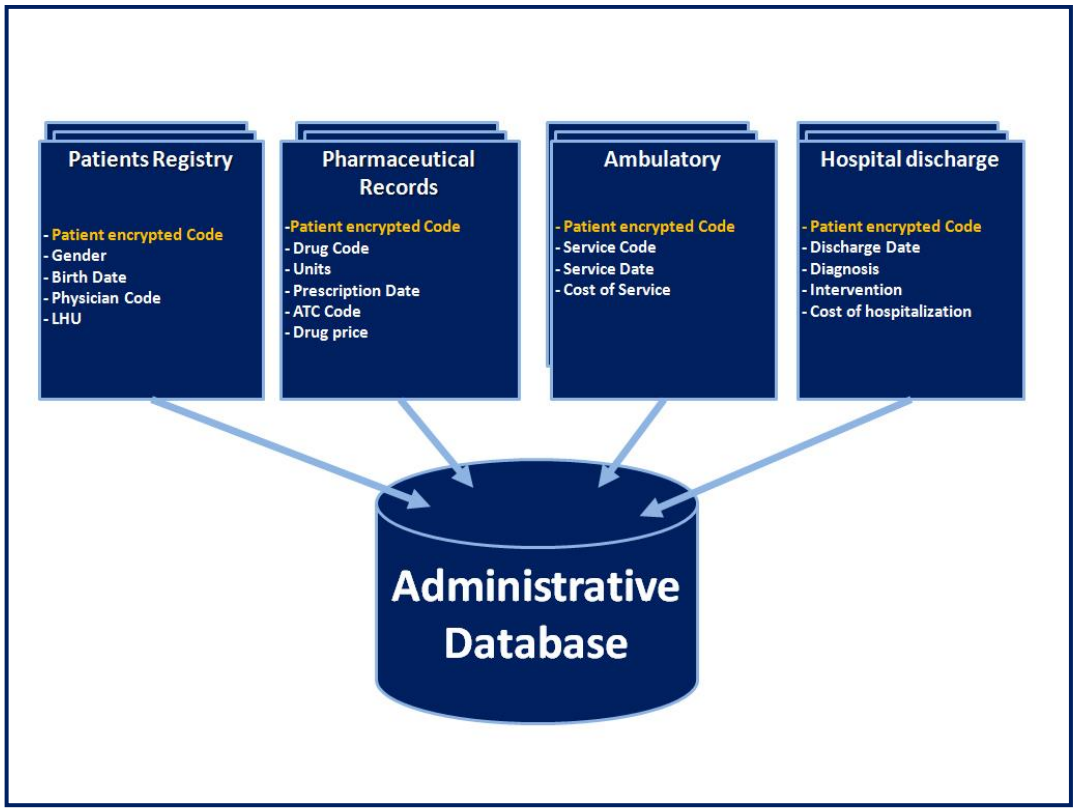

Figure 3: Administrative Database

2.4.1.1 Advantages

Automated databases have proved to have several important advantages, among which providing a very large sample size is the main one. These databases are, in addition, relatively inexpensive to use, especially considering the large sample size they provide. In fact, researchers, by using these data systems do not incur in the considerable cost of data collection, other than for those subsets of the populations for whom medical records are abstracted and/or interviews are conducted. Moreover, these databases are particularly reliable as they are simply population-based, and include outpatient drugs and diseases, therefore in this sense, they cannot be biased. Another advantage is that these databases scope and capabilities can be expanded by linking them to other electronic databases such as death records, maternal-child records, police accident records.

2.4.1.2 Limitations

The main limitation of administrative databases is the lack of diagnostic data. This feature is due to the fact that said databases were originally designed to face only administrative

and financial tasks. It is for those same reasons that they do not include information regarding patient lifestyle (smoking and alcohol consumption for example), symptoms and diagnoses (e.g. hypertension, hypercholesterolemia, diabetes), stage of pathology (absolute cardiovascular disease risk), and all intermediate outcome indicators (blood pressure, cholesterol, glycaemia). This means that the administrative databases need to be integrate with clinical database banks. In this manner it would be possible to access also missing information regarding patient characteristics, delineation of the interventions, assessments of the outcomes.

2.4.2 Clinic-Diagnostic Databases

Clinical databases include information regarding patient lifestyle (smoking and alcohol consumption for example), symptoms and diagnoses (e.g. hypertension, hypercholesterolemia, diabetes), stage of pathology (absolute cardiovascular disease risk), and all intermediate outcome indicators (blood pressure, cholesterol, glycaemia). This kind of tool provide us with the possibility to acquire, in a reliable and continuous manner, information about the characteristics of patients who have access to specific services and the clinical outcomes obtained. In other words, clinical databases offer the opportunity to elaborate studies which pertain specifically to the clinical field.

Apart from their rich potentiality, clinical databases present also with limitations. Such limitations are mainly of administrative nature such as the necessity for the patients to actively collaborate in order to allow for a proper and exhaustive collection of data. Other kinds of limitations can be envisioned in the necessary constant training of the relevant personnel. Furthermore, it is important to mention among the limitations also realization and maintenance costs [2].

2.4.3 Record Linkage

The information contained in the databases described above are sorted into tables, and each of them stands for the relevant real entity it exemplifies. The sorted data acquire a higher explicative value when they get interconnected; such operation is called record linkage. When there are keys shared by several databases, it is possible to extend the linkage operation to the tables belonging to all those said databases. This operation is known as cross database record linkage.

By linking several tables according to the “patient code” key, it is possible to trace the position of each patient within the administrative database. Subsequently, provided one has access to keys shared by multiple databases, it is possible to extent the record linkage operation to tables pertaining to different databases, obtaining, in this manner and as shown in figure 4, a database record linkage process.

In conclusion, the strategy to create an information system which makes itself accessible to Drug Utilization Research can be either gradual that is to say by creating first the administrative database and then the clinical one, or it can be partial as there is the creation of only one of the two types of databases. Whichever is the strategy chosen, it is necessary for it: (i) to be consistent with the set goals, (ii) to be able to integrate different information sources, and (iii) to share the collected data [2].

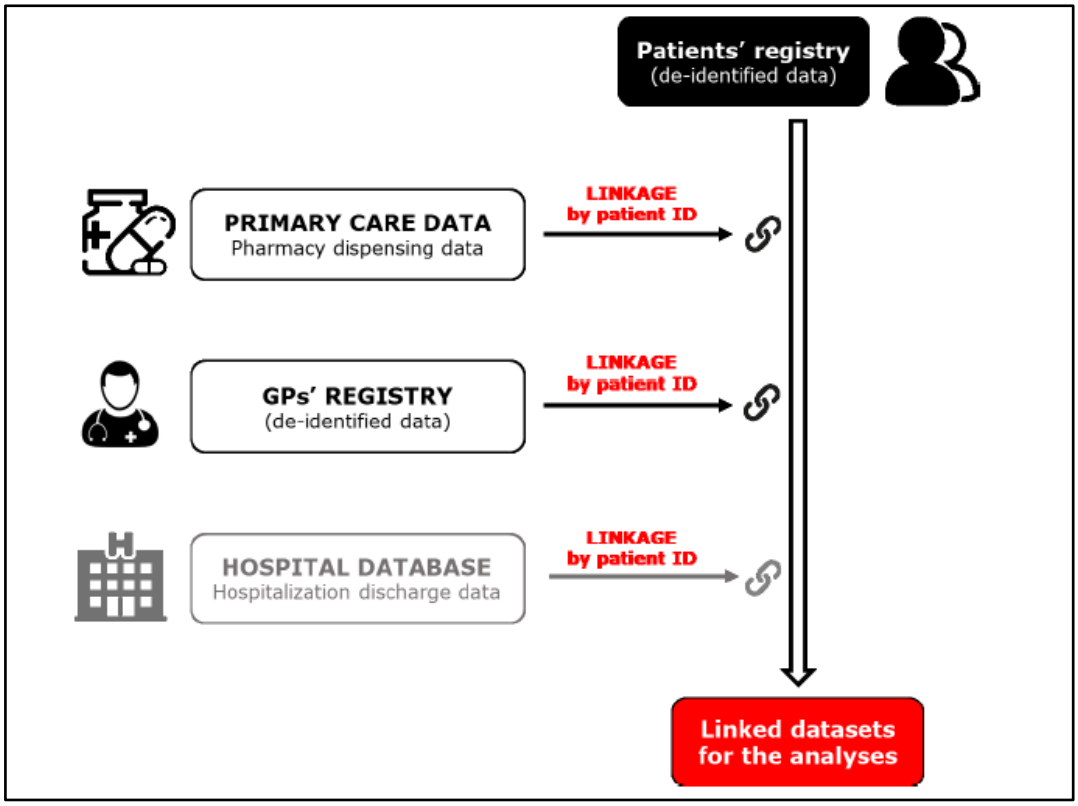

Figure 4 - Record linkage procedure.

2.5 Drug-Utilization Measurements: The ATC/DDD methodology

By drawing on two studies, a European and an international one, in 1996, World Health Organization (WHO) developed the ATC/DDD system—where ATC stands for Anatomical Therapeutic Chemical. The main purpose of the ATC classification is to work as a tool for presenting drug utilization statistics. The WHO recommends using it form the pertinent international comparisons [1,3].

Said classification system divides the considered drugs into different groups according to the organ on which they act and according to their chemical, pharmacological and therapeutic properties.

The drugs are divided into 14 main groups (first level), with two therapeutic/pharmacological subgroups (second and third levels). The fourth level is a therapeutic/pharmacological/chemical subgroup and the fifth level is the chemical substance (Table 2) [4].

Table 2. ATC main groups

ATC I Level	DESCRIPTION
A	ALIMENTARY TRACT AND METABOLISM
B	BLOOD AND BLOOD FORMING ORGANS
C	CARDIOVASCULAR SYSTEM
D	DERMATOLOGICALS
G	GENITO URINARY SYSTEM AND SEX HORMONES
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINES
J	ANTIINFECTIVES FOR SYSTEMIC USE
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
M	MUSKOLO-SKELETAL SYSTEM
N	NERVOUS SYSTEM
P	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS
R	RESPIRATORY SYSTEM
S	SENSORY ORGANS
V	VARIOUS

The complete classification of Amoxicillin (see Table 3) illustrates the structure of the code.

Table 3: Structure of ATC code

ATC Level	DESCRIPTION
J	ANTIINFECTIVES FOR SYSTEMIC USE (1st level, anatomical main group)
J01	ANTIBACTERIALS FOR SYSTEMIC USE (2nd level, therapeutic subgroup)
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS (3rd level, pharmacological subgroup)
J01CA	PENICILLINS WITH EXTENDED SPECTRUM (4th level, chemical subgroup)
J01CA04	AMOXICILLIN (5th level, chemical substance)

A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses, for example prednisolone is given several ATC codes because of the different uses of the different formulations.

The Defined Daily Dose (DDD) is defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. The DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose. The DDD is often a compromise based on a review of the available information about doses used in various countries. Drug utilization figures should ideally be presented as numbers of DDDs per 1000 inhabitants per day or, when drug use by inpatients is considered, as DDDs per 100 bed-days [5,6].

Each chemical substance has to be connected to the appropriate ATC code and DDD. The ATC/DDD system is of paramount importance to drug utilization research in order to improve quality of drug use. The DDD is a stable drug utilization metric that enables comparisons of drug consumption between healthcare systems, regions and countries and therefore makes it possible to examine trends in drug use over time and in different

contexts. The European WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway, is responsible for coordinating the use of the ATC/DDD methodology (http://www.whocc.no) [1].

2.6 Drug Utilization Indexes

- DDD/1000 inhabitants/ day

  In the analysis of the drug utilization figures has been adopted an international unit of measurement known as Defined Daily Dose (DDD). Given an active substance, DDD is the daily maintenance dose adults patient need to assume in conformity to their main therapeutic indication. DDDs per 1000 inhabitants per day is the manner in which drug utilization figures can be better analyzed. This measurement provides with the opportunity to compare utilization patterns over different geographical areas and/or healthcare districts [1,7].

- DDDs per 100 bed-days

  When it comes to the analysis of drug utilization within hospital, the unit of measurement applied is DDDs per 100 bed-days. Such unit of measurement can only be applied once the analysis focus on drug utilization within the hospital environment. For example, a figure of 70 DDD/100-bed-days provides an estimation of the therapeutic intensity and suggests that 70% of inpatients could receive a DDD of that given drug daily. This unit of measurement is particularly useful when it comes to the comparative analysis of hospitals [1,7].

- Prescribed Daily Dose (PDD)

  Because DDD is a unit of measurement, it is not necessarily equal either to the daily average doses actually prescribed, or to the one actually consumed over a day. In order to overcome DDD's limitations, the Prescribed Daily Dose (PDD) has been adopted. The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. PDD is a statistical indicator which can be useful in order to highlight prescribing behaviors related to one of more drugs within different geographical areas and different consecutive temporal spans. The PDD can be determined from studies of prescriptions or medical or pharmacy records. It is important to relate the PDD to

the diagnosis on which the dosage is based. The PDD will give the average daily amount of a drug that is actually prescribed.

For drugs where the recommended dosage differs from one indication to another (e.g. the antipsychotics), it is important to link the diagnosis to the PDD.

Moreover, in order to obtain a proper interpretation of PDD, it is essential to take into account also pharmacoepidemiological information (e.g. sex, age and whether we are dealing with a mono or a combined therapy) [1,7].

- Prevalence of Polypharmacy

  Polypharmacy is defined as the taking of five or more types of medication. It is the best option if it meets a therapeutic need and is supported by scientific guidelines. But it is inappropriate when it is not supported by any clinical evidence and when it does not take into account possible drug interactions [8]. In this thesis for the evaluation of prescribing practice, prevalence of polypharmacy was evaluated as percentage of patients with 1-4 drugs, 5-9 drugs, and ≥10 drugs during 1-year period, for each year considered (2014-2016). In details, the number of drugs in each quarter was calculated, and the highest number of drugs dispensed in a single quarter was used to define polypharmacy over the 1-year period [9].

- Prevalence of Drug use

  Prevalence of Drug use is given by that portion of individuals in a given population who, over a year, have been exposed to drug utilization. It is possible to define it as the ratio between the number of subjects within a certain population who have received at least a drug prescription (users), and the totality of said population over a specific period of time.

  In what follows, it has been calculated the prevalence rete for 100 potential users discriminated according to the different therapeutic categories. With the aim to compare the prevalence of use in a non-homogeneous population, that is in a population differing in age, it has been calculated the prevalence of use standardized with direct method [1,7].

$$\text{Prevalence rate} = \frac{\text{Number of Users}}{\text{Population}} \times 100 \text{ (o x 1000)}$$

Number of Users: number of users belonging to the specific drug category taken into account.

Population: the totality of the population taken in account.

- Standardized Prevalence Rate

  In this thesis, in order to compare the prevalence rates among populations which present with nonhomogeneous age structure, we have adopted the direct method and have calculated the rates standardized for age and distinguished by sex.

2.7 Study Drugs

In this thesis has been evaluated some of the most commonly used drug classes for chronic conditions: (ACE-inhibitors [C09AA, C09B], angiotensin receptor blockers [C09CA, C09D], anti-asthmatics [R03], antibiotics [J01], proton pump inhibitors [A02BC, A02BD], selective serotonin reuptake inhibitors [N06AB], serotonin-norepinephrine reuptake inhibitor [N06AX], and statins [C10AA]).

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Chapter 3

Thesis Objectives

3.1 Thesis Objectives

The present thesis describes the results of the first phase of the national collaborative project (EDU.RE.DRUG Project) founded by Italian Medicine Agency (AIFA), which is currently in progress.

The EDU.RE.DRUG Project (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients) aim to deeply investigate the prescribing practice among general practitioners (GPs) and the appropriate drug use by their patients in two Italian regions.

In details, the project consisted of three phases, with the objectives of:

- characterizing inappropriate prescription and drug use profiles and highlighting the most frequent events of inappropriateness (phase 1);
- implementing tailored interventions for GPs and their patients focused on this critical issue (phase 2);
- comparing the prescriptive behavior of GPs pre- and post-interventions, in order to define whether an effective change in prescribing has occurred (phase 3).

In Accordance with the first phase, the main objectives of the thesis project were:

i. to develop indicators of inappropriate prescribing suitable to Italian context;
ii. to retrospectively assess the prevalence of drug use of selected drug classes, with a particular focus on older patients;
iii. to compare two different geographical areas in Italy;
iv. to investigate the influence of socioeconomic and sociodemographic variables on prevalence of drug use of selected drug categories.

The results are showed in the papers reported in the following chapters.

Chapter 4

Results

4.1 A PRAGMATIC CONTROLLED TRIAL TO IMPROVE THE APPROPRIATE PRESCRIPTION OF DRUGS IN ADULT OUTPATIENTS: DESIGN AND RATIONALE OF THE EDU.RE.DRUG STUDY

This paper is under review by the journal Primary Health Care Research & Development.

Abstract

Introduction: Pharmacological intervention is an essential step in health promotion. However, drugs are often inappropriately used. It is necessary for countries to implement strategies to improve the rational use of drugs, including independent information for healthcare professionals and the public, which must be supported by well-trained staff. The primary objectives of the EDU.RE.DRUG (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients) study are the retrospective evaluation of rates of appropriate prescribing indicators (APIs) and the assessment of the effectiveness of informative and/or educational interventions addressed to General Practitioners (GPs) and their patients, aimed at improving prescribing quality and promoting proper drug use.

Methods and analysis: This is a prospective, multicentre, open-label, parallel-arm, controlled, pragmatic trial directed to GPs and their patients in two Italian regions (Campania and Lombardy). The study data are retrieved from administrative databases (Demographic, Pharmacy-refill, and Hospitalization databases) containing healthcare information of all beneficiaries of the NHS in the Local Health Units (LHUs) involved. According to LHU, the GPs/patients will be assigned to one of the following four intervention arms: A) intervention on GPs and patients; B) intervention on GPs; C) intervention on patients; D) no intervention (control). The intervention designed for GPs consists of reports regarding the status of their patients according to the APIs determined at baseline, and in two on-line Continuous Medical Education courses. The intervention designed for patients consists in flyers and posters distributed in GPs ambulatories and community pharmacies, focusing on correct drug use.

A set of indicators (such as potential drug-drug interactions, unnecessary duplicate prescriptions, inappropriate prescriptions in the older people), adapted to the Italian

setting, has been defined to determine inappropriate prescription at baseline and after the intervention phase. The primary outcome was a composite API.

Ethics and dissemination: The study was approved by the Ethics Committee of the University of Milan on 7th June 2017 (code 15/17). The investigators will communicate trial results to stakeholders, collaborators and participants via appropriate presentations and publications.

Registration details: NCT04030468. EudraCT number 2017-002622-21

4.1.1 Rationale

Medicines are meant to improve health of patients; they do have, however, the potential to harm human subjects. The process of drug prescribing is therefore a fundamental component of the care of patients [1]. Appropriateness of prescribing is a balance of pharmacological rationality, the need of individual patients and economic aspects. It occurs when patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirement, for an adequate time period and at the lowest cost to them and their community [1]. It can be defined as 'the outcome of the process of decision making that maximizes net individual health gains within the society's available resources' [2].

Optimization of drug prescribing has become an important public health issue worldwide [3,4,5]. That is because evidence indicates high prevalence of inappropriate prescribing of medicines, especially in older people, which are characterized by chronic conditions and multimorbidity, leading to an increased use of drugs (polypharmacy). Inappropriate prescribing occurs, for example, when the physician prescribes an incorrect dosage and/or duration of treatment, drugs with significant drug–drug and drug–disease interactions or fails to prescribe a beneficial drugs [6]. Notably, correct prescribing does not guarantee that drugs are used properly. Non-compliance to doctors' prescriptions is very common [7]. Therefore, patient involvement in the decision process could promote a conscious attitude, in compliance with the instructions received.

Inappropriate prescribing is associated with increased morbidity and mortality, increased cost of treatment and decreased quality of life [8]. World Health Organization data show that more than 50% of all drugs are inappropriately prescribed or dispensed, and 50% of

patients uses them improperly [1]. Nearly 8% of medical examinations of patients with more than 65 years lead to the prescription of a Potentially Inappropriate Medication (PIM) [9]. Another European survey [10] showed that 20% of older patients used at least 1 inappropriate medication, with substantial differences between Eastern Europe (41% in the Czech Republic) and Western Europe (range from 6% in Denmark to 27% in Italy). Using different definitions in various settings, observational studies showed that 21-40% of patients have received at least one inappropriate medication [11]. In two cohort studies in Italy, 18% of elderly outpatients had one or more PIM prescriptions [12], and a substantial proportion of subjects was exposed to prescriptions at risk of potential drug-drug interaction (pDDI) [13].

To limit the consequences of prescription of PIMs, improving rational use of drugs is a major focus to enhance quality and safety of care. It is thus necessary to implement a series of strategies, including information for healthcare professionals and the public from independent sources, which must be supported by well-trained staff [5]. Different strategies have been developed and validated in this context [1]. Of note, interventions that included in-depth and updated education on drug therapy to physicians led to significant improvements in their performance/behaviour. Training and feedback control of prescribing should be associated with availability of on-line references for immediate identification and verification of potential erroneous prescribing [14,15]. More generally, a good drug literacy allows more realistic perceptions and expectations, a shared medical decision making, and a responsible behaviour in using drugs. This approach seems promising and can be achieved through targeted campaigns of public education.

In this context, to measure inappropriateness is necessary to quantify the problem at baseline, to identify areas of concern which might require further review or development and evaluate the effect of interventions [16]. Moreover, the measure of inappropriateness in prescribing practice allows the physician to have a measure of his/her own performance, representing a point of comparison with colleagues within the same geographical area [17] and a guide to intervene on critical situations of individual patients, besides having a general potential to raise physicians' awareness about the topic. Given that prescribing is a mix of evidence-base for intervention with the drug,

diagnosis, clinical judgement and a certain element of clinical intuition, identifying objective measures of inappropriateness is extremely challenging [18]. Though, it is not surprising that the proposed indicators are umpteen, with different characteristics and potentials depending on the object of the measure and the context of application and need to be updated and contextualized. Among them, the explicit criteria [18,19,20] are clearly defined statements, which highlight PIMs in particular clinical circumstances. They are mainly based on trial evidence, expert opinion, and consensus techniques [21]. The development of a simple, inexpensive and time-efficient set of indicators which can be used routinely to evaluate prescribing practice and to assess the effectiveness of optimization strategies is therefore warranted.

In this context, the EDU.RE.DRUG (*Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients*) study has been designed to deeply investigate the prescribing practice among general practitioners (GPs) and the correct use of drugs by patients in two Italian regions and to assess the effectiveness of informative and/or educational interventions addressed to GPs and their patients, to improve prescribing quality and to promote proper drug use.

4.1.2 METHODS AND ANALYSIS

Study design

EDU.RE.DRUG is a prospective, pragmatic, multicentre, open-label, parallel-arm and controlled trial, started in April 2017.

Study setting and population

The clinical setting of the study is the general practice. The study population is composed by all GPs and all their adult patients aged ≥40 years from eight Local Healthcare Units (LHUs) in two Italian regions.

The LHU involved were: four in Campania region, in the southern part of Italy, and four in Lombardy region, in the north of Italy (Figure 1).

Data source and collection

In Italy, National Health Service (NHS) provides universal coverage largely free of charge at the point of delivery. The Regions are responsible for organising and delivering health care through the LHUs. The study data are retrieved from administrative databases containing healthcare data of all beneficiaries of the NHS in the LHUs involved: in 2017, about 2,800,000 beneficiaries for the four LHUs in Lombardy (Bergamo, Lecco, Val Padana-Mantova, Monza-Brianza) and 3,300,000 beneficiaries for the four LHUs in Campania (Avellino, Caserta, Napoli 1 Centro, Napoli 2 Nord) (ISTAT). These databases, set up and constantly updated by regional or local health authorities, are:

- Demographic Databases, containing data on residents who receive NHS assistance (birth date and sex), and on GPs (birth date, sex, number of patients).
- Pharmacy-refill Databases, containing data on drug prescriptions reimbursable by the NHS, including prescription date, dispensation date, the Anatomical Therapeutic Chemical (ATC) classification, marketing authorization code (AIC), number of boxes, and cost for NHS.
- Hospitalization Databases, containing data on hospital discharge at public or private hospitals of the Regions, including the admission date, the primary and secondary diagnoses, and the date of discharge.

Compliance with national and European laws on personal data is guaranteed by LHUs through the generation of unique anonymous codes for each patient and each prescriber, providing guarantees in respect of the privacy of every citizen.

Data used in this project cover a time period ranging between the years 2014-2017 (baseline) and 2018-2019 (follow-up).

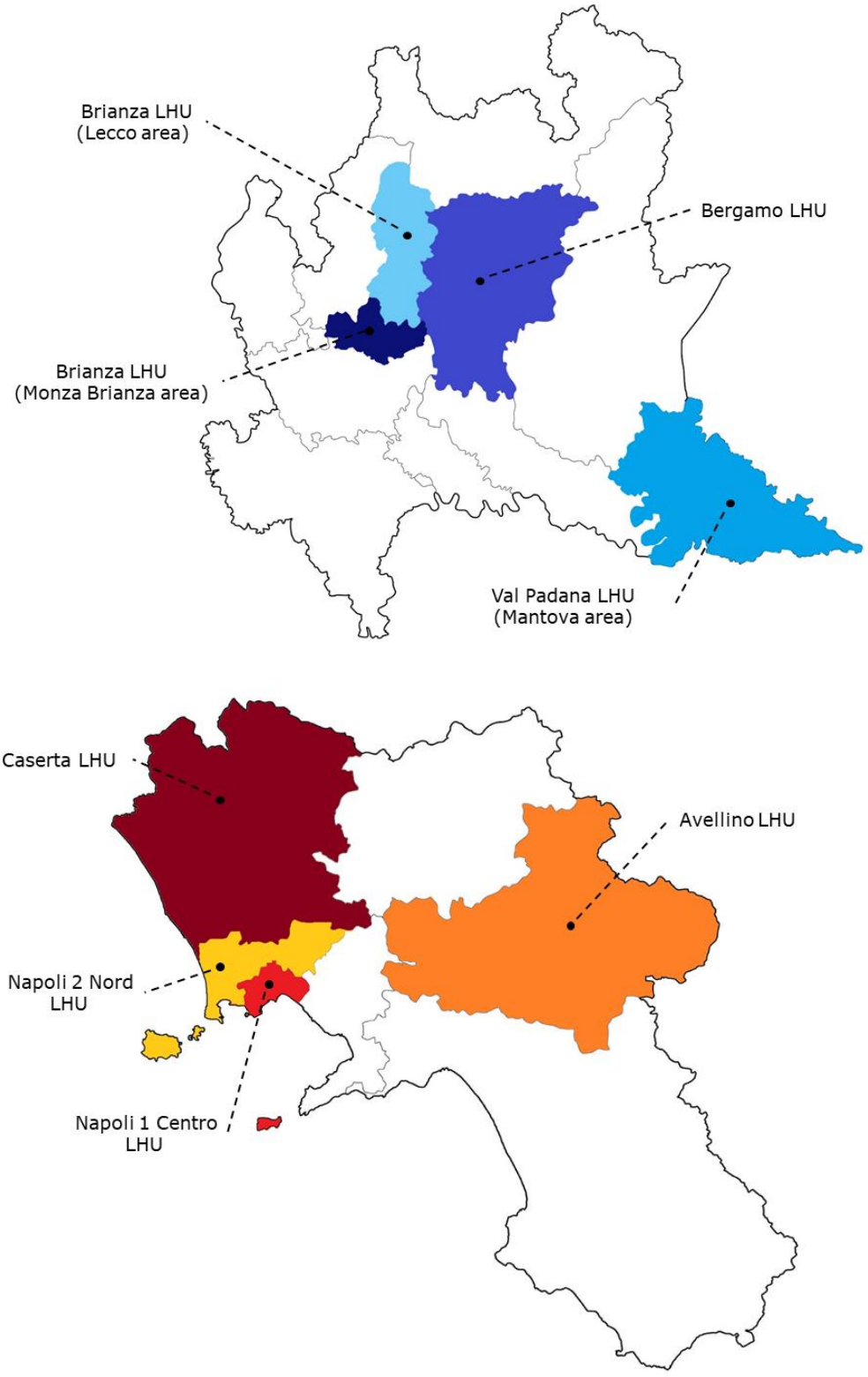

Figure 1 – Geographical maps showing LHUs involved in the EDU.RE.DRUG project

Definition of performance indicators

For the evaluation of prescribing practice, patients in polytherapy were defined as having 5-9 drugs or ≥10 single drugs prescribed in 1-year period.

Moreover, researchers selected some of the most commonly used drug classes (ACE-inhibitors [C09AA], angiotensin receptor blockers [C09CA], anti-asthmatics [R03], antibiotics [J01], proton pump inhibitors [A02BC], selective serotonin reuptake inhibitors [N06AB], serotonin-norepinephrine reuptake inhibitor [N06AX], and statins [C10AA]) to be described as percentage of patients on each treatment and as amount of defined daily doses (DDD) prescribed per 1000 inhabitants/die.

Definition of inappropriate prescribing indicators (APIs)

The research team reviewed the scientific literature on the topic and identified a set of indicators that had to:

- be explicit indicators, that require each prescription to be compared with a set of pre-defined standards, within the context of the individual patient;
- be applicable and valid regardless of the patient's clinical characteristics;
- include only drugs available on Italian market and reimbursed by Italian NHS (which are therefore traced into administrative databases).

Prescription of pDDIs has been defined based on *MediRisk software*, developed by Medilogy group, based on INXBASE by Medbase, a Finnish company formed by experts in pharmacotherapy, which produces medical decision support databases to safeguard effective and safe use of drugs. INXBASE is a drug-drug interaction database containing short, and concise evidence based information concerning consequences of and recommendations for more than 20.000 drug interactions [22]. Interaction are classified according to clinical significance (from minor “A” to contraindicated “D”) and documentation level (from ‘evidence from in vitro studies’ “0” to ‘evidence from randomised clinical trials, systematic reviews, or meta-analyses’ “4”). In this project, two drugs were considered potentially interacting if their coverage periods (calculated since dispensation date and based on DDDs) overlapped of at least 1 day. Only pDDIs with major “C” clinical significance excluded those with level of documentation “0”, and contraindicated “D” clinical significance were considered.

Therapeutic duplicates (TDs) have been defined as two or more prescribed drugs from the same chemical subgroup (same ATC code at the fourth level but different ATC code at the fifth level) [23] with at most 3 days between the two dispensation dates.

Only in the older population (aged ≥65 years), we defined the ERD-list (EDU.RE.DRUG list,) developed based on the updated Beers criteria [24], the STOPP&START criteria [25] and the EU-(7)-PIM list [26] (see Table 1). The three lists were merged and adapted to Italian setting by selecting only drugs available on the Italian market and reimbursed by Italian NHS. Moreover, the selection was limited to drugs always to be avoided in older patients, excluding drugs that should be used with caution or avoided in certain patients with certain diseases or conditions, as these circumstances cannot be evaluated through administrative databases.

The APIs in older people comprised also high scores (≥3) of the Anticholinergic Cognitive Burden (ACB) scale [27] and of the Sedative Load (SL) score [28] from the published lists, again selecting only drugs available on the Italian market and reimbursed by Italian NHS.

Definition of appropriate use indicator

For each medication, adherence rate will be assessed for the following chronic therapies [ATC]:

- antidiabetics [A10B]
- anti-hypertensive drugs [C02, C03, C07, C08, C09]
- lipid-lowering drugs [C10A]
- anti-osteoporosis drug [M05BA, M05B]

Adherence will be measured through the proportion of days covered (PDC) calculation [29]. PDC is defines as the number of days covered by medication divided by the total number of days in follow-up. For each prescription, the coverage will be calculated as total amount of drug divided by the specific DDD. PDC ranges from 0 to 1, with 1 corresponding to 100% medication adherence.

4.1.3 Study Intervention

The GPs and their patients have been assigned to one of the following arms (**figure 2**):

A: intervention on GPs and patients (LHUs of Napoli 2 Nord and Brianza-Lecco);

B: intervention on GPs (LHUs of Napoli 1 Centro and Bergamo);

C: intervention on patients (LHUs of Avellino and Val Padana-Mantova);

D: control group (LHUs of Caserta and Brianza-Monza Brianza).

The intervention addressing GPs consists in:

• feedback reports, describing inappropriate prescription status (prevalence of each pre-defined indicator of performance and of inappropriate prescribing, as listed above, evaluated in 2016) of their patients in comparison to median levels of each own LHU.

• two free on-line Continuous Medical Education (CME) courses about rational prescribing and appropriateness measurement. The first course was focused on the presentation of the project and on general aspects concerning the inappropriate prescribing in general practice and the categories of the most vulnerable patients, such as the elderly or poly-treated patients, with the presentation of clinical cases of possible inappropriate prescriptions. The second course concerned the measurement of APIs, the guided reading of reports, and recommendations for prescribing to the complex patient and for medication review.

Notably, participation to CME courses were not mandatory, as well as both the courses and the reports received at baseline would not necessarily lead to changes in GPs' prescriptive behaviour.

The intervention designed for patients consists in flyers and posters distributed in GPs' ambulatories and community pharmacies, focusing on correct drug use (efficacy/safety, adherence to GP indications, self-medication).

Time frame dedicated to the sending of feedback reports and to delivery of educational material was January-March 2018.

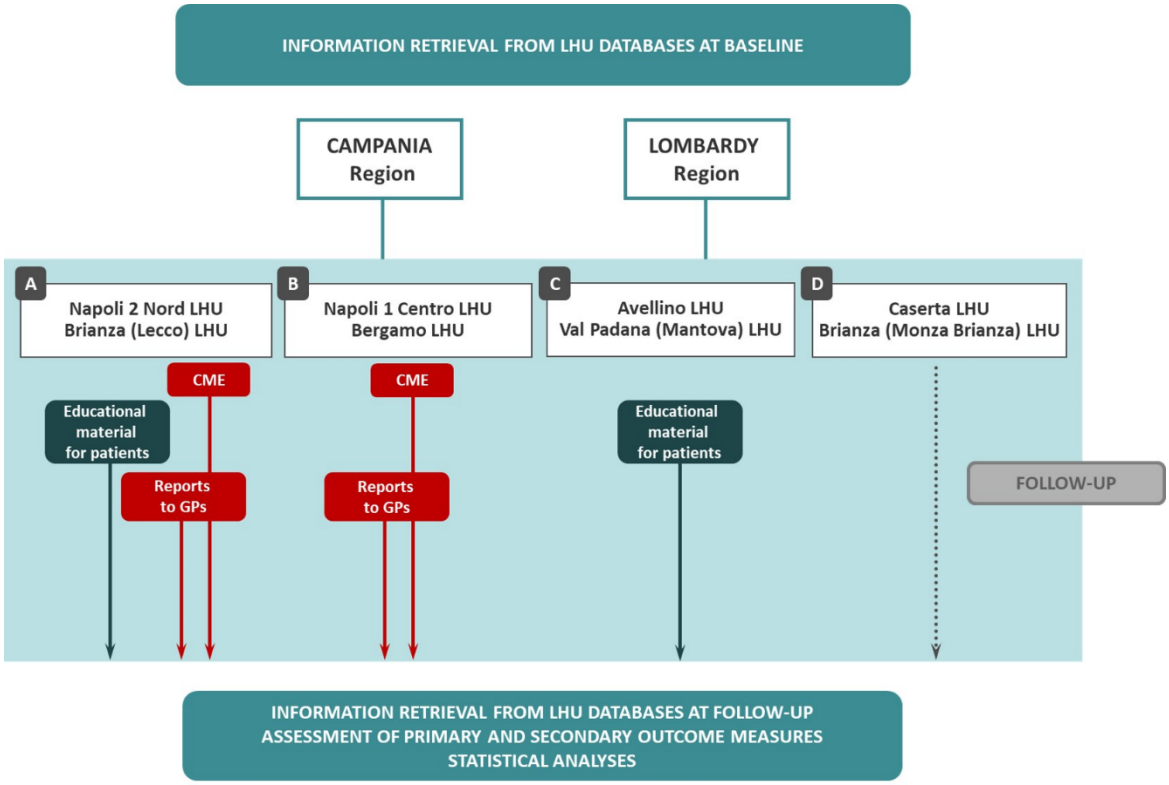

Figure 2. Flow chart of the study and description of the four intervention groups

4.1.4 Study Outcome

The study outcome was a composite outcome of API of ERD list, pDDIs, and TDs. The primary end point was therefore defined as the variation of the median prevalence of the composite API after the intervention in the groups with the intervention on GPs (A+B) compare to baseline. The prevalence will be calculated at GP's individual level, as the ratio between subjects with the composite API and total GP's over-40-years subjects.

The secondary end points comprised the (1) the variation of the median prevalence of each single API and performance indicator after the intervention, (2) evaluation of difference in efficacy among different types of intervention, (3) identification of predictors of poor prescription appropriateness, (4) health technology assessment (HTA) of intervention implemented, (5) level of GP satisfaction assessed through an ad hoc web-based questionnaire.

4.1.5 Sample Size and Statistical Analysis

The study design is a non-randomized, open-label, cluster intervention. All experimental units (GPs and/or patients) in each cluster receive the scheduled treatment. Assuming

that at least 40% of resident in the involved LHUs of the two Region (1,1 million in Lombardy and 1,3 million in Campania) receive at least one prescription during one-year period, considering a type I error of 5%, a power of 80% would allow to detect, at LHU level, a difference in the reduction of inappropriateness prevalence of at least 5% between intervention and control group.

1. Analysis of indicators

The indicators of performance and of inappropriate prescribing will be determined at baseline and after the intervention, by measuring the explicit indicators defined above within each GP on 1-year base. The unit of analysis will be the patient or his/her prescriptions, depending on the indicator, and GP will be identified as the clustering factor within each indicator will be examined.

The performance indicators will be evaluated separately on the subpopulations of 40-64 years and ≥65 years. Polytherapy will be evaluated as the percentage of patients with 5-9 drugs or with ≥10 drugs on total GP's subjects in each age class. Prescription of selected drug classes (as listed above) will be evaluated as percentage of patients on each treatment on total GP's subjects in each age class and as amount of DDD prescribed per 1000 inhabitants/die in each age class.

Regarding APIs, pDDIs and TDs will be evaluated on subjects ≥40 years old, while drugs in EDR list, ACB scale, and the SL score will be evaluated on subjects ≥65 years old. For each API, the percentage of patients with at least one prescription meeting the API criteria on total GP's subjects in the specific age class will be determined.

Adherence will be calculated by selecting all patients with a first prescription for the medication of interest within 1-year period. Patients will be required not to have prior prescription of that drug in the year before the index date (defined as the date of the first prescription fill in the period for the selected therapy), to select only incident users. Patients will be also required to have 1 year of enrolment after the index date to allow complete adherence evaluation at 1-year of follow-up.

2. Identification of determinants of inappropriate prescribing

A multilevel model will be considered to identify the association between several variables (related to patients, physicians or LHUs) and the composite API. The model will

allow to take into account the hierarchical structure of the data, with patients nested within physicians and physicians nested within LHU. The considered potential determinants will be measured at the patient level (age, sex, clinical profile using the Chronic Disease Score [30], and number of prescriptions received), at the physician level (age, sex, number of patients assisted), and at the LHU level (inhabitants, population density, number of GPs per 1,000 habitants).

3. Interventions effectiveness (pre-post analysis)

The primary and secondary outcomes will be evaluated in a 6 month-period before intervention (pre-intervention phase, October 2016-March 2017) and in a 6 month-period after the intervention (post-intervention phase, October 2018-March 2019). Depending on LHU and on type of data, administrative data usually require 3-6 months to be processed and made available. The difference (Δ pre-post) in the outcomes will be estimate separately for each LHU. Appropriate contrasts to compare Δ in the different groups of intervention and the corresponding confidence intervals will be estimated. The standard error for each contrast will be assessed by an appropriate normality assumption or, if this assumption is not plausible, by other methods such as the nonparametric bootstrap.

Since the study is not randomized, to consider the potential confounding due to physicians' and patient's characteristics, two additional analyses will be made at physician and patient level. Firstly, the Δ of each physician will be evaluated. A linear mixed regression model will be applied including the Δ as response variable and physicians and the LHU characteristics as well as the type of intervention as covariates. To take into account that physicians are clustered within LHU, a random effect for LHU will be considered. A generalized linear mixed regression model considering post-intervention prevalence of composite API as response variable will be estimated. In this model, patient-, physician- or LHU-level covariates will be included. Two random effects will be considered in the model: one for the physician, and one for the LHU. To take into account the baseline probability of being inappropriately treated, we will include in the model the prevalence of composite API for the patient's physician evaluated before the intervention.

To evaluate the effects of interventions in terms of the subsequent mortality risk, all patients receiving at least one prescription during the post phase will be selected and followed for one year. The vital status of each patient will be recorded during the year. A Cox proportional hazard regression model will be applied to evaluate the association between the intervention and mortality. The response variable will be the time to death and the model will include different covariates measured at the patient-, physician-, and LHU-level, the type of intervention, and the prevalence of composite API for the physician assigned to each patient as evaluated before the intervention.

4 Health Technology Assessment

A HTA of the intervention will be performed by using the following typical approaches (Husereau et al., 2013):

- systematic review of the literature, in order to define the status of our interventions
- efficacy and effectiveness
- social, legal, political, and ethical impacts
- cost and economic evaluation

Total expenditure for all PIMs will be calculate. Costing information may consist of actual costs, prices or tariffs, as appropriate. The cost analysis will be performed from the third-party payer (NHS) perspective. Costs will be calculated as the Net Ingredient Cost (NIC) of the dispensed drug and the total expenditure, which will include the pharmacist dispensing fee where appropriate.

5 Evaluation of GPs satisfaction

An ad hoc questionnaire will be administrated to GPs in anonymous web form, in order to detect their satisfaction about the intervention. It will be structured into questions focused on:

1. opinion on the utility/efficacy of CME courses
2. opinion on the utility/efficacy of feedback prescription reports
3. impact on professional practice

The frequency of degree of satisfaction will be determined for each response.

4.1.6 Patient and Public Involvement

This research will be done without patient involvement. Patients will be not invited to comment on the study design and not consulted to develop patient relevant outcomes. Patients will be not invited to contribute to the writing or editing of this document for readability or accuracy.

4.1.7 Strengths and limitations of this study

- This trial addresses a problem of great epidemiological, clinical, and socio-economic impact: the inappropriate prescription of drugs to adult patients in the outpatient setting.
- The definition of prescribing inappropriateness indicators adapted to the Italian context provides a useful tool both for the physician in the daily prescription activity and for the Local Health Units for the activities of evaluation and monitoring of the prescriptive performance.
- The use of existing data for baseline and outcome evaluation is a powerful and relative low-cost research tool that can be easily implemented on a larger scale. Despite this potential of prescription database analysis, a real measure of the appropriateness of prescriptions should be patient-based and evaluated by specialized personnel taking into consideration the characteristics of the patient.
- Since prescribing is uniquely managed by the doctor and is based on his/her final judgment, any intervention cannot impose decisions, but only educate the doctor and support his/her activity; as a consequence, the integration of improved decision-making processes into the daily prescribing practice requires multidimensional interventions maintained over time.

4.1.8 Expected Results and Impact

In Italy there are no official policy statements or regulatory guidelines on management of inappropriate prescribing. However, there is evidence of a growing awareness of the problem [31,32]. Relatively few trials have focused on interventions to improve appropriate prescribing in primary care. Importantly, in Italy GPs have a key role in drug prescribing, in summarizing pharmacological recommendations from different

specialists, and in implementing the therapeutic reconciliation after a hospital discharge. Thus, they are the obvious target of an intervention aimed to optimize drug management. This study, conducted through a retrospective evaluation on administrative databases of drug prescriptions and hospitalizations, will allow to explore different patterns of prescribing in real world setting and to analyse the complexity of drug prescription, highlighting possible dangerous prescribing habits.

The definition of indicators to describe inappropriate prescription and identify patients at higher risk of medicine-related problems based on Italian drug-utilization patterns will provide tools specifically tailored to the Italian context, but also adaptable to other national contexts. Moreover, data from EDU.RE.DRUG study will be used to identify predictors of inappropriate prescribing and therapeutic areas most affected by this problem, in order to establish priorities for actions, to focus efforts and optimize the scarce available resources.

4.1.9 Ethics

The protocol has been registered in ClinicalTrials.gov (identifier NCT04030468) and in EU Clinical Trials Register (identifier: EudraCT 2017-002622-21).

The study was approved by the Ethics Committee of the University of Milan on 07 June 2017 (code 15/17).

Procedures aimed at protecting personal data will be implemented in order to safeguard privacy and to prevent the identification of individual data (according to Italian law D.Lgs. n. 196/2003). Anonymized regional administrative data can be used without a specific written informed consent when patient information is collected for healthcare management and healthcare quality evaluation and improvement (according to art. 110 on medical and biomedical and epidemiological research, Legislation Decree 101/2018).

4.1.10 Dissemination

A variety of methods will be used to ensure the maximum visibility for the project and its results. Publication of our study protocol provides an important first step towards this direction. Moreover, the description of the study and the material for patients has been made available on the web site (http://www.sefap.it/web/ms/index.php?idms=11, in Italian language), as well as its main results will be published here.

Similarly, the study results, given their applicability and implications for the general population, will be disseminated in investigator meetings and in articles published in scientific journals.

Table 1. The ERD-list

ATC code	Drug Name	Reason for PIM
A02BC01	Omeprazole (PPI>8 weeks)	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
A02BC02	Pantoprazole (PPI>8 weeks)	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
A02BC03	Lansoprazole (PPI>8 weeks)	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
A02BC04	Rabeprazole (PPI>8 weeks)	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
A02BC05	Esomeprazole (PPI>8 weeks)	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
A10AB01	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB04	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB05	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels
A10AB06	Insulin, sliding scale (without concomitant treatment with basal insulin)	No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels

A10BB01	Glibenclamide	Risk of protracted hypoglycemia
A10BB07	Glipizide	Risk of protracted hypoglycemia
A10BB12	Glimepiride	Risk of protracted hypoglycemia
A10BD02	Glibenclamide	Risk of protracted hypoglycemia
A10BD05	Pioglitazone	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
A10BD06	Glimepiride/pioglitazone	Risk of protracted hypoglycemia/see pioglitazone
A10BD09	Pioglitazone	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
A10BF01	Acarbose	No proven efficacy
A10BG03	Pioglitazone	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
B01AA07	Acenocoumarol	Risk of bleeding, especially in people with difficult control of INR value
B01AC05	Ticlopidine	Risk of altered blood counts

B01AC56	Esomeprazole (PPI>8 weeks)	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
C01AA08	Metildigoxin	Elevated glycoside sensitivity in older adults (women>men); risk of intoxication
C01BA03	Disopyramide	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
C01BC03	Propafenone	High risk of drug interactions. Data suggest that for most older adults' rate control yields better balance of benefits and harms than rhythm control
C01BC04	Flecainide	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
C02AB01	Methyldopa	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)
C02AC05	Moxonidine	Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment)
C08CA05	Nifedipine	Increased risk of hypotension; myocardial infarction; increased mortality
G02CB03	Cabergoline	CNS side effects
G03AA09	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03AA10	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women

G03AB06	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03BA03	Testosterone	Potential for cardiac problems
G03CA01	Ethinylestradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA03	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA04	Estriol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CA09	Promestriene	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03CX01	Tibolone	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA01	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA11	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA14	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FA17	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women

G03FB05	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB08	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB09	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
G03FB12	Estradiol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
H01BA02	Desmopressin	High risk of hyponatremia
L02AB01	Megestrol	Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women
M01AB01	Indometacin	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; risk of CNS disturbances
M01AB05	Diclofenac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AB15	Ketorolac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AB16	Aceclofenac	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AC01	Piroxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AC05	Lornoxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AC06	Meloxicam	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal
M01AE03	Ketoprofen	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal

M01AE09	Flurbiprofen	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
M01AX01	Nabumetone	Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications
N02AD01	Pentazocine	Risk of delirium and agitation
N02AX02	Tramadol	More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea
N03AA02	Phenobarbital	Risk of sedation, paradoxical excitation High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages
N03AB02	Phenytoin	Narrow therapeutic window; increased risk of toxicity in older adults (e.g. CNS and hematologic toxicity)
N03AE01	Clonazepam	Risk of falls, paradoxical reactions
N03AX11	Topiramate	Risk of cognitive-related dysfunction (e.g., confusion, psychomotor slowing)
N04AA01	Trihexyphenidyl	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia
N04AA02	Biperiden	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia
N04AB02	Orphenadrine	Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia
N04BC01	Bromocriptine	Risk of CNS side effects
N05AC01	Propericiazine	Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia

N06AA02	Imipramine	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
N06AA04	Clomipramine	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
N06AA06	Trimipramine	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
N06AA09	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
N06AA10	Nortriptyline	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
N06AB03	Fluoxetine	CNS side effects (nausea, insomnia, dizziness, confusion); hyponatremia
N06AB05	Paroxetine	Higher risk of all-cause mortality, higher risk of seizures, falls and fractures. Anticholinergic adverse effects
N06AB08	Fluvoxamine	Higher risk of all-cause mortality, self-harm, falls, fractures and hyponatraemia

N06BA04	Methylphenidat	May cause or worsen insomnia; concern due to CNS-altering effects; concern due to appetite-supressing effects
R06AD02	Promethazine	Anticholinergic side effects (e.g. confusion, sedation)

CNS: central nervous system; GI: gastrointestinal; INR: international normalized ratio; PPI: Proton Pump Inhibitors.

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4.2 GEOGRAPHICAL VARIATION IN MEDICATION PRESCRIPTIONS: A MULTIREGIONAL DRUG-UTILISATION STUDY

This paper is under review by the journal Frontiers in Pharmacology.

Abstract

Background: Studies have emphasised the importance of geographical factors and general practitioner (GP) characteristics in influencing drug prescriptions.

Objectives: To: (i) ascertain the prevalence rate (PR) of use of drugs in six therapeutic categories used for chronic conditions; (ii) assess how geographical characteristics and GP characteristics may influence drug prescribing.

Methods: This study is part of the EDU.RE.DRUG Project, a national collaborative project founded by Italian Medicine Agency (AIFA). Cross-sectional analyses were undertaken employing the pharmacy-claim databases of four local health units (LHUs) located in two Italian regions: Lombardy and Campania. Six drug categories were evaluated: proton-pump inhibitors; antibiotics; respiratory-system drugs; statins; agents acting on the renin–angiotensin system; psychoanaleptic drugs. The PR was estimated according to drug categories at the LHU level. A linear multivariate regression analysis was undertaken to evaluate the association between the PR and geographical area, age and sex of GPs, number of patients, and percentage of patients aged >65 per GP.

Results: LHUs in Campania showed a PR that was significantly higher than that in Lombardy. Antibiotics showed the highest PR in all the LHUs assessed, ranging from 32.5% in Lecco (Lombardy) to 59.7% in Naples-2 (Campania). Multivariate linear regression analysis confirmed the association of the PR with geographical area for all drug categories. Being located in Campania increased the possibility of receiving a drug prescription from the categories considered, with estimates more marked for antibiotics, proton-pump-inhibitors, and respiratory-system drugs.

Conclusions: This study provides information about the PR of medications used for treating common and costly conditions in Italy and highlighted a significant geographical variation. These insights could help to develop area-specific strategies to optimise prescribing behaviour.

4.2.1 Introduction

Over the last century, advances in medical therapeutics have contributed to improve global health and to increase life expectancy. However, growing evidence suggests that therapeutic decisions are often potentially inappropriate, possibly resulting in negative outcomes, such as adverse drug events, hospitalisation, and increased healthcare resource utilisation [1].

Appropriate prescription of medications is one of the most important components of healthcare. It reflects the accuracy of the diagnosis, adherence to evidence-based guidelines, and susceptibility to drug-marketing and regulatory factors. It is particularly challenging in older patients, mainly due to including age-related changes in pharmacokinetics and pharmacodynamics, high numbers of concurrent medications, functional status, and burden of co-morbid illness [2].

A lot of research has tried to analyse and understand the factors which influence physician prescribing decisions and practice. Among the major determinants of drug prescription, studies suggested the role of geographical differences. Scholars have shown that drug use varies across regions in Europe and the USA by more than would be expected based on population age and health status alone [3,4]. Such variations may be dependent upon differences in the prescribing habits of general practitioners (GPs) and socioeconomic status of patients [5]. Furthermore, variations in prescription patterns among different regions and between areas within the same region in Italy have been documented [6,7]. For instance, the Italian National Observatory on Drug Prescription (OsMed) revealed that, in 2016, the overall prescription for all reimbursed drugs, expressed in defined daily doses (DDDs) per 1000 inhabitants per day, was 900.7 in northern Italy and 1,048.8 in southern Italy [8]. Such geographical variations found further confirmation in the work of Piovani et al. [9] conducted in a paediatric population, where a strong inverse correlation between prescription patterns and latitude was observed.

Despite an increasing attention to variations in use of prescribed drugs, little is known about the drivers of variations in the prescribing patterns of GPs. Very few studies attempted to quantify the geographical variation in drug prescriptions for chronic conditions among adults and the elderly in Italian regions [10,11].

Recently, the Italian Medicine Agency (AIFA) funded the EDU.RE.DRUG Project (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients). The EDU.RE.DRUG Project aims to evaluate the appropriateness of drug prescription in people aged ≥40 years living in Lombardy or Campania.

The present analysis is part of this national collaborative project. We wished to: (i) describe the prescription pattern for medications belonging to six therapeutic categories used for chronic conditions; (ii) assess how geographical factors and GP characteristics may influence prescription patterns.

4.2.2 Materials and Methods

Study Design

This was a retrospective drug-utilisation study based on use of administrative health-related databases. The study was carried out according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [12].

Study setting and population

Italian National Health Service (INHS) provides all citizens and legal foreign residents with economic coverage of drugs with documented clinical efficacy and which are used for treating serious and chronic diseases. The amount of public money to be spent on healthcare is established annually by the central government. The money is assigned to regions to provide the essential levels of care (LEA), which must be assured homogenously to citizens throughout the country. Each region allocates the funds to its local health units (LHUs) mainly on an age-adjusted capitation basis. Assigned funds are used by LHUs for the direct provision of inpatient and outpatient care, for GP

remuneration, and for the cost reimbursement of healthcare services afforded by independent and university hospitals and/or accredited private providers. [13].

The study was conducted in the primary care setting, involving selected LHUs of two Italian regions: Lombardy and Campania. Lombardy is one of the largest Italian regions, situated in the north of the country, with a population of over 10,019,000 inhabitants. Campania is situated in the south of the country and had a population of ~5,839,000 inhabitants on 1 January 2017 [14].

The LHUs involved in the study were: Naples-1 and Naples-2 in Campania, and Bergamo and Lecco in Lombardy, with an overall population of ~3.4 million inhabitants. Patients aged ≥40 years, receiving at least one prescription of the study drugs, were included in our study.

Sources and collection of data

The study data were obtained from administrative databases containing information on all beneficiaries of INHS in the LHUs involved. These databases are set-up and updated constantly by regional or local health authorities. Demographic databases contain anonymised data on residents (birth date and sex), and on prescribers (GPs) (birth date and sex) of each LHU. The pharmacy databases contain data on drug prescriptions dispensed by local pharmacies and reimbursed by INHS, including: patient's anonymous unique code; prescriber's (GP) anonymous unique code; prescription date; dispensation date; Anatomical Therapeutic Chemical (ATC) classification; marketing authorisation code (AIC); number of DDDs; number of boxes; cost for INHS [15].

Pharmacy databases were linked to demographic databases by deterministic record-linkage procedures through the unique and anonymous personal identification codes. Such codes were created by a database manager, uninvolved in the data analysis, in full preservation of individuals' privacy.

Drug-utilisation data obtained from these databases have been validated previously and used in drug-utilisation studies [16-21].

Drug categories

We analysed prescriptions of drugs belonging to six therapeutic categories, pre-selected based on the higher prevalence in terms of gross public expenditure and consumption.

The six therapeutic categories were: proton pump inhibitors (PPIs) [A02BC]; antibiotics [J01]; respiratory-system drugs (RSDs) [RO3]; 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors [C10AA]; agents acting on the renin–angiotensin system (C09, including angiotensin-converting enzyme inhibitors [C09AA] and angiotensin-II antagonists [C09CA]) and psychoanaleptic drugs (N06, including selective serotonin reuptake inhibitors [N06AB] and other antidepressants [N06AX]).

In Italy, drugs for the treatment of chronic conditions are fully covered by INHS and, therefore, traceable through administrative databases.

Study outcomes

The year considered for this analysis was 2016. Medication use for the identified therapeutic categories among adults (≥40 years) was estimated as prevalence rate (PR), calculated for each GP as the proportion of patients who received at least one prescription of the selected drugs per 100 GP patients of the same age range in 2016 The mean PR at the LHU level was adjusted by age using a direct standardisation method whereby the standard population (also known as the 'reference population') was the Italian population as extrapolated from Italian Statistical Agency (ISTAT) data on 1 January 2017.

Statistical analyses

Continuous variables (number of patients per GP and age of GP) are expressed as median and interquartile-range deviation, as the Shapiro-Wilk test showed that they did not have a normal distribution. Categorical data are given as percentage.
PR at the LHU level was expressed as mean GP's PR and 95% confidential interval. ANOVA was used to compare the distributions of PRs by LHUs.

A multivariate linear regression analysis was undertaken for each selected therapeutic category. The PR was the dependent variable, whereas the geographical area, number of patients per GP, age of GP, sex of GP, and percentage of patients aged >65 years per GP were inserted as independent variables.

Data management was undertaken with Microsoft SQL server (version 2018). Statistical analyses were carried out with SPSS v17.1 (IBM, Armonk, NY, USA). $P < 0.05$ was considered significant.

4.2.3 Results

In 2016, for an overall population of 15,858,250 (5,839,084 in Campania and 10,019,166 in Lombardy) GPs dispensed 31,584,437 prescriptions (22,331,915 prescriptions for Campania and 9,252,522 prescriptions for Lombardy). Prescriptions for ATC-selected categories (n = 11,609,123) accounted for 36.7% of the total drugs prescribed. Figure 1 shows the regional databases available and data selection employed.

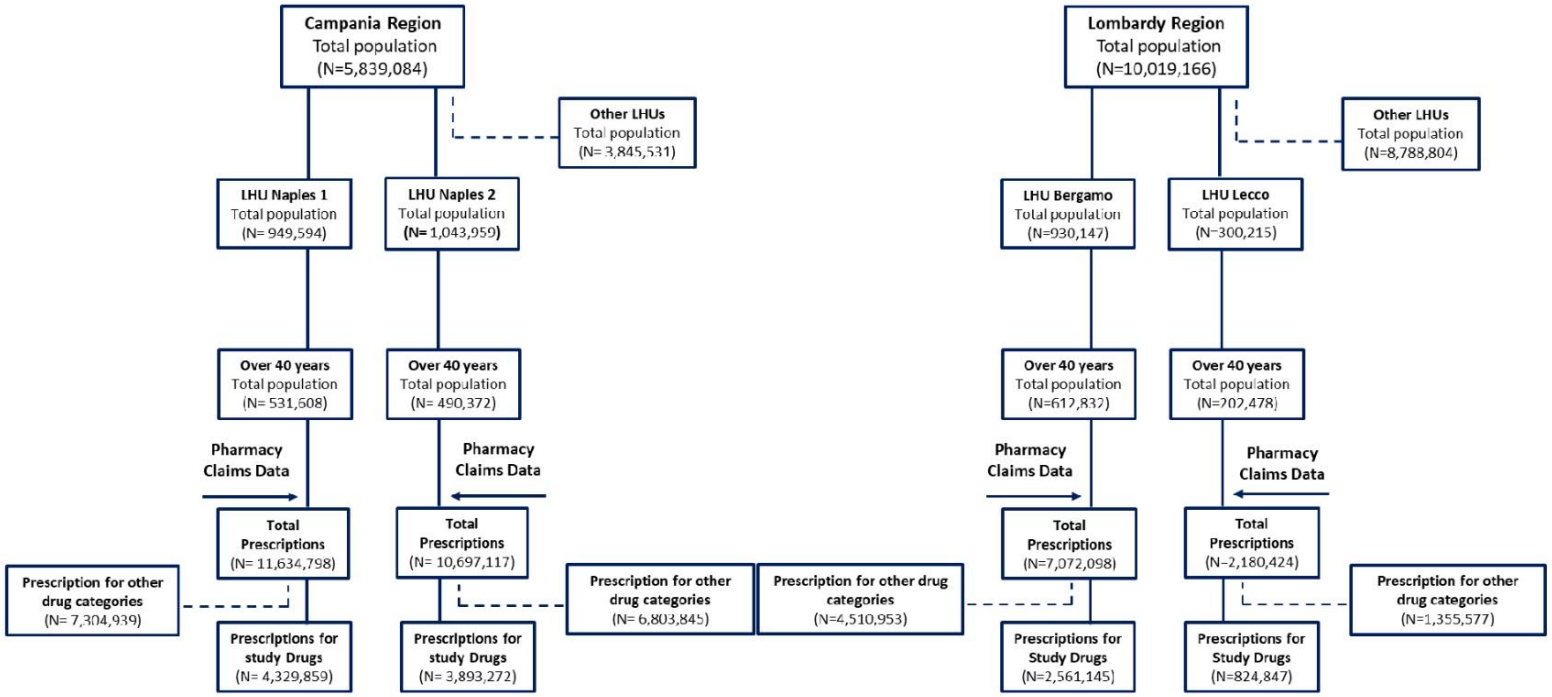
Table 1 shows the main characteristics of GPs of the four LHUs. The number of GPs ranged from 205 in Lecco to 777 in Naples-2.
Most GPs were men (75.8%) and the median age was ~61 years.

The percentage of patients aged ≥65 years per GP was 21.0%, with geographical variability (ranging from 15.0% for Naples-2 to 25.2% for Lecco; $p < 0.001$). A regional difference regarding the median number of patients for each GP (~1500 in northern Italy *versus* ~1300 in southern Italy) was noted.

Table 1 GP characteristics at the LHU level

	Northern Italy		Southern Italy		
	Bergamo LHU (930,124 patients aged ≥40 years)	**Lecco LHU (300,215 patients aged ≥40 years)**	**Naples-1 LHU (832,780 patients aged ≥40 years)**	**Naples-2 LHU (893,871 patients aged ≥40 years)**	**Total LHUs (2,956,990 patients aged ≥40 years)**
GPs (N)	660	205	718	777	2,360
Patients per GP, median (IQR)	1,519 (257)	1,553 (233)	1,267 (528)	1,305 (669)	1,401.50 (470)
Patients aged ≥65 years per GP (%)	23.0	25.2	22.8	15.0	21.0
Age of GP, median (IQR)	59 (9)	60 (8)	62 (6)	60 (6)	61 (7)
Sex of GP					
M (%)	67.1	71.2	78.7	81.9	75.8
F (%)	32.9	28.8	21.3	18.1	24.2

Figure 1. Flow Chart of Data Selection



Prevalence rates at LHUs level

Table 2 (and Supplementary Table S1) shows PR for each selected drug category stratified by LHU (and for age class: 40-64 and >=65 years old). A significant difference in the PR among LHUs was documented: in particular, LHUs located in the south of Italy showed a higher PR compared with LHUs located in the north of Italy for all drug categories ($p < 0.001$).

Among the drug categories evaluated, antibiotics showed the higher PR, ranging from 32.5% in Lecco to 59.7% in Naples-2. Psychoanaleptic drugs showed the lowest PRs, with the smallest variations among LHUs, (8.7% in Bergamo, 7.0% in Lecco, 8.3% Naples-1, and 8.6% Naples-2). PR for PPIs (A02BC) ranged from 21.9% in Lecco to 41.3% in Naples-2.

Multivariate Analysis

The regression model (Table 3 and Supplementary Tables S2 and S3) showed an association of the PR with geographical area for all drug categories, with lower PRs in Northern Italy compared to Southern Italy. The coefficients were notable for: (i) antibiotics; (ii) PPIs; (iii) RSDs. Indeed, the average PR for antibiotics was ~21% lower in northern Italy than in southern Italy (B: −21.80; 95% confidence interval (CI): −22.65 to −20.97; $p < 0.001$). For PPIs, northern Italy showed a lower mean PR compared with that in southern Italy (B: −17.33; 95%CI: −18.08 to −16.57; $p < 0.001$). Similar findings were observed for RSDs (B: −10.76; 95%CI: −11.30 to −10.22; $p < 0.001$).

With regard to the number of patients per GP, we observed a significant positive association for all selected drugs. Similar results were observed with the percentage of patients aged >65 years per GP, with the exception of a negative association for antibiotics (B: −0.37; 95%CI: -0.43; −0.31; $p < 0.001$) and RSDs (B: −0.11; 95%CI: −0.15 to −0.07; $p < 0.001$). We also observed a trend in decreasing PRs with increasing age of the GP.

The sex of GPs was significantly associated with the PR for drugs based on the renin–angiotensin system (B: 0.44; 95%CI: 0.06 to 0.82; $p = 0.022$) and for antibiotic treatments

(B:-0.96; 95%CI:-1.77 to -0.14; p = 0.021): female GPs had a higher C09 mean PR compared with male GPs, while low average of antibiotic PR.

Table 2 Prevalence rate of medication use by ATC group at the LHU level

	Northern Italy				Southern Italy				
	Bergamo LHU		Lecco LHU		Naples-1 LHU		Naples-2 LHU		
	Standardised prevalence %	95%CI	Standardised prevalence %	95%CI	Standardised prevalence %	95%CI	Standardised prevalence %	95%CI	*p**
A02BC	24.1	(23.9; 24.2)	21.9	(21.7; 22.1)	40.0	(39.9; 40.2)	41.3	(41.1; 41.5)	<0.001
C09	16.4	(16.3; 16.5)	19.8	(19.6; 20.0)	21.9	(21.8; 22.0)	22.2	(22.1; 22.4)	<0.001
C10AA	15.3	(15.2; 15.4)	13.9	(13.7; 14.0)	19.3	(19.2; 19.4)	22.6	(22.4; 22.7)	<0.001
J01	35.3	(35.1; 35.4)	32.5	(32.3; 32.8)	53.9	(53.7; 54.1)	59.7	(59.4; 59.9)	<0.001
N06	8.7	(8.6; 8.8)	7.0	(6.9; 7.1)	8.3	(8.3; 8.4)	8.6	(8.5; 8.7)	<0.001
R03	10.3	(10.2; 10.4)	9.4	(9.3; 9.6)	20.4	(20.2; 20.5)	21.8	(21.6; 21.9)	<0.001

A02BC: Proton pump inhibitors; C10AA: HMG CoA reductase inhibitors; J01: antibiotics; RO3: respiratory-system drugs;

C09: ACE inhibitors (C09AA) + angiotensin-II antagonists (C09CA); N06: selective serotonin reuptake inhibitors (N06AB) + another antidepressants (N06AX).

*ANOVA

Table 3 Multivariate linear regression (95%CI): prevalence rate (%) for general practitioners (n = 2,360)

Characteristic	A02BC		(R^2=0.509)	C09		(R^2=0.305)	C10AA		(R^2=0.290)	J01		(R^2=0.616)	N06		(R^2=0.068)	R03		(R^2=0.471)
	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*
Geographical area																		
Southern Italy		Reference			Reference			Reference			Reference			Reference			Reference	
Northern Italy	−17.33	(−18.08; −16.57)	<0.001	−5.74	(−6.13; −5.34)	<0.001	−6.23	(−6.65; −5.82)	<0.001	−21.80	(−22.65; −20.97)	<0.001	−0.71	(−0.97; −0.45)	0.001	−10.76	(−11.30; −10.22)	<0.001
Patients per GP*	0.61	(0.47; 0.75)	<0.001	0.24	(0.16; 0.31)	<0.001	0.40	(0.32; 0.47)	<0.001	0.91	(0.76; 1.07)	<0.001	0.11	(0.06; 0.16)	<0.001	0.35	(0.25; 0.45)	<0.001
Age of GP	-0.04	(−0.10; 0.15)	0.152	−0.05	(−0.08; −0.02)	0.001	−0.04	(-0.07; −0.01)	0.019	−0.12	(−0.18; −0.05)	<0.001	−0.06	(−0.07; −0.04)	<0.001	−0.08	(-0.12; -0.04)	<0.001
Sex of GP																		
M		Reference			Reference			Reference			Reference			Reference			Reference	
F	−0.22	(−0.95; 0.51)	0.554	0.44	(0.06; 0.82)	0.022	−0.20	(−0.60; 0.19)	0.313	−0.955	(−1.77; −0.14)	0.021	0.16	(−0.09; 0.41)	0.223	0.16	(-0.36; 0.68)	0.550
% Patients ≥ 65 years per GP	0.10	(0.05; 0.15)	<0.001	0.26	(0.23; 0.29)	<0.001	0.13	(0.10; 0.16)	<0.001	−0.371	(−0.43; −0.31)	<0.001	0.09	(0.07; 0.10)	<0.001	−0.11	(-0.15; -0.07)	<0.001

*Patients per GP has been multiplied by 100

4.2.4 Discussion

The prescribing of medicines is a complex process that goes on in every healthcare setting, and whose principles are based on the doctor's choice of the right drug for the right patient [22].

Several studies suggested that some factors may have a role in influencing the physicians' prescribing behaviour. Such factors for instance include, the age and sex of the physician or the patient, or the socio-economic characteristics of the practicing area [23].

In our study, we highlighted that some characteristics of GPs and geography might affect the prescribing of drugs in terms of the PR.

In particular, a higher PR in southern Italy than in northern Italy was observed. The greatest difference in the PR between regions was observed for antibiotics, PPIs and RSDs.

This finding is in accordance with observations from other studies conducted in a similar setting [9,24,25]. Piovani et al. in 2012 showed a mean antibiotic PR of 46.5% in the North of Italy, while Southern Regions showed a mean PR of 61.1% [9]. This geographical difference was observed again in a subsequent study by the same authors, indicating that the PR of antibiotics and RSDs in Southern Regions was higher (up to 57.5% and 27.0%, respectively) than in the rest of Italy. The authors pointed out the role of socioeconomic and sociodemographic factors in explaining a higher PR in south Italy [24]. Furthermore, studies analysing the PR for antibiotics in Campania showed results consistent with our data and indicated that the PR was also influenced by per capita income [11,25,26].

Notably, the selected drug categories include medications used to treat common and costly conditions, and the observed geographical differences may reflect differences in socio-demographic indicators between the two Italian Regions. Indeed, the differences observed between the two regions in terms of prescription of drugs for chronic diseases may also be due to differences in the socioeconomic context of the two regions. According to a recent report from ISTAT, southern regions have a lower income and socioeconomic level than those of northern Italy. Indeed, the gross domestic product (GDP) is ~€18,216 in Campania compared with ~€36,807 in Lombardy [27].

Supplementary Table S4 shows demographic and socioeconomic characteristics by geographical area. The Lombardy region, with 22.2% of patients aged ≥65 years, had an older population than the Campania region (18.2%). Private health expenditure per household showed quite high geographical variability (ranging from €752 in the north to €303 in the south). Similar findings were observed for public-health expenditure per capita (ranging from €3,452.4 in Lombardy to €1,479.6 in Campania). There is evidence that a lower income and lower level of education is associated with greater use of health services reimbursed by INHS [28]. Although we have no data to confirm that hypothesis in our study, we can assume that a higher GDP and higher level of education in Lombardy can be associated with a lower PR of reimbursed drugs for chronic conditions [29].

Furthermore, geographical differences in the prescribing patterns between different areas of the same country may also have several causes beyond socioeconomic differences. In Italy, many health policies are designed and implemented at Regional level. Among these, there may be indications orienting the prescribing practice, essentially with the aim of cost containment (for example, towards the choice of drugs with comparable efficacy but lower costs) or of risk minimization (for example, towards the choice of drugs associated with a better tolerability profile of with less reporting of medication errors or adverse events) [6,7].

Other aspects of a GP's practice appear to have an impact on the prevalence rates. In our study, a high number of patients per GP was associated with a greater likelihood of receiving prescriptions. This relationship may be because a high number of listed patients may imply a greater diversity of illnesses and, consequently, a greater diversity of therapeutic needs [30,31]. Moreover, GPs with a high percentage of people aged >65 years showed a greater PR. This finding, consistent with data from other studies, could be explained by the higher number of comorbidities usually affected elderly patients [30]. Interestingly, the stratification of the regression by Region revealed that the positive association between older age of GP's patients and PR was more marked in Lombardy than in Campania (Supplementary Table S2 and S3).

Several associations found in our analysis were already been observed by other researchers. Orzella et al. showed that younger GPs were more likely to prescribe medications and suggested that the number of years in practice could be a proxy of prescribing behaviour [11]. The sex of the GP did not seem to have an influence on the PRs. However, consensus on the influence of this factor on the prescribing attitude is lacking. Some studies showed that female GPs are more likely to write prescriptions [11,32], whereas in other studies male GPs had higher rates of drug use than females [30,33].

Our study had two main limitations. First, pharmacy-claim data do not contain information about over-the-counter (OTC) medications and out-of-pocket expenditure, which could imply underestimation. Second, a dispensed prescription does not ensure that the medication was assumed by the patient. This, in turn, implies that the PR may be an overestimate, as some individuals filled out their prescriptions but did not take the drug. Nevertheless, these two limitations are common in drug-utilisation studies carried out with administrative data.

Importantly, our study was not designed nor aimed to assess the appropriateness of drug prescription. Therefore, the quantification of use of the selected drug categories does not imply a qualitative judgment *per se,* as our data did not allow us to evaluate if these prescriptions were appropriate. The purpose of our analysis was to provide a picture of the PR for prescription of major drug groups with respect to the geographical area in which they were prescribed and the characteristics of prescribers. Further research is required to achieve consistent assessment of the level of potential prescribing inappropriateness among GPs. These actions have been envisaged as the next steps in the EDU.RE.DRUG project. The present work represents the first step of this research project.

On the other hand, as a main strength of our study, we used a population-based database, covering a defined and stable population, which corresponded to ~26% of the Italian population [13]. The age distribution and sex distribution of the population was

similar to the total Italian population. Therefore, we believe that this study provides a reliable representation of Italy, with an up-to-date overview of drug use and an evaluation of the relationship between geographical areas, GP characteristics, and the PR of drug prescription in a real-life context.

Although it is important to be aware of the limitations of cross-sectional studies and their usefulness in the formulation of future interventions [35,36], our data could be very useful in planning interventions aimed at improving the practice of drug prescribing. Successful elements from activities in other countries should also be implemented.

4.2.5 Conclusion

Geographical variations and GP characteristics are associated with prescription of medications for treating common and costly conditions in Italy. This study is the first step towards the characterisation of these differences, and future work is needed to deepen and understand the reasons behind these geographical differences.

4.2.6 Ethical Considerations

Ethics approval was granted by the Ethics Committee of the University of Milan on June 2017 (code 15/17) and of LHU Naples 1 on October 2017 (code 2017/0091873).

Procedures aimed at protecting personal data have been implemented in order to safeguard privacy and to prevent the identification of individual data (according to Italian law D.Lgs. n. 196/2003). Anonymized regional administrative data can be used without a specific written informed consent when patient information is collected for healthcare management and healthcare quality evaluation and improvement (according to art. 110 on medical and biomedical and epidemiological research, Legislation Decree 101/2018).

Supplementary Table S1 Average Prevalence rates by LHUs and by age groups

	Northern Italy		Southern Italy		
	Bergamo LHU	Lecco LHU	Naples-1 LHU	Naples-2 LHU	ANOVA Test
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (± SD)	*p*
40-64 years					
A02BC	14.2 (±5.1)	13.8 (±4.5)	27.5 (±8.6)	28.6 (±8.5)	<0.001
C09	8.8 (±2.2)	10.7 (±2.5)	12.7 (±3.6)	14.0 (±3.5)	<0.001
C10AA	6.8 (±2.5)	6.1 (±2.3)	9.8 (±3.5)	12.7 (±3.6)	<0.001
J01	31.0 (±6.0)	29.1 (±5.5)	46.7 (±10.3)	53.1 (±9.6)	<0.001
N06	5.7 (±1.8)	5.1 (±1.5)	5.6 (±2.4)	5.9 (±2.3)	<0.001
RO3	8.2 (±2.7)	7.8 (±2.5)	16.1 (±6.0)	17.1 (±5.8)	<0.001
≥65 years					
A02BC	40.4 (±9.1)	34.8 (±7.7)	58.9 (±10.7)	61.2 (±10.5)	<0.001
C09	28.9 (±5.2)	34.5 (±6.0)	36.1 (±7.9)	35.3 (±7.8)	<0.001
C10AA	29.2 (±6.8)	26.5 (±5.7)	33.9 (±7.7)	37.4 (±7.6)	<0.001
J01	42.2 (±7.4)	37.4 (±6.2)	63.7 (±12.0)	68.9 (±11.1)	<0.001
N06	13.4 (±4.0)	9.9 (±3.2)	12.4 (±4.8)	12.7 (±5.3)	<0.001
RO3	13.8 (±4.3)	11.9 (±3.4)	26.8 (±8.7)	29.4 (±9.2)	<0.001

Supplementary Table S2 Multivariate linear regression Campania (CI 95%)

Characteristics	A02BC (R^2=0.055)			C09 (R^2=0.064)			C10AA (R^2=0.100)			J01 (R^2=0.034)			N06 (R^2=0.028)			R03 (R^2=0.014)		
	B	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**
Patients per GP*	0.8	(0.6; 0.9)	<0.001	0.5	(0.4; 0.5)	<0.001	0.6	(0.5; 0.7)	<0.001	0.6	(0.4; 0.8)	<0.001	0.2	(0.1; 0.2)	<0.001	0.3	(0.2; 0.4)	<0.001
Age of GP	0.01	(-0.08; -0.10)	0.751	0.03	(-0.02; 0.08)	0.193	0.01	(-0.04; 0.06)	0.730	-0.23	(-0.34; -0.13)	<0.001	-0.02	(-0.05; 0.00)	0.105	-0.08	(-0.15; -0.01)	0.027
Sex of Gp																		
M	Reference			Reference			Reference			Reference			Reference			Reference		
F	-0.14	(-1.21; 0.92)	0.793	0.46	(-0.11; 1.04)	0.114	-0.09	(-0.65; 0.46)	0.743	-1.06	(-2.33; 0.21)	0.102	0.05	(-0.30; 0.41)	0.772	0.07	(-0.76; 0.89)	0.869

*Patients per GP had been multiplied by 100

Supplementary Table S3 Multivariate linear regression Lombardy (CI 95%)

Characteristics	A02BC (R^2=0.020)			C09 (R^2=0.070)			C10AA (R^2=0.026)			J01 (R^2=0.023)			N06 (R^2=0.046)			R03 (R^2=0.055)		
	B	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**	**B**	**CI 95%**	***p*-value**
Patients per GP*	0.45	(0.2; 0.7)	<0.001	0.5	(0.4; 0.7)	<0.001	0.3	(0.2; 0.5)	<0.001	0.004	(0.2; 0.7)	<0.001	0.2	(0.1; 0.3)	<0.001	0.1	(0.0; 0.2)	0.011
Age of GP	-0.05	(-0.11; 0.01)	0.123	-0.06	(-0.10; 0.02)	0.002	-0.03	(-0.07; 0.00)	0.084	-0.09	(-0.16; -0.03)	0.003	-0.06	(-0.09; -0.04)	<0.001	-0.09	(-0.12; -0.06)	<0.001
Sex of Gp																		
M	Reference			Reference			Reference			Reference			Reference			Reference		
F	-0.40	(-1.29; 0.49)	0.373	0.21	(-0.32; 0.75)	0.436	-0.45	(-1.01; 0.12)	0.124	-0.53	(-1.41; 0.36)	0.242	0.22	(-0.13; 0.57)	0.216	0.34	(-0.09; 0.77)	0.118

*Patients per GP had been multiplied by 100

Supplementary Table S4 Demographic and socioeconomic characteristics, 2016

	Lombardy	Campania	Italy
Demographic characteristics			
Population size (N)[1]	10,019,166	5,839,166	60,589,445
Patients aged ≥65 years (%)[1]	22.2	18.2	22.3
Socio-economic characteristics			
GPD per capita (€)[1]	36,807.08	18,216.76	27,718.82
Poverty rate (%)[1]	5.5	24.4	12.3
Private health expenditure per household (€)[2]	752	303	560
Public health expenditure (per capita) (€)[2]	3,452.4	1,479.6	2,466.0

[1] Available from: www.istat.it/. Accessed: November, 2018.
[1] Rapporto Oasi 2017. Available from: www.pensionaticisllombardia.it/public/pdf/pdf_2426_rapporto-oasi-2017.pdf. Accessed: November, 2018. [34]
[3] Rapporto OsMed, 2017. Available from: www.aifa.gov.it/content/luso-dei-farmaci-italia-rapporto-osmed-2017. Accessed: November, 2018. Italian [with English abstract]. [8]

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4.3 PREVALENCE OF ANTIBIOTIC PRESCRIPTION IN SOUTHERN ITALIAN OUTPATIENTS: REAL-WORLD DATA ANALYSIS OF SOCIOECONOMIC AND SOCIODEMOGRAPHIC VARIABLES AT A MUNICIPALITY LEVEL

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Abstract

Purpose: The aim of this study was to analyze the geographic variation in systemic antibiotic prescription at a regional level and to explore the influence of socioeconomic and sociodemographic variables.

Methods: This study was a retrospective analysis of reimbursement pharmacy records in the outpatient settings of Italy's Campania Region in 2016. Standardized antibiotic prescription rates were calculated at municipality and Local Health Unit (LHU) level. Antibiotic consumption was analyzed as defined daily doses (DDD)/1000 inhabitants per day (DID). Logistic regression was performed to evaluate the association between antibiotic prescription and sociodemographic and socioeconomic determinants at a municipality level.

Results: The average antibiotic prevalence rate was 46.8%. At LHU level, the age-adjusted prevalence rates ranged from 41.1% in Benevento to 51.0% in Naples2. Significant differences were found among municipalities, from 15.2% in Omignano (Salerno LHU [Sa-LHU]) to 61.9% in Moschiano (Avellino [Av-LHU]). The geographic distribution also showed significant differences in terms of antibiotic consumption, from 6.7 DID in Omignano to 41.6 in San Marcelino (Caserta [Ce-LHU]). Logistic regression showed that both municipality type and average annual income level were the main determinants of antibiotic prescription. Urban municipalities were more than eight times as likely to have antibiotic high prevalence rates compared to rural municipalities (adjusted odds ratio [OR]: 8.62; 95% confidence interval [CI]: 4.06–18.30, $P<0.001$). Low average annual income level municipalities were more than eight times as likely to have antibiotic high prevalence rates compared to high average annual income level municipalities (adjusted OR: 8.48; 95% CI: 3.45–20.81, $P<0.001$).

Conclusion: We provide a snapshot of Campania's antibiotic consumption, evidencing the impact of both socioeconomic and sociodemographic factors on the prevalence of

antibiotic prescription. The observed intraregional variability underlines the lack of shared therapeutic protocols and the need for careful monitoring. Our results can be useful for decision makers to plan educational interventions, thus optimizing health resources and improving rational drug use.

4.3.1 Introduction

Antibiotic consumption in Europe has increased over the last few years, making them the most prescribed drugs in outpatient populations [1,2]. Antibiotics may be prescribed for the treatment of various diseases [3–7], but more than one-third of Europeans take them unnecessarily or without a prescription, contrarily to European Union (EU) recommendations [8].

Antibiotic overuse and misuse contribute not only to the development of resistance but also to treatment failure and increase in mortality. Different studies have shown a correlation between the irrational use of antimicrobial drugs and antibiotic resistance to bacterial pathogens [9–11]. The World Health Organization (WHO) advocates the correct use of antibiotics to avoid antibiotic resistance, which has reached alarming levels worldwide [8] Thus, the interest in the epidemiology of antibiotic use has increased. Within Europe, major differences in antibiotic consumption rates have been noted [12–16]. These geographical variations have been attributed to socioeconomic (eg, financial wellbeing and access to health insurance), sociodemographic (eg, urbanization), and cultural (eg, educational level, prescribing norms, and patient demands) factors [17,18]. Several studies show that the Italian consumption of systemic antibiotics is higher than the European average, both in hospitals and in the outpatient population [2,19,20]. Furthermore, there is evidence that antibiotic prescription rates vary among different Italian regions and also among areas within the same region, showing that the differences in antibiotic use are influenced by both national policies and geographical typology [21–26]. There is still a considerable variability between antibiotic consumption in southern (44.9%) and northern (31.6%) Italian regions. Particularly, antibiotic consumption in Campania is the highest in Italy [27]. Italian health policies have been decentralized at a regional level since 2001. However, regional antibiotic prescribing patterns in southern Italy have not been investigated in depth. Administrative health-related databases, such as pharmaceutical records, can be useful tools to explore drug exposure in a real-world

setting [28]. The aim of this study is to evaluate the prevalence of systemic antibiotic use at the individual municipalities in southern Italy, considering the influence of socioeconomic and sociodemographic variables.

4.3.2 Materials and Methods

Study Design

We conducted a descriptive cross-sectional drug use study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [29].

Study setting

The Italian National Health Service (NHS) has been decentralized at national, regional, and local levels, since 2001. Campania, one of the largest Italian regions situated in the south of the country, had a population of 5,850,850 Inhabitants up to January 1, 2016 (according to http://demo. istat.it/pop2016/index.html). As all other Italian regions, it provides health care services (free or at a nominal charge) to all citizens and legal foreign residents through Local Health Units (LHUs). Each LHU corresponds to a geographic area in Campania and is constituted by health care districts, which aggregate different municipalities. There are five geographic areas in Campania: Naples (including three LHUs, such as Na1, Na2, and Na3), Avellino LHU (Av-LHU), Benevento LHU (Bn-LHU), Caserta LHU (Ce-LHU), and Salerno LHU (Sa-LHU). Overall, there are 550 municipalities.

Data source

For this study, the following two administrative databases of Campania were analyzed: civil registry, containing demographic information (ie, age, gender, LHU, and municipality of residence) of all residents covered by the Regional Health System (RHS), and pharmaceutical databases, containing records of the drugs dispensed by retail pharmacies and reimbursed by the NHS, information regarding the patient's identification code, drug code, dose, formulation, number of packages, date of prescription, date of dispensation, and drug price. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [30]. The above databases had been previously validated and used to produce drug-utilization information [31–32,46–52]. Data sources were matched by record linkage analysis through a unique and anonymous personal identification code. Such code was created by a database manager,

uninvolved in the data analysis, preventing patient identification. Therefore, neither ethical committee approval nor informed consent forms were required.

Study drugs

Prescribed drugs, in Italy, are categorized into the following two classes: class A includes lifesaving drugs and treatments for chronic diseases that are fully reimbursed by the NHS and class C includes all nonreimbursable drugs. Most antibiotic drugs fall into class A. We conducted the analysis of all reimbursable antibiotic prescriptions dispensed by retail pharmacies in Campania between January 1, 2016, and December 31, 2016. Only systemic antibiotics belonging to the J01 subgroup, according to the ATC classification system, were included [30].

Study population

The entire Campania's population (ie, 5,850,850 inhabitants) was divided into ten groups by age (0–6, 7–14, 15–24, 25– 34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years) and distributed into the 550 municipalities. In our analysis, official data on resident population in the Italian municipalities, which are available on Demo Istat website (http://demo.istat. it/pop2016/index.html), were up to date until January 1, 2016.

Study outcomes

Prevalence was used as a measure to estimate the degree of exposure to antibiotic prescription. Antibiotic prevalence rates were calculated, at municipality and LHU levels, as the proportion of the population who received more than one prescription per 100 inhabitants in 2016. Prevalence rates were probably influenced by the heterogeneous demographic distribution among the age groups. Hence, they were adjusted using a direct standardization method, where the standard population (also known as reference population) was the population in Campania up to January 1, 2016:

$$\textit{Directly Standardized Rate} = \frac{\sum_{i=1}^{m} w_i \cdot T_i}{\sum_{i=1}^{m} w_i} \cdot k$$

where *Ti = ni/n* is the rate in stratum *i* of the study population, *ni* is the number of cases in stratum *i* of the study population, *n* is the size of the study population in stratum *i*, *wi* is the size of stratum *i* of the reference population, *m* is the number of considered

stratum, and *k* is the multiplicative constant. Antibiotic drug consumption was expressed as the number of defined daily doses (DDD)/1000 inhabitants/day (DID) [33]. DDD is the assumed average maintenance dose, per day, for a drug used for its main indication in adults [30]. The DID was calculated as follows: active substance divided by the number of inhabitants/1000.

Covariates

The municipalities were also classified as rural or urban to evaluate if this difference was a significant variable [34].

The average annual income data were defined as the total household income for each municipality and obtained from the Ministry of Economy and Finance website (http://www. mef.gov.it/).

Statistical analysis

The age-adjusted prevalence rates were categorized into quintiles and mapped by the patient's municipality of residence. Antibiotic consumption (DID) was also mapped for the different municipalities. Differences in prevalence rates between each LHU and the standard population were expressed as prevalence ratios (PRs).

PRs indicate whether the prevalence rate at LHU level was higher or lower than that of the standard population. Confidence intervals (CIs) were computed using standard methods (at 95% confidence level) [35].

Univariate and multivariate logistic regression models were conducted to evaluate 1) the association between the highest and lowest antibiotic prevalence rates (ie, highest vs lowest quintile of prevalence) and 2) some determinants such as municipality type (rural or urban), average annual income level per capita, and number of general practitioners (GPs) and average annual medication consumption per 1000 inhabitants. All analyses were performed using the SPSS software Version 17.1 for Windows (SPSS Inc., Chicago, IL, USA), and a *P*-value of <0.05 was considered to be statistically significant. Maps for antibiotic prevalence rates were generated by a custom script that uses an Application Programming Interface (API) offered by MapBox (www.mapbox.com).

Ethics statement

All procedures performed in this study were in accordance with the current national law from Italian Medicines Agency [45]. The article does not contain clinical studies, and all

patients' data were fully anonymized. For this type of study, formal consent is not required. Permission to use anonymized data for the present study was granted by the responsible authority, Unità del Farmaco, Regione Campania.

4.3.3 Results

Prevalence rates at LHU level

In 2016, 2,738,118 patients in Campania received at least one antibiotic prescription. The total antibiotic prevalence rate was 46.8%. Differences were observed in age-adjusted antibiotic prevalence rates, ranging from 41.1% in Benevento to 51.0% in Na2. PRs ranged from 0.88 (95% CI: 0.87–0.89) in Benevento to 1.09 (95% CI: 1.08–1.10) in Na2. Figure 1 shows that three of the seven LHUs had PRs significantly higher than expected (ie, Caserta, Na2, and Na3) for antibiotics, while in Av, Na1, Sa, and Bn, PRs were lower than expected.

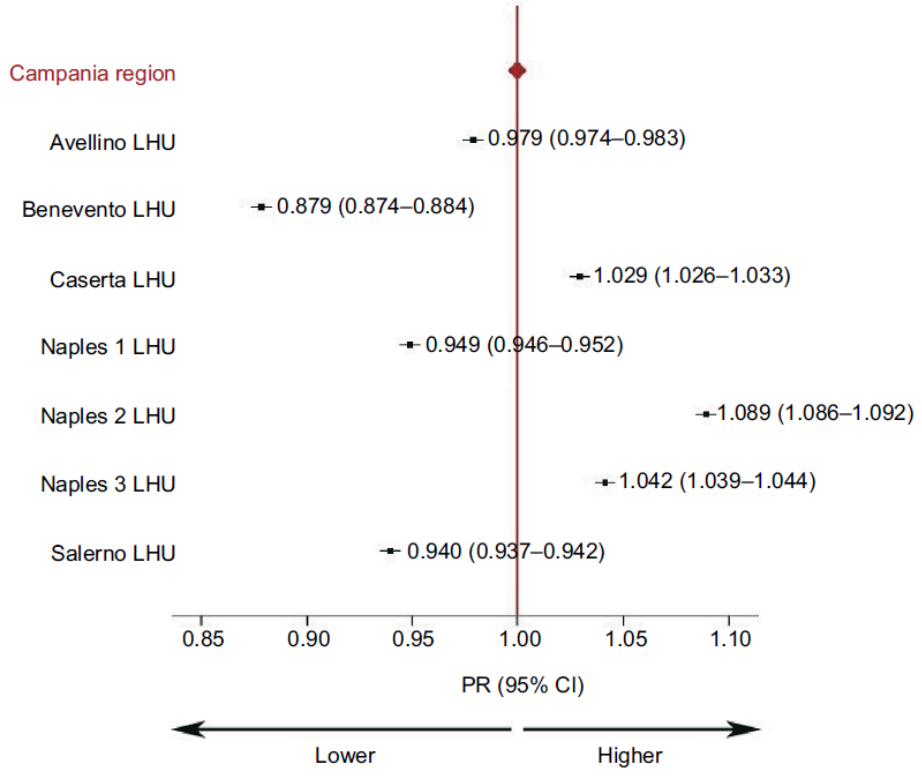

Figure 1 PRs at LHU level.

Note: PRs indicate differences in prevalence rates between each LHU and standard population (Campania).
Abbreviations: CI, confidence interval; LHU, Local Health Unit; PR, prevalence ratio.

Prevalence rates at municipalities' level

Figure 2a shows the distribution of antibiotic prevalence rates, in quintiles by municipality, within each LHU. Significant differences were found in the distribution of standardized prevalence rates between the different municipalities: from a minimum of 15.2% in Omignano (Sa-LHU) to a maximum of 61.9% in Moschiano (Av-LHU). In most municipalities of the northwestern and southern areas of Campania (ie, Benevento and Salerno areas), the prevalence rates of antibiotics were lower compared to other areas. Conversely, coastal areas around Naples and eastern Avellino showed higher prevalence rates, from 50.9 to 61.9%. Figure 2b shows the geographic distribution (by municipality) of antibiotic consumption, expressed in DID. Major differences were found between municipalities: from 6.7 DID in Omignano (Sa-LHU) to 41.6 in San Marcelino (Ce-LHU).

Figure 2 (a)

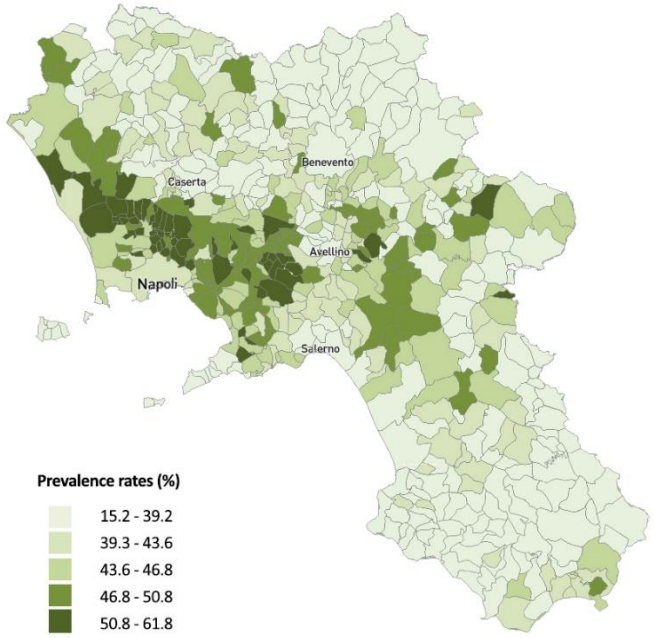

Figure 2 (b)

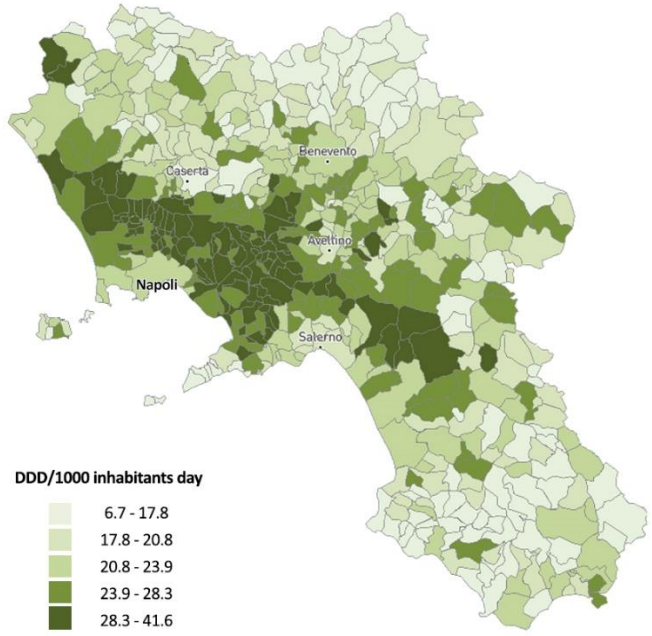

Figure 2 (a) Standardized antibiotic prevalence rates (%). (b) Antibiotic consumption (DDD/1000 inhabitants/day).

Abbreviation: DDD, defined daily doses.

Multivariate analysis

Table 1 reports the results of the univariate and multivariate logistic regression analyses, which showed that two independent variables made a statistically significant contribution to the model: both municipality type and average annual income level were the main determinants of antibiotic prevalence rates. A strong significant association with prevalence rates (quintile 5 [highest] vs quintile 1 [lowest]) was municipality type. Urban municipalities (adjusted odds ratio [OR]: 8.62; 95% CI: 4.06–18.30, *P*<0.001) were more than eight times as likely to have antibiotic prevalence rates in quintile 5 compared to rural municipalities. Equivalent results were found for the average annual income level: municipalities with low (adjusted OR: 8.48; 95% CI: 3.45–20.81, *P*<0.001) and medium (adjusted OR: 4.64; 95% CI: 1.98–10.88, *P*<0.001) average annual income levels were more than eight and four times, respectively, as likely to have antibiotic prevalence rates in quintile 5 compared to high average annual income level municipalities.

Table 1 Multivariate analysis of antibiotic prevalence quintile 5 (highest) vs quintile 1 (lowest)

Characteristics	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Municipality Type				
Rural	Reference		Reference	
Urban	7.111 (3.782 – 13. 371)	< 0.001*	8.621 (4.061 – 18. 301)	< 0.001*
Average Annual Income Levels				
High	Reference		Reference	
Medium	2.734 (1.278 – 5.849)	0.010*	4.645 (1.983 – 10. 884)	< 0.001*
Low	7.862 (3.423 – 18. 058)	< 0.001*	8.479 (3.453 – 20. 818)	< 0.001*

Notes: Univariate and multivariate logistic regression models including antibiotic prevalence levels (highest vs lowest quintile of prevalence) as dependent variable and municipality type and average annual income levels as independent variables were performed. **P*<0.05 was considered to be statistically significant.

Abbreviations: CI, confidence interval; OR, odds ratio.

4.3.4 Discussion

This study analyzed the prevalence of antibiotic use and consumption, at a municipality level, within Italy's Campania region. Previous studies have already evaluated intraregional variations in antibiotic prescribing patterns in Italy [21,23,36], but this study shows the relationship between antibiotic prevalence rates and socioeconomic (eg, financial and wellbeing) and sociodemographic (eg, urbanization) factors. To our knowledge, there are a limited number of similar multivariate analyses in the literature, especially at intraregional level [16,18,36,37]. Differences in interregional antibiotic prescribing rates have been already described in the literature, with a higher consumption in southern Italy compared to the northern regions [25,36]. Particularly, antibiotic consumption in Campania is described as the highest in Italy [38]. A similar north–south gradient has been observed at the European level.

In 2016, EU population-weighted mean consumption of antibiotics for systemic use in the community was 21.9 DID, ranging from 10.4 in the Netherlands to 36.3 in Greece. Data collected by the European Surveillance of Antimicrobial Consumption (ESAC) revealed that Italy was among EU countries with higher antibiotics consumption (27 DID) [39].

Our study showed differences for the age-adjusted prevalence rates between the different LHUs. Large differences were found in the distribution of standardized antibiotic prevalence rates among the different municipalities (from 15.2% in Omignano, Sa-LHU, to 61.9% in Moschiano, Av- LHU) and in the antibiotics consumption, expressed in DID (from 6.7 in Omignano, Sa-LHU, to 41.6 in San Marcellino, Ce-LHU). It is noteworthy that in most northwestern and southern municipalities of Campania (eg, Benevento and Salerno), prevalence rates and antibiotic consumption were lower than in coastal areas around Naples and eastern Avellino. This fact underlines that, even in settings characterized by high prevalence rates (such as Campania), there are areas with lower rates than expected and that variability is often very high, even within the same LHU. Hence, antibiotic usage is influenced by both national policies and geographical typology, as described previously [21–26,36]. Our study shows that municipality type influenced antibiotic prescription prevalence. Urban municipalities were more than eight times as likely to have antibiotic prevalence rates in quintile 5 (high prevalence rates) compared to rural municipalities. The high antibiotic consumption observed in the more urbanized

municipalities was probably due to a greater access to medical care, such as a higher availability of health care providers. Klein et al [17] described that a higher number of health providers translated in an increase in antibiotic prescribing rates per capita. Our study showed that another factor influencing the prescription rates of antibiotics was per capita income at a municipality level. Municipalities with low average annual income levels were more than eight times as likely to have antibiotic prevalence rates in quintile 5 compared to high average annual income level municipalities. These results could be of great interest for designing interventions to improve prescription patterns. Similar findings, regarding the relationship between the prevalence of antibiotic use (in children) and annual average income, have already been observed in three Italian regions (Lombardy, Lazio, and Puglia), where children/ adolescents living in districts in the lowest quintile of annual average income were more exposed to receive an antibiotic prescription [36]. Similar evidences have been described also in other EU countries, such as Germany and Switzerland.13,15 As underlined by Piovani et al [36], in countries where antibiotics prescription is reimbursed (including Italy), the confounding role of out-of-pocket drug consumption cannot be excluded, especially in studies based on administrative pharmacy records. Sianesi40 suggested that income deprivation is a combination of other linked deprivations, including education, which is relevant and affects the appropriateness of drug use [16].

The intraregional variability observed in our study can also be explained by different prescribing patterns among physicians and different local health policies. Several studies showed that the physicians' attitudes and knowledge determine the quality of antibiotic prescription [41]. As already stated, geographical variations in antibiotic prescribing rates have also been observed in other EU countries [13–15]. In this regard, several investigations have confirmed that socioeconomic and sociodemographic factors (eg, population, annual income, demographic structure, and cultural values) are significant determinants to explain differences in antibiotic consumption [17,18,42]. Gaygisiz et al [42] showed that the high variability in antibiotic use was influenced by cultural values (65%), followed by socioeconomic (63%) and personality (55%) factors. There are some limitations to our analysis. In this cross-sectional study, we analyzed pharmacy records, which, although being a powerful tool, might lead to some underestimations:

Pharmaceutical records do not provide information about private practice prescriptions and out-of-pocket expenditure. Therefore, the consumption of antibiotics could have been underestimated. Furthermore, we were unable to explore the prescriptions' appropriateness because the diagnosis details were unavailable from our data sources even if this is a common limitation of drug utilization studies carried out by administrative databases. Our results could be highly useful in planning policy interventions. However, it is important to be aware of the limitations of cross-sectional studies in its usefulness in making sweeping policy recommendations. The main strengths of our study lie in providing an overview of the use and consumption of antibiotics in Campania and exploring the relationship between socioeconomic and sociodemographic factors and antibiotic consumption in a real-life setting. The analysis is useful for exploring the dynamics that are currently characterizing the use of antibiotic therapy in a regional context. Antibiotic overuse and misuse contribute to the development of resistance, treatment failure, and high health costs. Local policies, following WHO's recommendations, should provide training and information to citizens and health care professionals to optimize health resources also implementing successful elements from other EU countries' activities [43]. Synergies between different actors involved in health care delivery can help in achieving better results [44] Further studies are needed to explore attitudes toward medications, which are crucial factors that could influence antibiotic use patterns.

4.3.5 Conclusion

Our study provides a snapshot of Campania's antibiotic drug consumption in 2016, evidencing the impact of both socioeconomic and sociodemographic factors on the prevalence of antibiotic prescription in the study's population.

Major differences were found among the different municipalities in Campania, regarding the distribution of age-standardized antibiotic prevalence rates and antibiotic consumption. Municipality type and average annual income level were the main determinants of antibiotic prescription prevalence. Our analysis underlines the lack of shared therapeutic protocols and can represent a foundational work to create them. Such protocols represent a key factor for

decision-makers to improve the quality of care. Once protocols are established, they can be effectively enforced by issuing educational interventions aimed at the optimization of health resources and correct utilization of drugs.

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4.4 DRUG UTILIZATION PATTERN OF ANTIBIOTICS: THE ROLE OF AGE, SEX AND MUNICIPALITIES IN DETERMINING VARIATION.

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Abstract

Propose : To analyze drug prescription and antibiotic use by age and sex in Italy's Campania Region, and to estimate the distribution of prescription rates in children (≤14 years old), adults (between 15 and 65 years old), and the older adults (≥65 years old) at a municipality level.

Methods : Retrospective analysis of pharmacy records in Campania (Southern Italy), in 2016. Difference in antibiotic prescriptions in different age groups was assessed by prevalence rates. Age-adjusted prevalence rates were categorized into quintiles and mapped by the patient's municipality of residence. Relationship between prevalence rates, for the different age groups, was estimated using the non-parametric Spearman rank correlation test.

Results : 2,738,118 were patients with at least one antibiotic prescription. Antibiotics prescription was higher in children aged <5 years and in the older adults aged >70 years. Prevalence rate distribution was different among municipalities in all age groups. In coastal areas around Naples, northern Caserta, and eastern Avellino (50.2–68.0%) were recorded higher rates for children and both for adults (46.3–59.5%) and the older adults (71.0–89.5%). A positive correlation between the rank distribution of prevalence rates at municipality level was identified for children and adults (rs=0.56; *P*<0.01), adults and the older adults (rs=0.79; *P*<0.01), and children and the older adults (rs=0.46; *P*<0.01). Among the studied age groups, the most prescribed antibiotic class was Penicillin (except the older adults aged ≥85 years) ranging from 45% in children to 27.2% in the older adults. Fluoroquinolones were the least prescribed antibiotic class, ranging from 0.2% in children to 30.2% in the older adults.

Conclusion : A considerably high use of antibiotic drugs has been detected in Campania Region, with values exceeding the regional and national average. Prescriptions at municipal level differs from one age group to another. Antibiotic use is often unjustified,

and to decrease the number of prescriptions and improve their appropriateness, several measures at territorial level are recommended.

4.4.1 Introduction

Antibiotics are the most prescribed drugs in outpatient populations,[1,2] but more than 30% of patients take them unnecessarily [3,4]. The World Health Organization (WHO) advocates the correct use of antibiotics to avoid antibiotic resistance, which has reached alarming levels across the globe [4].

Antibiotics are widely prescribed therapeutic agents for children and the older adults in community settings. Although some conditions do not typically benefit from antibiotic therapy, these drugs are frequently used to treat colds and bronchitis (which are the most common conditions in children); and bacterial infections such as urinary tract infections (UTIs), pneumonia, and skin/soft tissue infections (common in the older adults) [5]. It has been estimated that nearly 50% of children's antibiotic prescriptions are unnecessary [6] and do not comply with national guidelines [7].

Antibiotic misuse causes unnecessary expenditure, overuse of health services (as patients keep consulting their general practitioners [GPs] for subsequent similar problems), unnecessary side effects, and the possible development of antibiotic resistance [6,7]. Thus, antibiotic misuse and overuse impact many aspects of public health [6].

Different antibiotic prescribing patterns exist according to age and geographical settings [5]. Indeed, differences in antibiotic prescription rates were found not only between different countries but also at a regional level. In Europe, these geographical variations have been attributed to socioeconomic (eg financial wellbeing and access to health insurance), sociodemographic (eg urbanization), and cultural (eg educational level, prescribing norms, and patient demands) factors [8,9]. Furthermore, there is evidence that antibiotic prescription rates vary considerably according to age and sex [5,10]. In Italy, where the consumption of systemic antibiotics is higher than the European average [2,11,12], antibiotic prescription rates vary among different regions [5,13,14], showing a higher antibiotic consumption in Southern Italy. Particularly, Campania is the region with the highest antibiotic consumption [15]. According to earlier estimates of a recent study, in this region, there is a strong relationship between antibiotic prevalence rates and

sociodemographic and socioeconomic factors at a municipality level [16]. Nevertheless, this work did not analyze prescriptive patterns related to age, sex and type of class of antibiotic drugs. Reason why, the aims of the present study are to (a) analyze outpatient drug prescriptions records in Campania to describe patterns of antibiotic use by age and sex, and (b) estimate the distribution of prevalence prescription rates in children, adults, and the older adults ≥ 65 years at a municipality level.

4.4.2 Material and Methods

Setting

The Italian National Health Service (NHS) has been decentralized at national, regional, and local level since 2001 [17]. Campania, one of the largest regions of southern Italy, had a population of 5,850,850 inhabitants up to 1 January 2016 [18]. As all other Italian regions, it provides health care services (free or at a nominal charge) to all citizens and legal foreign residents through Local Health Units (LHUs). Each LHU corresponds to a geographic area in Campania, which are five: Naples (including three LHUs: Na1, Na2, Na3), Avellino (Av-LHU), Benevento (Bn-LHU), Caserta (Ce-LHU), and Salerno (Sa-LHU). Each one is constituted by healthcare districts, which aggregate different municipalities. Overall there are 550 municipalities.

Data source

For the present study, we analysed pharmacy claims databases of Campania region. These databases contain records of all drugs dispensed by retail pharmacies and reimbursed by the NHS, information regarding the patient's identification code, drug code, number of Defined Daily Doses (DDD), formulation, number of packages for each claim, date of prescription, date of dispensation, and drug price. All drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [19].

Pharmacy claims databases were linked to civil registries, containing demographic information (ie age, sex, LHU and municipality of residence) of all residents covered by the Regional Health System (RHS). The above databases had been previously validated and used to produce drug-utilization information [20-25].

Data sources were matched by record linkage analysis through a unique and anonymous personal identification code. Such code was created by a database manager uninvolved

in the data analysis, preventing patient identification. Therefore, informed consent forms were not required.

Cohort definition

We conducted a descriptive cross-sectional drug use study which included the entire Campania population of 5,850,850 inhabitants. Noteworthy is that the study sample represented about 10% of the total Italian population.

The whole studied cohort was divided into three groups (children aged ≤14 years, adults aged between 15 and 65 years, and the older adults aged ≥65 years) and distributed into the 550 municipalities. The entire Campania's population was also stratified by age (0–6, 7–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years) and by sex. In our analysis, official data on resident population in the Italian municipalities, which are available on Demo Istat website, were up to date until January 1, 2016 [18].

Outcomes

Prevalence rate was used as a measure to estimate the degree of exposure to antibiotic prescription.

Prescription data for the year 2016 with all dispensed ATC-code 'J01' drugs were analyzed. Study drugs are listed in Supplementary material. The outpatient parenteral therapy (OPAT) was not included in the analyses.

Antibiotic prevalence rates for the overall treated patients were calculated as the proportion of the population who received at least one prescription of 'J01' drugs (ATC-II level) in 2016. While, antibiotic prevalence rates for patients treated with different drug class (ATC-III level), were calculated as the proportion of the population who received at least one prescription of penicillins, cephalosporins, macrolides, fluoroquinolones and the other drug classes involved in the study, in order to focus on drugs with prevalence rate >1%. Prevalence rates were estimated by age and sex.

At municipality level, prevalence rates for adults and the older adults were adjusted by age using a direct standardization method, where the standard population (also known as reference population) was the population in Campania up to January 1, 2016.

Statistical analysis

The age-adjusted prevalence rates were categorized into quintiles and mapped by the patient's municipality of residence. Values were presented as mean ± standard deviation (STD). The coefficient of variation (CV) was also calculated as a measure of dispersion (CV = STD/mean). Confidence intervals (CIs) were not calculated as they were not relevant due to the high number of individuals in the study population. The relationship between prevalence rates for children, adults, and the older adults was estimated using the non-parametric Spearman rank correlation test.

A logistic regression analysis was performed for each of the most common antibiotic classes to evaluate the association between receiving an antibiotic prescription and gender, age group and municipality type.

All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA), and a *p*-value of <0.05 was considered to be statistically significant. Maps for antibiotic prevalence rates were generated by a custom script that uses an Application Programming Interface (API) offered by MapBox (www.mapbox.com).

4.4.3 Results

In 2016, 2,738,118 patients in Campania received at least one antibiotic prescription. The total antibiotic prevalence rate was 46.8%, 50.3% for females and 43.2% for males. While, the prevalence rates among different age groups, were 43.8% for children, 42.4% for adults, and 65.8% for older adults.

Penicillins were the most commonly prescribed antibiotic class (ie, 57.8% of the population treated with antibiotics) showing that 27.0% of the total population in Campania received at least one prescription of this type of drug.

The prescription rate for cephalosporins was 14.3% of the total population, 13.1% for macrolides and 12.6% for fluoroquinolones.

Figure 1 shows Campania's antibiotic prevalence rates regarding age and sex, in 2016.

Antibiotics prescription was higher in children aged <5 years and in the older adults aged >70 years. Particularly, the highest prevalence rates values were noted for 4-year-old children (60.7%) and 71-year-old individuals (80.3%). After the age of 4, prevalence rates

decreased rapidly, reaching the lowest value at 14 years (31.6%). Thereafter, rates progressively increased, reaching the highest value at 71 years of age. Among children, prevalence rates were slightly higher in males than females (46.8% vs 45.4%, respectively). Among adults, females had average antibiotic prevalence rates higher than males (52.0% vs 44.7%, respectively). The prevalence rates trend was again inverted in the older adults group (70.2% for males vs 67.5% for females). The highest prevalence rates value was reached by 71-year-old females (81.8%), while the lowest one was reached by 33-year-old males (29.3%).

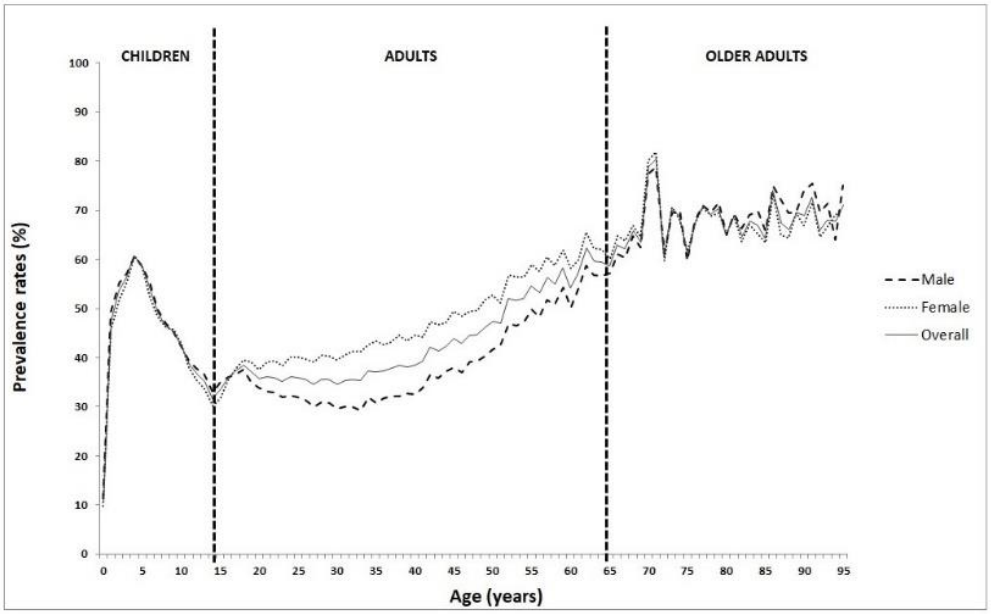


Figure 1 Antibiotic prevalence rates by age and sex in Campania, 2016.

Table 1 shows antibiotic use of the most commonly prescribed antibiotic classes by gender and age group in 2016, as a percentage of people receiving at least one antibiotic prescription.

Penicillins were the most prescribed antibiotic class in all age groups, except for the older adults aged ≥85 years. Regarding the treated population, prevalence rates ranged from 67.9% in children aged ≤6 years to 45.2% in the older adults aged ≥85 years. For the class

of Fluoroquinolones, the results were clearly different, in fact they are the class of antibiotics prescribed less frequently in children ≤ 6 years of age (0.3%) while in terms of prescription records higher values in the older adults (50.0%). The percentage of patients treated with macrolides gradually decreased from 41.7% in children aged ≤6 years to 22.0% in the older adults aged ≥85 years. Finally, the percentage of treated with cephalosporins was similar between children group and the older adults' group, reaching the highest value in the older adults aged ≥85 years (45.3%).

Patterns of antibiotic use were assessed by using prescription prevalence rates according to age within each LHU. In children, standardized prevalence rates at LHU level ranged from 33.1% in Benevento to 47.9% in Naples2 (mean 42.7±5.0%, CV=0.12). In adults, they ranged from 37.9% in Benevento to 46.1% in Naples2 (mean 41.9±2.6%, CV=0.06); and in the older adults, from 59.9% in Benevento to 71.8% in Naples2 (mean 65.3±4.2%, CV=0.06).

Table 1 Prevalence rates of antibiotic prescription stratified by drug classes and patients' characteristics

	Penicillins N=1,582,549 (57.8%)	Cephalosporins N=833,889 (30.5%)	Macrolides N=765,284 (27.9%)	Fluoroquinolones N=736,308 (26.9%)	Others* N=417,655 (15.3%)	Overall treated patients N= 2,738,118
Gender						
F	862,985 (57.4%)	451,770 (30.0%)	422,431 (28.1%)	411,307 (27.4%)	301,722 (20.1%)	1,503,703
M	719,564 (58.3%)	382,119 (31.0%)	343,053 (27.8%)	325,001 (26.3%)	115,933 (9.4%)	1,234,415
Age groups						
Children						
0–6	127,138 (67.9%)	72,752 (38.9%)	78,138 (41.7%)	575 (0.3%)	6,823 (3.6%)	187,176
7–14	118,214 (58.2%)	70,278 (34.6%)	69,628 (34.3%)	2,143 (1.1%))	1,019 (5.0%)	20,296
Adults						
15–24	137,433 (54.4%)	66,179 (26.2%)	73,914 (29.3%)	32,475 (12.9%)	30,838 (12.2%)	252,522
25–34	148,174 (56.3%)	65,219 (24.8%)	71,196 (27.1%)	53,608 (20.4%)	38,668 (14.7%)	263,089
35–44	189,157 (57.8%)	85,303 (26.0%)	88,258 (27.0%)	80,213 (24.5%)	51,113 (15.6%)	327,471
45–54	249,173 (59.8%)	109,563 (26.3%)	109,656 (26.3%)	118,767 (28.5%)	66,721 (16.0%)	416,694
55–64	241,738 (60.4%)	114,034 (28.5%)	105,252 (26.3%)	135,817 (33.9%)	66,664 (16.6%)	400,461
Older adults						
65–74	210,445 (58.3%)	118,85 (32.9%)	93,295 (25.8%)	153,245 (42.5%)	70,959 (19.7%)	360,94
75–84	120,187 (50.8%)	90,751 (38.4%)	56,058 (23.7%)	114,27 (48.3%)	52,544 (22.2%)	236,376
85>=	40,89 (45.2%)	40,96 (45.3%)	19,889 (22.0%)	45,195 (50.0%)	23,135 (25.6%)	90,429

*Others: J01AA Tetracyclines, J01BA Amphenicols, J01EE combinations of Sulfonamides and Trimethoprim, Incl. derivatives, J01FF Lincosamides, J01GB other Aminoglycosides, J01MB other Quinolones, J01XA Glycopeptide Antibacterials, J01XD Imidazole derivatives, J01XE Nitrofuran derivatives, J01XX other antibacterials.

Notes: Drug classes were not mutually exclusive. Prevalence rates were calculated by dividing the number of patients receiving almost one prescription of a specific drug class by the total of patients treated with antibiotics

Figure 2 shows the distribution of antibiotic prevalence rates, in quintiles by municipality within each LHU, for children (Fig. 2a), adults (Fig. 2b), and the older adults (Fig. 2c). Distribution of prevalence rates differed among the age groups.

Among children, higher rates were observed in the coastal areas around Naples, northern Caserta, and eastern Avellino (50.2–68.0%). For the Coastal areas around Naples up to southern Caserta and western Avellino, high prevalence rates were recorded both for adults (46.3–59.5%) and the older adults (71.0–89.5%). Benevento and Salerno showed lower prevalence rates compared to other areas for the three age groups.

For children, prevalence rates reached the lowest value in Corleto Monteforte (Sa-LHU) with 11.3%, and the highest in Guardia Lombardi (Av-LHU) with 68.0% (mean 41.8±10.0%). For adults, the lowest value was in Omignano (Sa-LHU) with 11.4% and the highest in Moschiano (Av-LHU) with 59.5% (mean 40.9±6.7%, CV=0.16). For the older adults' group, prevalence rates reached the lowest value in Romagnano al Monte (Sa-LHU) with 10.6% and the highest in Marzano di Nola (Av-LHU) with 89.5% (mean 62.2±9.9%, CV=0.16).

We found a statistically significant correlation of the rank distribution (rs) at municipality level of the prevalence rates between children and adults (rs=0.56; $P<0.01$). Furthermore, a positive correlation was also found between adults and the older adults (rs=0.79; $P<0.01$), and children and the older adults (rs=0.46; $P<0.01$).

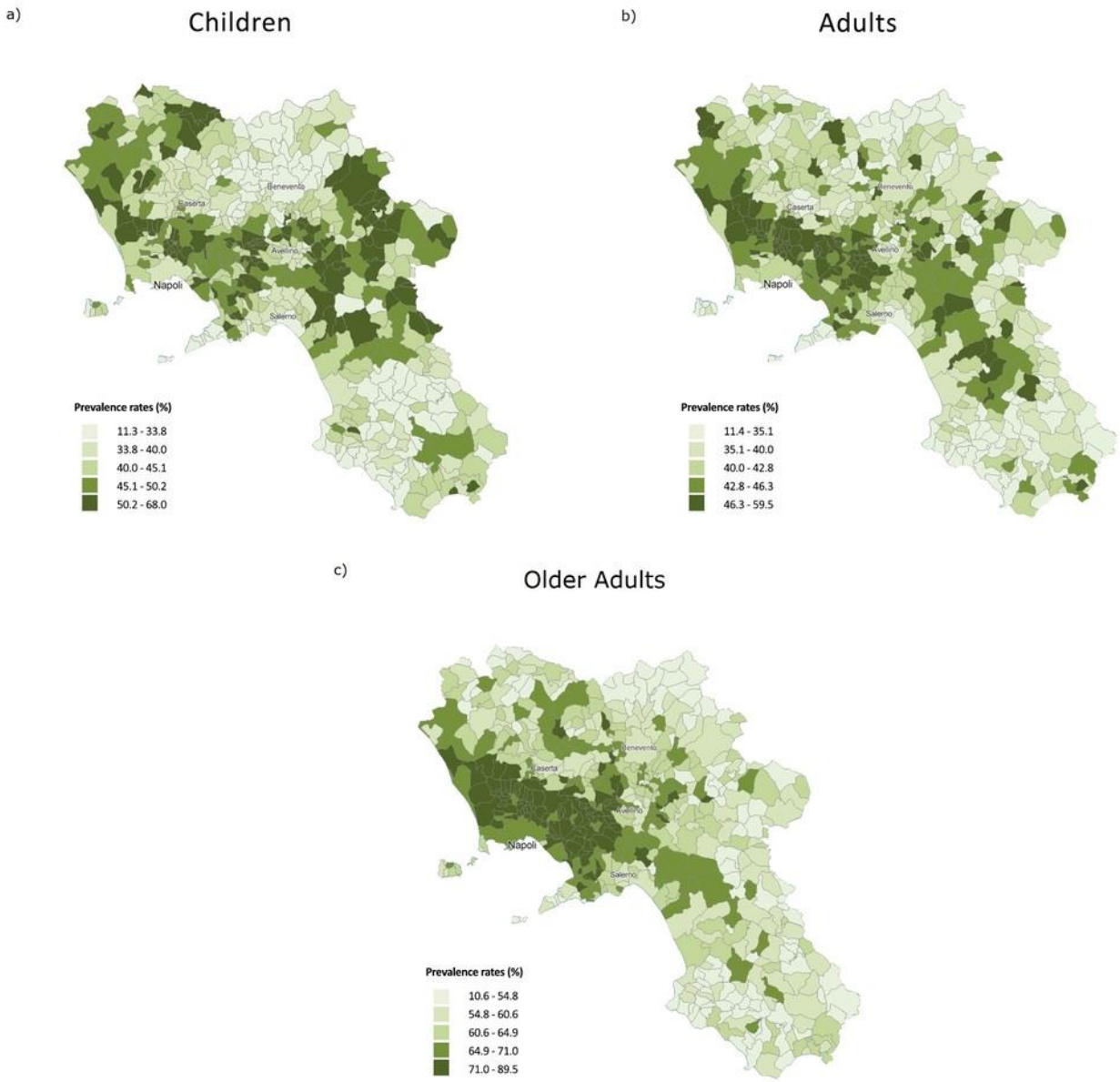


Figure 2a Antibiotic prevalence rates (%) in children at a municipality level in Campania.

Figure 2b Antibiotic prevalence rates (%) in adults at a municipality level in Campania.

Figure 2c Antibiotic prevalence rates (%) in older adults ≥ 65 years at a municipality level in Campania.

Table 2 reports the results of the multivariate analysis for each of the most commonly prescribed antibiotic classes. The age group and municipality type were the main determinants of receiving at least one drug prescription for each of the antibiotic classes. In particular, being a child compared to an adult was the factor associated with the highest risk of drug exposure for penicillins, fluoroquinolones and macrolides (Penicillins, OR=1.22, 95% C.I. 1.21, 1.23; Macrolides, OR=1.66, 95% C.I. 1.21, 1.23). Instead, patients older than 65 years old (the older adults age group) compared to adults had a higher risk of receiving at least a prescription of cephalosporins (OR=2.48, 95% C.I. 2.46, 2.49) and Fluoroquinolones (OR=1.57, 95% C.I. 1.56, 1.58).

Furthermore, living in a urban municipality also slightly increased the probability of receiving a prescription of penicillins (OR=1.09, 95% C.I. 1.08, 1.10), cephalosporins (OR=1.08, 95% C.I. 1.07, 1.09) and fluoroquinolones (OR=1.08, 95% C.I. 1.08, 1.09).

Table 2 Multivariate regression analysis of antibiotic prescription

Characteristics	Penicillins		Cephalosporins		Fluoroquinolones		Macrolides	
	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Gender								
Female	Reference		Reference		Reference		Reference	
Male	1.039 (1.034 - 1.044)	<0,001*	1.034 (1.029 - 1.040)	<0,001*	1.024 (1.018 - 1.029)	<0,001*	0.961 (0.956 - 0.966)	<0,001*
Age Groups								
Children	1.220 (1.211 - 1.229)	<0,001*	0.021 (0.020 - 0.021)	<0,001*	1.531 (1.520 - 1.543)	<0,001*	1.655 (1.643 - 1.667)	<0,001*
Adults	Reference		Reference		Reference		Reference	
Older adults	0.826 (0.821 - 0.831)	<0,001*	2.477 (2.463 - 2.492)	<0,001*	1.569 (1.560 - 1.579)	<0,001*	0.883 (0.877 - 0.889)	<0,001*
Community								
Rural	Reference		Reference		Reference		Reference	<0,001*
Urban	1.094 (1.085 - 1.102)	<0,001*	1.084 (1.074 - 1.093)	<0,001*	1.084 (1.074 - 1.094)	<0,001*	0.978 (0.969 - 0.987)	<0,001*

**p*-value less of 0.05 was considered to be statistically significant.

Abbreviations: OR, odds ratio; CI, confidence interval.

4.4.4 Discussion

In Italy, differences in interregional antibiotic prescribing rates have already been described in the literature, with a higher consumption in southern Italy compared to the northern regions [5,6,10,26]. However, to the best of our knowledge, this is the first study comparing intraregional differences in antibiotic prescription rates for children, adults, and the older adults at municipality level in Italy [10]. Particularly, antibiotic consumption in Campania is described as the highest in Italy [15].

In our study, we found considerable differences at municipality level for antibiotic prevalence rates in children (11.3–68.0%), adults (11.4–59.5%), and the older adults (10.6–89.5%). These data confirmed the results from a previous study conducted in the same cohort of patients, which showed higher prevalence rates in coastal areas around Naples up to southern Caserta and eastern Avellino. Furthermore, the study concluded that higher prevalence rates were related to urban municipalities and low average annual income levels [16]. In our study, we observed a statistically significant correlation of rank distributions of prevalence rates at municipality level between children, adults, and the older adults. Different factors may explain these geographical differences observed in all three groups, such as socio-cultural, demographic, economic determinants, as well as different prescribing attitudes between physicians [5].

In 2016, antibiotics represented 8.4% of the total pharmaceutical expenditure in Campania, with a per capita value of 15€. A large variability existed among prevalence prescription rates and the different LHUs, with a lowest expenditure value in Benevento (12€ per capita) and the highest in Naples3 (18€ per capita) [15].

In this study we also analyzed antibiotic prescription rates according to age. The highest prevalence rates were observed in patients aged 71 years (80.3%) followed by 4-year-old children (60.7%). High prescription rates were also observed in other studies for same age groups [5,27].

In children, the high consumption of antibiotics could be due to their use to treat acute otitis media and upper respiratory tract infections, two of the most prevalent pediatric infections and a major source of inappropriate antibiotic prescribing in outpatient

settings [28]. In Europe, respiratory infections represent the second leading condition in children according to the Disability-Adjusted Life Years (DALY) score [6]. However, this does not justify antibiotic overuse in this age group because common cold and sore throat are usually viral pathological conditions, self-limiting, and often easily self-managed [6]. On the other hand, the implementation of clinical practice guidelines on the correct use of antibiotics to treat acute otitis media in children could avoid antibiotic therapy in 75% of the cases [6]. In the older adults, higher antibiotic prescription rates are justified due to major health problems related to age [9].

We also noted differences in antibiotic prevalence rates by sex, even though doctors are often impartial when prescribing drugs. The analysis showed a higher use of antibiotics in females when aged between 17 and 77 years. In an observational study conducted in Spain, antibiotic prescription rates were also higher in females aged between 15 and 65 years, and it was proportionately related to the frequency of medical visits [29,30]. This relationship was later confirmed by one systematic review in 2016 [31] and a study conducted in the Italian region of Lombardy [5]. Furthermore, other studies have also described higher antibiotic prescription rates in females, mainly due to the treatment of UTIs and a greater number of consultations [29]. The prevalence rates trend was reversed in the older adults group. In males, the prevalence rate of antibiotic prescription was higher in the older adults, possibly because of a higher prevalence rate of chronic diseases [10], higher GPs consultation rates, and increased UTIs [31].

Our analysis showed that the most prescribed antibiotic class were penicillins (ie, 57.8% of the population treated with antibiotics), followed by cephalosporins (30.5%), macrolides (27.9%), and fluoroquinolones (26.9%). Indeed, penicillin is regarded as the first-choice drug when treating the most common infectious diseases in children [6] and the most common respiratory drug infections in patients of all ages [5]. Cephalosporins are used as a second-line therapy to treat the most common pediatric respiratory infections (ie, non-type I allergy to penicillin, treatment failure with antibacterial agents, and presence of severe symptoms) [6]. Of note, in some countries cephalosporins can only be used in hospitals [5]. The overuse of oral cephalosporins is deemed to be

unjustified since these are not recommended as a first-choice therapy for acute otitis media or pharyngo-tonsillitis, the two most common pediatric infectious diseases.

The most prescribed antibiotic class recorded in the three age groups was the Penicillin, except for patients aged ≥85 years. According to a summary of European data on antibiotic consumption, penicillin was the most frequently used antibiotic throughout the countries, as we also saw in our study, while the use of other antibiotic classes varied considerably between countries [32]. This trend has also been evidenced in other studies [13,30,31].

In the older adults ≥85 years, the most prescribed antibiotic class were fluoroquinolones (50.0%), thus confirming the results of a case control study conducted in Lombardy with the same population [5]. The European Surveillance of Antimicrobial Consumption (ESAC) stated that the outpatient use of quinolones has been one of the fastest growing antibiotic classes since the start of their survey in 1997. In Italy, quinolones' highest prescription rate was recorded in 2009, and it continues to increase [26].

Still, this does not justify fluoroquinolones' high prescription rates. Some evidence has demonstrated that their use for treating community-acquired respiratory tract infections, such as pneumonia, has increased in the United States, especially among patients aged ≥65 years [5]. However, in most European countries they are not recommended as first-line antibiotics for the treatment of lower respiratory tract infections in ambulatory care. The inappropriate use of fluoroquinolones, both in the older adults and to treat respiratory diseases, will inevitably lead to the emergence of resistant pneumococcus (*Streptococcus pneumoniae*) and resistant Gram-negative organisms [26].

There are some limitations to our study. We performed a cross-sectional study using pharmaceutical records, which do not provide information about diagnosis. Therefore, we were unable to explore the prescriptions' appropriateness because the diagnosis details were unavailable from our data sources.

The main strengths of our study lie in providing an overview of antibiotics use based on data sources with full coverage of the antibiotic prescriptions for a geographically defined, stable population [34,35]. Antibiotic overuse and misuse contribute to the

development of resistance, treatment failure, and high health costs. Local policies, following WHO's recommendations, should provide training and information to citizens and health care professionals to optimize health resources. Successful elements from other countries' activities should also be implemented [36,37].

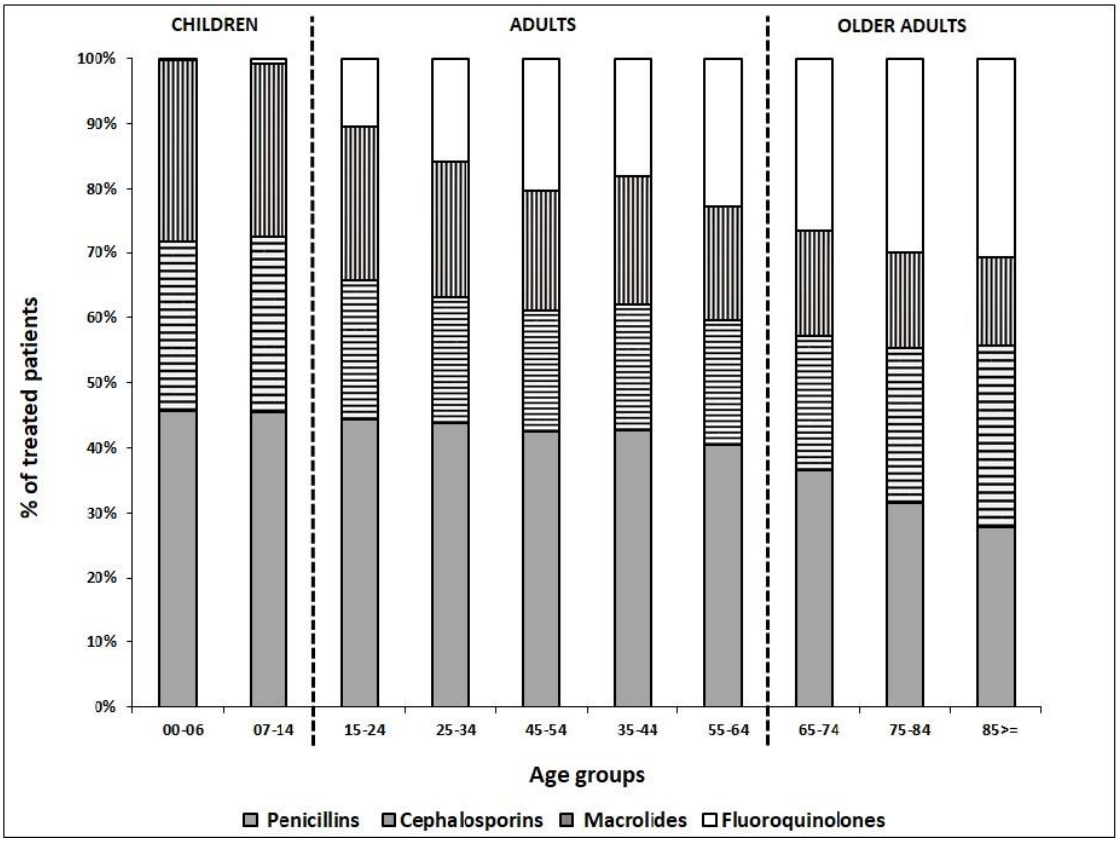
Modifying prescribing patterns is not an easy task. There is evidence that interventions combining educational material and prescribing feedback have successfully promoted appropriateness in drug prescription [38-40]. Furthermore, synergies between different actors involved in healthcare delivery can help achieving better results.

4.4.5 Conclusion

Our study highlights antibiotic prescription differences at a municipality level in Campania and shows large differences within the same Local Health Unit (LHU) according to age. Despite national and international guidelines, aiming to optimize antibiotic prescription in community outpatients, antibiotic use in Campania is considerably higher than in other Italian regions or countries [2]. Moreover, the use of second-line antibiotics is common. On the other hand, we evidenced that different levels of NHS expenditure exist within the same geographical area.

In such context, this study could be a valid background to be used in planning formal audits concerning the prescribing approach to relevant clinical needs in community-acquired infections.

Supplementary Figure S1



Supplementary Table S1

ATC	ATC Description
J01A	**TETRACYCLINES**
J01AA	**Tetracyclines**
J01AA02	Doxycycline
J01AA03	Chlortetracycline
J01AA04	Lymecycline
J01AA05	Metacycline
J01AA06	Oxytetracycline
J01AA07	Tetracycline
J01AA12	Tigecycline
J01B	**AMPHENICOLS**
J01BA	**Amphenicols**
J01BA01	Chloramphenicol
J01BA02	Thiamphenicol
J01C	**BETA-LACTAM ANTIBACTERIALS, PENICILLINS**
J01CA	**Penicillins with extended spectrum**
J01CA01	Ampicillin
J01CA04	Amoxicillin
J01CA06	Bacampicillin
J01CA12	Piperacillin
J01CE	**Beta-lactamase sensitive penicillins**
J01CE01	Benzylpenicillin
J01CE02	Phenoxymethylpenicillin
J01CE08	Benzathine Benzylpenicillin
J01CE09	Procaine Benzylpenicillin
J01CF	**Beta-lactamase resistant penicillins**
J01CF05	Flucloxacillin
J01CR	**Combinations of penicillins, incl. beta-lactamase inhibitors**
J01CR01	Ampicillin and Beta-Lactamase Inhibitor
J01CR02	Amoxicillin and Beta-Lactamase Inhibitor
J01CR05	Piperacillin and Beta-Lactamase Inhibitor
J01CR50	Combinations of Penicillins
J01D	**OTHER BETA-LACTAM ANTIBACTERIALS**
J01DB	**First-generation cephalosporins**
J01DB01	Cefalexin
J01DB03	Cefalotin
J01DB04	Cefazolin
J01DB05	Cefadroxil
J01DB09	Cefradine
J01DC	**Second-generation cephalosporins**
J01DC02	Cefuroxime
J01DC04	Cefaclor
J01DC06	Cefonicid

J01DC10	Cefprozil
J01DD	**Third-generation cephalosporins**
J01DD01	Cefotaxime
J01DD02	Ceftazidime
ATC	**ATC Description**
J01DD04	Ceftriaxone
J01DD08	Cefixime
J01DD09	Cefodizime
J01DD13	Cefpodoxime
J01DD14	Ceftibuten
J01DD16	Cefditoren
J01DE	**Fourth-generation cephalosporins**
J01DE01	Cefepime
J01E	**SULFONAMIDES AND TRIMETHOPRIM**
J01EE	**Combinations of sulfonamides and trimethoprim, incl. derivatives**
J01EE01	Sulfamethoxazole and Trimethoprim
J01F	**MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS**
J01FA	**Macrolides**
J01FA01	Erythromycin
J01FA02	Spiramycin
J01FA06	Roxithromycin
J01FA07	Josamycin
J01FA09	Clarithromycin
J01FA10	Azithromycin
J01FA12	Rokitamycin
J01FA14	Flurithromycin
J01FA15	Telithromycin
J01FA16	Solithromycin
J01FF	**Lincosamides**
J01FF01	Clindamycin
J01FF02	Lincomycin
J01G	**AMINOGLYCOSIDE ANTIBACTERIALS**
J01GB	**Other aminoglycosides**
J01GB01	Tobramycin
J01GB03	Gentamicin
J01GB06	Amikacin
J01GB07	Netilmicin
J01M	**QUINOLONE ANTIBACTERIALS**
J01MA	**Fluoroquinolones**
J01MA02	Ciprofloxacin
J01MA04	Enoxacin
J01MA06	Norfloxacin
J01MA12	Levofloxacin
J01MA14	Moxifloxacin
J01MA17	Prulifloxacin

J01MA22	Tosufloxacin
J01MA23	Delafloxacin
J01MB	**Other quinolones**
J01MB01	Rosoxacin
J01MB02	Nalidixic Acid
J01MB03	Piromidic Acid
ATC	**ATC Description**
J01MB04	Pipemidic Acid
J01MB05	Oxolinic Acid
J01MB06	Cinoxacin
J01MB07	Flumequine
J01X	**OTHER ANTIBACTERIALS**
J01XA	**Glycopeptide antibacterials**
J01XA01	Vancomycin
J01XA02	Teicoplanin
J01XA04	Dalbavancin
J01XD	**Imidazole derivatives**
J01XD01	Metronidazole
J01XE	**Nitrofuran derivatives**
J01XE01	Nitrofurantoin
J01XX	**Other antibacterials**
J01XX01	Fosfomycin
J01XX03	Clofoctol
J01XX08	Linezolid
J01XX09	Daptomycin
J01XX11	Tedizolid

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Chapter 5

General Discussion and Conclusion

5.1 General Discussion

Real World Data (RWD) are an important tool to evaluate drug therapies in real clinical practice, as they measure therapeutic processes, evaluate clinical outcomes and resource allocation in the population. They put researchers in the condition to verify, within the clinical practice, the "value" of a therapeutic intervention, and they do so by providing a picture of the general health condition of the population. In fact, the analysis of the prescriptive profile allows to evaluate the degree of rationality of a pharmacological treatment and provide complex information useful in the field of public healthcare [1].

RWDs are deemed so important that, at international level, there is general agreement regarding the necessity to promote the concept of a learning health system; that is to say a system able to employ all the information RWDs generate in order to both enhance outcomes for patients and better economic performances, including those in the pharmaceutical domain [2].

Although many studies have been carried out using real world data, they are not widely used to support pharmaceutical policies.

Inappropriate prescribing is a common problem, especially among aged patients for, in this regard, there are limited prescribing guidelines [3,4,5]. It causes many preventable adverse events and treatment failures and for this reason there have been many attempts, over the recent years, to develop quality prescribing indicators. Some of these indicators were based on the analysis of prescriptions issued by GPs (for example, using prescribing analysis and cost tabulation data).

Other indicators required very detailed analysis and assessment of clinical records (for example, the medication appropriateness index), which would not be feasible for the large-scale assessment of all GPs.

However, the use of a consensus methodology, which combines evidence available in the literature with professional expert opinion, has proved to be the most effective method to create quality indicators [6].

Evidence-based indicators currently available in the literature are country-specific. Therefore, such indicators cannot be simply and directly transferred from one country to another without an intermediate process which would allow for variation in professional culture or clinical practice.

Despite all these attempts to formulate prescribing indicators are a clear sign of the growing interest of the scientific community in addressing the issue of inappropriate prescribing, there is still a paucity of studies investigating this phenomenon in the Italian population [7].

Within this context, with this research project, we defined a set of explicit indicators for potential inappropriate prescription and drug use and we adapted them to the Italian drug formulary, providing tools specifically tailored to the Italian setting.

The definition of these specific indicators allows us to estimate the appropriateness of therapies that are available and traceable in our country. In addition, these specific indicators put us in the condition to make both temporal and geographical comparisons.

Besides providing specifically tailored indicators, in this thesis, by using administrative health-care databases from two Italian regions, Campania and Lombardy, we also retrospectively assessed geographical variations in drug prescription across selected drug classes (those specifically targeting aged people).

In this respect, our study found many differences between the two regions involved in the study. In general, compared to Lombardy LHUs (in the North of Italy), patients belonging to the Campania LHUs (in the South of Italy) are exposed to higher prevalence rate for all selected drug categories.

Particularly, the drug category that showed the highest geographical variability was antibiotics.

It is interesting to note that such geographical variability has been found not only among different Italian regions, but also among different areas within the same region.

Our study showed that, at a municipality level, another factor influencing the prescription rates of antibiotics was per capita income. Municipalities with low average annual income levels were more than eight times as likely to have antibiotic prevalence rates in quintile 5 compared to high average annual income level municipalities.

Our study has highlighted how socioeconomic and socio-demographic factors can influence the appropriateness of drug use.

The intraregional variability observed in our study can also be explained by different prescribing patterns among physicians and different local health policies.

This is a problem that should be taken into great consideration in the implementation of tailor-made interventions aimed at improving prescriptive practice. In addition, the monitoring of antibiotic use is also an important indicator to improve prescriptive appropriateness.

5.2 Strengths and Weakness

The relevance of our study is strengthened by the size of our sample and the ability to draw on information from a real-world setting. In fact, it is well known that findings from randomized clinical trials (RCTs) are not always representative of clinical practice specially when it comes to evaluate compliance. Conversely, observational studies such as the present report allow us to explore health outcomes in routine care without incurring into the limits of RCTs. Nevertheless, we acknowledge that a number of potential limitations might have influenced our results. The presence of unrecognized confounders could lead to overestimate the magnitude of the association between exposure and especially if compared to RCTs results. In particular, our findings may be subject to confounding by indication due to the lack of randomization.

Pharmacy claims data do not contain information about Over-The-Counter (OTC) medications and out-of-pocket expenditure and this could imply a general underestimation of data. In addition, our dataset does not include information about diagnosis. Therefore, we were unable to explore prescriptions' appropriateness as diagnosis details were not part of our data sources.

Despite these limitations, our findings are in line with findings from other highlighted studies.

5.3 Thesis Impact

The results of the work presented in this thesis can and indeed have an impact in a number of areas.

This thesis has contributed to the field of PIP by providing a set of explicit indicators for both potential inappropriate prescription and drug use which were subsequently adapted to the Italian drug formulary. In this way, the work presented here has provided tools which are specifically tailored to the Italian context. Moreover, the definition of these specific indicators has allowed us to estimate the appropriateness of all the available and traceable therapies in our country. Those same indicators have also enabled us to make both temporal and geographical comparisons. To date, four publications have arisen from this thesis, as well as several poster and oral presentations at academic conferences.

Beside the academic world, the findings of this thesis have also potential impacts in the area of policy. A set of indicators, which have been shown in paragraph 4.1, could, in fact, be disclosed and shared with GPs and other healthcare professionals. In this way, knowledge regarding the extension of inappropriate prescribing could raise awareness among professionals and make evident the need to implement new, tailor-made, policies apt to improve prescriptive practice.

One such effective policy measure could be the extension of the role of pharmacists, as they could optimise drug prescribing and improve medicines management. Pharmacists could, in fact, advise patients and prescribers and intervene in case of drug-related problems; they could do so in partnerships with GPs.

Overall, the results of this thesis may contribute to make evident the fact that the implementation of interventions aimed at improving prescriptive practice in the elderly would bring about benefits to both the patients' health and the health expenditure system.

Moreover, the fact that the findings of this thesis have been largely disseminated might have as likely result an improvement of prescribers' knowledge and beliefs concerning the consequences of PIP. Such improvement could lead to behavioural changes resulting in a more rational prescribing.

Finally, the thesis' main findings could raise awareness of PIP so as to highlight its importance even among the general public.

5.4 Conclusion

This thesis has shown how useful real-world data can be to evaluate drug prescription appropriateness.

In order to improve quality of prescription, it would be extremely important to design shared therapeutic protocols. Such protocols would be a key factor for decision-makers to improve the quality of care. Once protocols are established, they can be effectively implemented by issuing educational interventions and data monitoring aimed at both the optimization of health resources and the correct utilization of drugs.

5.5 Future Perspective

The thesis reports only the first results of the EDU.RE.DRUG project but in spite of that, it has highlighted a high drug consumption rate, and a high potential inappropriate drug prescription in primary care setting. Even taking into account the fact that, in some specific cases, the phenomena depicted by our results may have a clinical justification, potentially inappropriate prescription has, nonetheless, been associated with negative outcomes in many previous studies. Therefore, such association which emerges as clear also in our results, suggests that our project describes and highlights a real and worrying situation which is characterized by drug-related issues. For this reason, it would be extremely important to implement strategies aimed at promoting proper prescription and drug use. Yet, to the best of our knowledge, relatively few trials have focused on those strategies which would be needed to improve appropriate prescribing in primary care.

Therefore, the findings of the present study may work as basis for future studies aimed at implementing health policies and educational efforts to improve medications prescriptions.

In Italy GPs have a key role in prescribing drugs, in summarizing pharmacological recommendations from specialists and in carrying out the therapeutic reconciliation after a hospital discharge. Therefore, they are the preferred target of an intervention aimed to optimize drug management. Nevertheless, an optimal strategy must necessarily include also all the actors involved in the prescriptive process as well as the patients themselves. In the following phases of our study we will evaluate the effectiveness of training and information interventions aimed not only at general practitioners but also to their patients.

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Chapter 6

Appendix

Appendix I. Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
ANTICHOLINERGICS				
First-generation antihistamines • Brompheniramine • Carbinoxamine • Chlorpheniramine • Clemastine • Cyproheptadine • Dexbrompheniramine • Dexchlorpheniramine • Dimenhydrinate • Diphenhydramine (oral) • Doxylamine • Hydroxyzine • Meclizine • Promethazine • Pyrilamine • Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Moderate	Strong
ANTIPARKINSONIAN AGENTS				
• Benztropine (oral) • Trihexyphenidyl	Not recommended for prevention or treatment of extrapyramidal symptoms with antipsychotics; more effective agents available for treatmeant of Parkinson disease effective agents available for treatment of Parkinson disease.	Avoid	Moderate	Strong
ANTISPASMODICS				
• Atropine (excludes ophthalmic) • Belladonna alkaloids • Clidinium-chlordiazepoxide • Dicyclomine Homatropine excludes opthalmic) • Hyoscyamine • Methscopolamine • Propantheline • Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
ANTITHROMBOTICS				
• Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
ANTI-INFECTIVE				
• Nitrofurantoin	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available.	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Low	Strong
CARDIOVASCULAR				
• Peripheral alpha-1 blockers for treatment of hypertension • Doxazosin • Prazosin • Terazosin	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile.	Avoid use as an antihypertensive	Moderate	Strong
• Central alpha-agonists		Avoid as first-line antihypertensive	Low	Strong
• Clonidine for first-line treatment of hypertension • Other CNS alpha-agonists • Guanabenz • Guanfacine • Methyldopa • Reserpine (>0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension.	Avoid other CNS alpha-agonists as listed	Low	Strong
• Disopyramide	May induce heart failure in older adults because of potent negative inotropic action; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
CARDIOVASCULAR				
• Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure.	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
• Digoxin for first-line treatment of atrial fibrillation or of heart failure	**Use in atrial fibrillation:** should not be used as a first-line agent in atrial fibrillation. **Use in heart failure**: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all of the evidence concerns use in HFrEF. There is strong evidence for other agents as first-line therapy to reduce hospitalizations and mortality in adults with HFrEF. In heart failure, higher dosages are not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in those with stage 4 or 5 chronic kidney disease	Avoid this rate control agent as first line therapy for atrial fibrillation. Avoid as first-line therapy for heart. If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day failur	Atrial fibrillation: low Heart failure: low Dosage >0.125 mg/day: moderate	Atrial fibrillation: strong Heart failure: strong Dosage >0.125 mg/day: strong
• Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia.	Avoid	High	Strong
• Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; may be reasonable first-line therapy in patients with concomitant heart failure.	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
CENTRAL NERVOUS SYSTEM				
• Antidepressants, alone or in combination • Amitriptyline • Amoxapine • Clomipramine • Desipramine • Doxepin >6 mg/day • Imipramine • Imipramine • Nortriptyline • Protriptyline • Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo	Avoid	High	Strong
• Antipsychotics, first (conventional) and second (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	Moderate	Strong
BARBITURATES				
• Amobarbital • Butabarbital • Butalbital • Mephobarbital • Pentobarbital • Phenobarbital • Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
BENZODIAZEPINES				
Short and intermediate acting: • Alprazolam • Estazolam • Lorazepam • Oxazepam • Temazepam • Triazolam *Long acting:* • Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) • Clonazepam • Clorazepate • Diazepam • Flurazepam • Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long acting agents; in g eneral, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults. May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia	Avoid	Moderate	Strong
• Meprobamate	High rate of physical dependence; sedating.	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") • Eszopiclone • Zaleplon • Zolpidem	Nonbenzodiazepinecbenzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased hospitalizations; motor vehicle crashes; minimal emergency room visits/improvement in sleep latency and duration	Avoid	Moderate	Strong
• Ergoloid mesylates (dehydrogenated ergot alkaloids) • Isoxsuprine	Lack of efficacy A	Avoid	High	Strong
ENDOCRINE				
Androgens • Methyltestosterone • Testosterone	Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
• Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
• Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 µg twice weekly) with their healthcare provider	Avoid systemic estrogen (eg, oral and topical patch) Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, recurrent lower urinary tract infections, and other vaginal symptoms	Oral and patch: high Vaginal cream or vaginal tablets: moderate	Oral and patch: strong Topical vaginal cream or tablets: weak
• Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except for patients rigorously diagnosed by evidence-based criteria with growth hormone deficiency due to an established etiology	High	Strong
• Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapid acting insulin dosed levels without concurrent use of basal or long-acting according to current blood glucose insulin.	Avoid	Moderate	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
• Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
SULFONYLUREAS, LONG ACTING				
• Chlorpropamide • Glimepiride • Glyburide (also known as glibenclamide)	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
GASTROINTESTINAL				
• Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	Moderate	Strong
• Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
• Proton-Pump Inhibitors	Risk of Clostridium difficile infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2-receptor antagonists)	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
PAIN MEDICATIONS				
• Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non–cyclooxygenase-selective NSAIDs, oral: • Aspirin >325 mg/day • Diclofenac • Diflunisal • Etodolac • Fenoprofen • Ibuprofen • Ketoprofen • Meclofenamate • Mefenamic acid • Meloxicam • Nabumetone • Naproxen • Oxaprozin • Piroxicam • Sulindac • Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3-6 months and in ~2%-4% of patients treated for 1 year; these trends continue with longer duration of use. Also, can increase blood pressure and induce kidney injury. Risks are dose related	Avoid chronic use, unless other alternatives are not effective, and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
• Indomethacin Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults. Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
SKELETAL MUSCLE RELAXANTS				
• Carisoprodol • Chlorzoxazone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
GENITOURINARY				
• Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

Appendix II. Beers Criteria for Potentially Inappropriate Medication Use in Older Adults due to Drugs-Disease or drug-Syndrome Interactions. That may exacerbate the Disease or syndrome.

Disease or Syndrome	Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
CARDIOVASCULAR					
HEART FAILURE	• Avoid: Cilostazol • Avoid in heart failure with reduced ejection fraction: • Nondihydropyridine CCBs (diltiazem, • verapamil) • Use with caution in patients with heart failure who are asymptomatic; • avoid in patients with symptomatic heart failure: • NSAIDs and COX-2 inhibitors • Thiazolidinediones (pioglitazone, rosiglitazone) • Dronedarone	Potential to promote fluid retention and/or exacerbate heart failure (NSAIDs and COX-2 inhibitors, non-dihydropyridine CCBs, thiazolidinediones); potential to increase mortality in older adults with heart failure (cilostazol and dronedarone)	As noted, avoid or use with caution	Cilostazol: low Nondihydropyridine CCBs: moderate NSAIDs: moderate COX-2 inhibitors: low Thiazolidinediones: high Dronedarone: high	Cilostazol: strong Nondihydropyridine CCBs: strong NSAIDs: strong COX-2 inhibitors: strong Thiazolidinediones: Strong Dronedarone: strong
SYNCOPE	AChEIs Nonselective peripheral alpha-1 blockers (ie, doxazosin, prazosin, terazosin) Tertiary TCAs Antipsychotics: • Chlorpromazine • Thioridazine • Olanzapine	AChEIs cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia. Nonselective peripheral alpha-1 blockers cause orthostatic blood pressure changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension. Tertiary TCAs and the antipsychotics listed increase the risk of orthostatic hypotension or bradycardia.	Avoid	AChEIs, TCAs, and antipsychotics: high Nonselective peripheral alpha-1 blockers: high	AChEIs and TCAs: Strong Nonselective peripheral alpha-1 blockers and antipsychotics: weak

CENTRAL NERVOUS SYSTEM					
DELIRIUM	• Anticholinergics • Antipsychotics Benzodiazepines • Corticosteroids (oral and parenteral) • H2-receptor antagonists - Cimetidine - Famotidine - Nizatidine - Ranitidine - Meperidine • Nonbenzodiazepine, benzodiazepine • receptor agonist hypnotics: • eszopiclone, zaleplon, zolpidem	Avoid in older adults with or at high risk of delirium because of potential of inducing or worsening delirium. Avoid antipsychotics for behavioral problems of dementia and/or delirium unless non-pharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid	H2-receptor antagonists: low All others: moderate	Strong
DEMENTIA OR COGNITIVE IMPAIRMENT	• Anticholinergics • Benzodiazepines • Nonbenzodiazepine, benzodiazepine • receptor agonist hypnotics - Eszopiclone - Zaleplon - Zolpidem • Antipsychotics, chronic and as-needed use	Avoid because of adverse CNS effects. Avoid antipsychotics for behavioral problems of dementia and/or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid	Moderate	Strong
HISTORY OF FALLS OR FRACTURES	• Antiepileptics • Antipsychotics Benzodiazepines	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting	Avoid unless safer alternatives are not available;	Opioids: moderate All others: high	Strong

	• Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics - Eszopiclone - Zaleplon - Zolpidem • Antidepressants - TCAs - SSRIs - SNRIs • Opioids	benzodiazepines are not safer than long-acting ones. If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (ie, antiepileptics, opioid-receptor agonists, antipsychotics, antidepressants, nonbenzodiazepine and benzodiazepine receptor agonist hypnotics, other sedatives/hypnotics) and implement other strategies to reduce fall risk. Data for antidepressants are mixed but no compelling evidence that certain antidepressants confer less fall risk than others.	avoid antiepileptics except for seizure and mood disorders Opioids: avoid except for pain management in the setting of severe acute pain (eg, recent fractures or joint replacement)		
PARKINSON DISEASE	• Antiemetics - Metoclopramide - Prochlorperazine - Promethazine • All antipsychotics (except quetiapine, clozapine, pimavanserin)	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Exceptions: Pimavanserin and clozapine appear to be less likely to precipitate worsening of Parkinson disease. Quetiapine has only been studied in low-quality clinical trials with efficacy comparable to that of placebo in five trials and to that of clozapine in two others.	Avoid	Moderate	Strong

GASTROINTESTINAL					
HISTORY OF GASTRIC OR DUODENAL ULCERS	• Aspirin >325 mg/day • Non–COX-2–selective NSAIDs	May exacerbate existing ulcers or cause new/additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (ie, proton-pump inhibitor or misoprostol)	Moderate	Strong
KIDNEY/URINARY TRACT					
CHRONIC KIDNEY DISEASE STAGE 4 OR HIGHER (CREATININE CLEARANCE <30 ML/MIN)	• NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylated salicylates)	May increase risk of acute kidney injury and further decline of renal function.	Avoid	Moderate	Strong
URINARY INCONTINENCE (ALL TYPES) IN WOMEN	• Estrogen oral and transdermal (excludes intravaginal estrogen) • Peripheral alpha-1 blockers - Doxazosin - Prazosin - Terazosin	Lack of efficacy (oral estrogen) and aggravation of incontinence (alpha-1 blockers)	Avoid in women	Estrogen: high Peripheral alpha-1 blockers: moderate	Estrogen: strong Peripheral alpha-1 blockers: strong
LOWER URINARY TRACT SYMPTOMS, BENIGN PROSTATIC HYPERPLASIA	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence.	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Strong

Appendix III. Beers Criteria for Potentially Inappropriate Medication: Drugs to be used with caution in older adults.

Drug(s)	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
• Aspirin for primary prevention of cardiovascular disease and colorectal cancer	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease.	Use with caution in adults ≥70 years	Moderate	Strong
• Dabigatran • Rivaroxaban	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults ≥75 years	Use with caution for treatment of VTE or atrial fibrillation in adults ≥75 years	Moderate	Strong
• Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.	Use with caution in adults ≥75 years	Moderate	Strong
• Antipsychotics • Carbamazepine • Diuretics • Mirtazapine • Oxcarbazepine • SNRIs • SSRIs • TCAs • Tramadol	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong
• Dextromethorphan/ quinidine	Limited efficacy in patients with behavioral symptoms of dementia (does not apply to treatment of PBA). May increase risk of falls and concerns with clinically significant drug interactions. Does not apply to treatment of pseudobulbar affect.	Use with caution	Moderate	Strong
• Trimethoprim/sulfamethoxazole	Increased risk of hyperkalemia when used concurrently with an ACEI or ARB in presence of decreased creatinine clearance	Use with caution in patients on ACEI or ARB and decreased creatinine clearance	Low	Strong

Appendix IV. Beers Criteria for Potentially Clinically Important Drug-Drug Interactions that should be avoided in older adults.

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
RAS inhibitor (ACEIs, ARBs, aliskiren) or potassium-sparing diuretics (amiloride, triamterene)	Another RAS inhibitor (ACEIs, ARBs, aliskiren)	Increased risk of hyperkalemia	Avoid routine use in those with chronic kidney disease stage 3a or higher	Moderate	Strong
Opioids	Benzodiazepines	Increased risk of overdose	Avoid	Moderate	Strong
Opioids	Gabapentin, pregabalin	Increased risk of severe sedation-related adverse events, including respiratory depression and death	Avoid; exceptions are when transitioning from opioid therapy to gabapentin or pregabalin, or when using gabapentinoids tomreduce opioid dose, although caution should be used in all circumstances	Moderate	Strong
Anticholinergic	Anticholinergic	Increased risk of cognitive decline	Avoid; minimize number of anticholinergic drugs	Moderate	Strong
Antidepressants (TCAs, SSRIs, and SNRIs) **Antipsychotics** **Antiepileptics** **Benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs")** **Opioids**	Any combination of three or more of these CNS-active drugs	Increased risk of falls (all) and of fracture (benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics)	Avoid total of three or more CNS-active drugsa; minimize number of CNS-active drugs	Combinations including benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics or opioids: high All other combinations: moderate	Strong
Corticosteroids, oral or parenteral	NSAIDs	Increased risk of peptic ulcer disease or gastrointestinal bleeding	Avoid; if not possible, provide gastrointestinal protection	Moderate	Strong
Lithium	ACEIs	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations	Moderate	Strong
Lithium	Loop diuretics	Increased risk of lithium toxicity	Avoid; monitor lithium oncentrations	Moderate	Strong
Peripheral α-1 blockers	Loop diuretics	Increased risk of urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Phenytoin	Trimethoprim-sulfamethoxazole	Increased risk of phenytoin toxicity	Avoid	Moderate	Strong
Theophylline	Cimetidine	Increased risk of theophylline	Avoid	Moderate	Strong

		toxicity			
Theophylline	Ciprofloxacin	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Ciprofloxacin	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Macrolides (excluding azithromycin)	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Trimethoprim-sulfamethoxazole	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor closely for bleeding	High	Strong

Appendix V. Beers Criteria for Medication that should be avoided or have their dosage reduced with varying levels of kidney function in older adults.

Medication Class and Medication	Creatine Clearance at which action required, ml/min	Rationale	Recommandation	Quality of Evidence	Strenght of Recommandation
ANTI-INFECTIVE					
Ciprofloxacin	<30	Increased risk of CNS effects (eg, seizures, confusion) and tendon rupture.	Doses used to treat common infections typically require reduction when CrCl <30 mL/min	Moderate	Strong
Trimethoprim/sulfamethoxazole	<30	Increased risk of worsening of renal function and hyperkalemia	Reduce dose if CrCl 15-29 mL/min Avoid if CrCl <15 mL/min	Moderate	Strong
CARDIOVASCULAR OR HEMOSTASIS					
Amiloride	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Lack of evidence for efficacy and safety in patients with a CrCl <25 mL/min	Avoid	Moderate	Strong
Dabigatran	<30	Lack of evidence for efficacy and safety in individuals with a CrCl <30 mL/min. Label dose for patients with a CrCl 15-30 mL/min based on pharmacokinetic data.	Avoid; dose adjustment advised when CrCl >30 mL/min in the presence of drug-drug interactions	Moderate	Strong
Dofetilide	<60	QTc prolongation and torsade de pointes	Reduce dose if CrCl 20-59 mL/min Avoid if CrCl <20 mL/min	Moderate	Strong
Edoxaban	15-50 <15 or >95	Lack of evidence of efficacy or safety in patients with a CrCl <30 mL/min	Reduce dose if CrCl 15-50 mL/min Avoid if CrCl <15 or >95 mL/min	Moderate	Strong
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	<50	Lack of efficacy or safety evidence in patients with a CrCl <30 mL/min	Nonvalvular atrial fibrillation: reduce dose if CrCl 15-50 mL/min; avoid if CrCl <15 mL/min. Venous thromboembolism treatment and for VTE prophylaxis with hip or knee	Moderate	Strong

			replacement: avoid if CrCl <30 ml/min		
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
CENTRAL NERVOUS SYSTEM AND ANALGESICS					
Duloxetine	<30	Increased gastrointestinal adverse effects (nausea, diarrhea)	Avoid	Moderate	Strong
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce Dose Extended release: avoid	Moderate	Strong
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong
HYPERURICEMIA					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

Appendix VI. STOPP/START Criteria 2013-2014

STOPP CRITERIA
A. CARDIOVASCULAR SYSTEM
A1. Digoxin at a long-term dose > 125 µg/day with impaired renal function (*increased risk of toxicity*)
A2. Loop diuretic for dependent ankle edema only i.e. no clinical signs of heart failure (*no evidence of efficacy, compression hosiery usually more appropriate*)
A3. Loop diuretic as first-line monotherapy for hypertension (*safer, more effective alternatives available*)
A4. Thiazide diuretic with a history of gout (*may exacerbate gout*)
A5. Beta-blocker in combination with verapamil (*risk of symptomatic heart block*)
A6. Use of diltiazem or verapamil with NYHA class III or IV heart failure (*may worsen heart failure*)
A7. Aspirin with a past history of peptic ulcer disease without histamine H2-receptor antagonist or proton pump inhibitor (*risk of bleeding*)
A8. Aspirin at dose > 150 mg/day (*increased bleeding risk, no evidence for increased efficacy*)
A9. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (*no proven added benefit*)
A10. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (*no proven benefit*)
A11. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (*high risk of bleeding*)
B. CENTRAL NERVOUS SYSTEM AND PSYCHOTROPIC DRUGS
B1. Tricyclic antidepressants (TCAs) with dementia (*risk of worsening cognitive impairment*)
B2. TCAs with glaucoma *(likely to exacerbate glaucoma)*
B3. TCAs with cardiac conductive abnormalities (*pro-arrhythmic effects*)
B4. TCAs with constipation (*likely to worsen constipation*)
B5. TCAs with an opiate or calcium channel blocker (*risk of severe constipation*)
B6. TCA's with prostatism or prior history of urinary retention (*risk of urinary retention*
B7. Long-term (i.e. > 1 month), long-acting benzodiazepines, e.g. chlordiazepoxide, fluazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites, e.g. diazepam (*risk of prolonged sedation, confusion, impaired balance, falls*)
B8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (*risk of confusion, hypotension, extrapyramidal side effects, falls*)
B9. Long-term neuroleptics (> 1 month) in those with parkinsonism (*likely to worsen extrapyramidal symptoms*)
B10. Anticholinergics to treat extrapyramidal sideeffects of neuroleptic medications (*risk of anticholinergic toxicity*)
B11. Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatremia (*non-iatrogenic hyponatremia < 130 mmol/l within the previous 2 months*)
B12. Prolonged use (> 1 week) of first-generation antihistamines, i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine (*risk of sedation and anti-cholinergic side effects*)

C. GASTROINTESTINAL SYSTEM
C1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhea of unknown cause (*risk of delayed diagnosis, may exacerbate constipation with overflow diarrhea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis*)
C2. Prochlorperazine (Stemetil) or metoclopramide with parkinsonism (*risk of exacerbating parkinsonism*)
C3. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (*dose reduction or earlier discontinuation indicated*)
C4. Anticholinergic antispasmodic drugs with chronic constipation (*risk of exacerbation of constipation*)
D. RESPIRATORY SYSTEM
D1. Theophylline as monotherapy for COPD (*safer, more effective alternative; risk of adverse effects due to narrow therapeutic index*)
D2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-tosevere COPD (*unnecessary exposure to long-term side effects of systemic steroids*)
D3. Nebulized ipratropium with glaucoma (*may exacerbate glaucoma*)
E. MUSCULOSKELETAL SYSTEM
E1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 -receptor antagonist, PPI or misoprostol (*risk of peptic ulcer relapse*)
E2. NSAID with moderate-to-severe hypertension (*risk of exacerbation of hypertension*)
E3. NSAID with heart failure (*risk of exacerbation of heart failure*)
E4. Long-term use of NSAID (> 3 months) for symptom relief of mild osteoarthritis (*simple analgesics preferable and usually as effective for pain relief*)
E5. Warfarin and NSAID together (*risk of gastrointestinal bleeding*)
E6. NSAID with chronic renal failure* (*risk of deterioration in renal function*)
E7. Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthrtitis or osterarthritis (*risk of major systemic corticosteroid side-effects*)
E8. Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol (*allopurinol first-choice prophylactic drug in gout*)
F. UROGENITAL SYSTEM
F1 Bladder antimuscarinic drugs with dementia (*risk of increased confusion, agitation*)
F2. Antimuscarinic drugs with chronic glaucoma (*risk of acute exacerbation of glaucoma*)
F3. Antimuscarinic drugs with chronic constipation (*risk of exacerbation of constipation*)
F4. Antimuscarinic drugs with chronic prostatism (*risk of urinary retention*)
F5. Alpha-blockers with long-term urinary catheter in situ, i.e. more than 2 months (*drug not indicated*).
G. ENDOCRINE SYSTEM
G1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus (*risk of prolonged hypoglycemia*)

G2. Beta-blockers in those with diabetes mellitus and frequent hypoglycemic episodes i.e. _ 1 episode per month (*risk of masking hypoglycemic symptoms*)
G3. Estrogens with a history of breast cancer or venous thromboembolism (*increased risk of recurrence*)
G4. Estrogens without progestogen in patients with intact uterus (*risk of endometrial cancer*)
H. DRUGS THAT ADVERSELY AFFECT FALLERS
H1. Benzodiazepines (*sedative, may cause reduced sensorium, impair balance*)
H2. Neuroleptic drugs (*may cause gait dyspraxia, parkinsonism*)
H3. Vasodilator drugs with persistent postural hypotension, i.e. recurrent > 20mmHg drop in systolic blood pressure (*risk of syncope, falls*)
I. ANALGESIC DRUGS
I1. Use of long-term powerful opiates, e.g. morphine or fentanyl as first-line therapy for mild-to-moderate pain (*World Health Organization analgesic ladder not observed*)
I2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (*risk of severe constipation*)
J. DUPLICATE DRUG CLASSES
Any duplicate drug class prescription, e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors (*optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug*).

Appendix VII. Table 2. STOPP/START Criteria 2013-2014

START CRITERIA
A. CARDIOVASCULAR SYSTEM
A1. Warfarin in the presence of chronic atrial fibrillation
A2. Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin
A3. Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm
A4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg
A5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years
A6. Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure
A7. ACE inhibitor following acute myocardial infarction
A8. Beta-blocker with chronic stable angina
B. RESPIRATORY SYSTEM
B1. Regular inhaled Beta2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD
B2. Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted FEV1 < 50%
B3. Home continuous oxygen with documented chronic type 1 respiratory failure (pO_2 < 8.0 kPa, pCO_2 < 6.5 kPa) or type 2 respiratory failure (pO_2 < 8.0 kPa, pCO_2 > 6.5 kPa)
C. CENTRAL NERVOUS SYSTEM
C1. L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability
C2. Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months
D. GASTROINTESTINAL SYSTEM
D1. Proton pump inhibitor with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation
D2. Fiber supplement for chronic, symptomatic diverticular disease with constipation
E. MUSCULOSKELETAL SYSTEM
E1. Disease-modifying antirheumatic drug (DMARD) with active moderate/severe rheumatoid disease lasting > 12 weeks
E2. Bisphosphonates in patients taking maintenance corticosteroid therapy
E3. Calcium and vitamin D supplement in patients with known osteoporosis (previous fragility fracture, acquired dorsal kyphosis)
F. ENDOCRINE SYSTEM
F1. ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy, i.e. overt urinalysis proteinuria or microalbuminuria (> 30 mg/24 hours) ± serum biochemical renal impairment

Appendix VIII. List of drugs for ACB score

ATC code	Drug Name	Score
A02BA01	Cimetidine	1
A02BA02	Ranitidine	1
A03AA07	Dicyclomine (Dicycloverine)	3
A03AX08	Alverine	1
A03BA01	Atropine	3
A03BA03	Hyoscyamine	3
A03BA04	Belladonna	2
A03CA02	Clidinium	1
A03CA34	Propantheline	3
A04AB02	Dimenhydrinate	3
A04AD01	Scopolamine	3
A07DA03	Loperamide	1
B01AA03	Warfarin	1
B01AC07	Dipyridamole	1
B01AC30	Dipyridamole	1
C01AA05	Digoxin	1
C01BA01	Quinidine	1
C01BA03	Disopyramide	1
C01DA14	Isosorbide	1
C02DB02	Hydralazine	1
C03BA04	Chlorthalidone	1
C03CA01	Furosemide	1
C03EB01	Furosemide/Triamterene	2
C03DB02	Triamterene	1
C07AB02	Metoprolol	1
C07AB03	Atenolol	1
C07CA02	Chlorthalidone	1
C07CB02	Chlorthalidone/Metoprolol	2
C07CB03	Chlorthalidone/Atenolol	2
C08CA05	Nifedipine	1
C09AA01	Captopril	1
C09BA01	Captopril	1
D07AB02	Hydrocortisone	1
G04BD02	Flavoxate	3
G04BD04	Oxybutynin	3
G04BD06	Propiverine	3
G04BD07	Tolterodine	3
G04BD08	Solifenacin	3
G04BD09	Trospium	3
G04BD10	Darifenacin	3
G04BD11	Fesoterodine	3
H02AB07	Prednisone	1

ATC code	Drug Name	Score
M03BA03	Methocarbamol	3
M03BC01	Orphenadrine	3
N04AB02	Orphenadrine	3
M03BX07	Colchicine	1
M04AC01	Colchicine	1
M03BX08	Cyclobenzaprine	2
N02AA01	Morphine	1
N02AB02	Meperidine	2
N02AB03	Fentanyl	1
N02AG01	Atropine/Morphine	3
N02AJ06	Codeine	1
N02BG06	Nefopam	2
N03AF01	Carbamazepine	2
N03AF02	Oxcarbazepine	2
N04AA01	Trihexyphenidyl	3
N04AC01	Benztropine	3
N04BB01	Amantadine	2
N05AA01	Chlorpromazine	3
N05AA02	Methotrimeprazine (Levomepromazine)	2
N05AB03	Perphenazine	3
N05AB06	Trifluoperazine	3
N05AC02	Thioridazine	3
N05AD01	Haloperidol	1
N05AE02	Molindone	2
N05AG02	Pimozide	2
N05AH01	Loxapine	2
N05AH02	Clozapine	3
N05AH03	Olanzapine	3
N05AH04	Quetiapine	3
N05AH05	Asenapine	1
N05AX08	Risperidone	1
N05AX12	Aripiprazole	1
N05AX13	Paliperidone	1
N05AX14	Iloperidone	1
N05BA01	Diazepam	1
N05BA05	Clorazepate	1
N05BA12	Alprazolam	1
N05BB01	Hydroxyzine	3
N06AA01	Desipramine	3
N06AA02	Imipramine	3
N06AA04	Clomipramine	3
N06AA06	Trimipramine	3
N06AA09	Amitriptyline	3

ATC code	Drug Name	Score
N06AA10	Nortriptyline	3
N06AA12	Doxepin	3
N06AA17	Amoxapine	3
N06AB05	Paroxetine	3
N06AB08	Fluvoxamine	1
N06AX05	Trazodone	1
N06AX12	Bupropion	1
N06AX16	Venlafaxine	1
R03DA04	Theophylline	1
R05DA04	Codeine	1
R05DA20	Codeine	1
R06AA02	Diphenhydramine	3
R06AA04	Clemastine	3
R06AA08	Carbinoxamine	3
R06AA09	Doxylamine	3
R06AB01	Brompheniramine	3
R06AB04	Chlorpheniramine	3
R06AD01	Alimemazine	1
R06AD02	Promethazine	3
R06AE05	Meclizine	3
R06AE07	Cetirizine	1
R06AE09	Levocetirizine	1
R06AX02	Cyproheptadine	2
R06AX13	Loratadine	1
R06AX27	Desloratadine	1

Appendix IX. List of drugs for SL score

ATC code	Drug Name	Score
A03CA02	Chlordiazepoxide with klidin	1
A03CA05	Diazepam with glycopyrronium	1
A03CA07	Oxazepam with ambutonium	1
A03FA01	Metoclopramide	1
A04AD01	Scopolamine	1
G04BE30	Meprobamate with testosterone and yohimbine	1
M01AB51	Indometacin with ethylmorphine	1
M01AE51	Ibuprofen with codeine	1
N02AA01	Morphine	1
N02AA05	Oxycodone	1
N02AA55	Oxycodone	1
N02AB03	Fentanyl	1
N02AE01	Buprenorphine	1
N02AG01	Morphine	1
N02AJ17	Oxycodone	1
N02AJ06	Codeine	1
N02AX02	Tramadol	1
N02BA51	Metoclopramide with ASA	1
N02CC	Triptans	1
N03AB	Hydantoin derivatives	1
N03AF	Carbamazepine and derivatives	1
N03AG01	Valproic acid	1
N03AX12	Gabapentin biperiden	1
N05A	Traditional antipsycotics	2
N05AD	Butyrophenones	2
N05AF	Thioxanthenes	2
N05AH02	Clozapine	1
N05AH03	Olanzapine	1
N05AH04	Quetiapine	1
N05AL01	Sulpiride	2
N05AN01	Lithium	2
N05AX08	Risperidone	1
N05B	Anxiolytics	2
N05BA01	Diazepam with kinin, orphenadrine, baclofen, tizanidine	1
N05BB01	Hydroxyzine	2
N05BC51	Meprobamate with kinin, orphenadrine, baclofen, tizanidine	1
N05CX01	Meprobamate with kinin, orphenadrine, baclofen, tizanidine	1
N05C	Hypnotics and sedatives	2
N05CF01	Zopiclone	2

ATC code	Drug Name	Score
N05CF02	Zolpidem	2
N05CF03	Zaleplon	2
N05CM02	Clometiazole	2
N05CM09	Valerian	2
N05CX01	Meprobamate with ergot alcaloid	1
N06AA04	Clomipramine	2
N06AA06	Trimipramine	2
N06AA09	Amitriptyline	2
N06AA10	Nortriptyline	2
N06AA12	Doxepin	2
N06AB03	Fluoxetine	1
N06AB04	Citalopram	1
N06AB05	Paroxetine	1
N06AB06	Sertraline	1
N06AB08	Fluvoxamine	1
N06AX03	Mianserin	2
N06AX05	Trazodone	1
N06AX06	Nefazodone	1
N06AX11	Mirtazapine	1
N06AX16	Venlafaxine	1
N06AX17	Milnacipran	1
N06CA01	Amitriptyline + chlordiazepoxide	2
N06CA01	Amitriptyline + perphenazine	2
R03DA74	Theophylline	1
R03DA04	Theophylline, combinations	1
R05CB02	Bromhexine	1
R05DA01	Ethylmorphine	1
R05DA04	Codeine	1
R05DA20	Codeine	1
R06AE05	Meclozine	1
R06AE53	Cyclizine (with diazepam)	1
S01FA02	Scopolamine	1