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Adherence patterns across multiple medications in chronic diseases: an innovative drug utilization model

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ABBREVIATIONS

Acronym	Description
ABC	Ascertaining Barriers to Compliance
ACCI	Adjusted Charlson Comorbidity Index
ADR	Adverse drug reaction
AI	Artificial intelligence
ARB	Angiotensin receptor blocker
ATC	The Anatomical Therapeutic Chemical classification
BMI	Body mass index
BP	Blood pressure
CAT	Communication assessment tool
CH	Calinski & Harabasz
CMA	Continuous medication availability
DDD	Defined Daily Dose
DPP-4	Dipeptidyl Peptidase 4
DRG	Diagnosis-Related Group
DU	Drug utilization
EHD	Electronic healthcare database
EHR	Electronic healthcare record
EMERGE	The ESPACOMP Medication Adherence Reporting Guidelines
ESPACOMP	International Society for Medication Adherence
EU	European Union
FUW	Follow-up window
GBTM	Group based trajectory model
GLP-1	Glucagon-Like Peptide-1
HbA1c	Hemoglobin A1c
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD-9	International Classification of Diseases - 9th revision
ICD-9-CM	International Classification of Diseases - 9th revision - Clinical Modification
ICPC	International Classification of Primary Care
LDL	Low density lipoprotein
MA	Medication Adherence
MCS	Multisource Comorbidity score
MEMS	Medication Event Monitoring System
ML	Machine learning
MPR	Medication Possession Ratio
NHG	Nederlands Huisartsen Genootschap (Dutch General Practitioners' Association)
NHS	National Health System
OAD	Oral antidiabetics
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
OW	Observation window
PDC	Proportion of days covered
Sac/Val	sacubitril/valsartan
SGLT2	Sodium-Glucose Co-Transporter 2
T2DM	Type 2 Diabetes mellitus
WHO	World Health Organization

SUMMARY

Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies to improve medication adherence (MA). Hence, MA is a key factor associated with the effectiveness of all pharmacological therapies but is particularly critical for medications used for chronic conditions. The treatment of chronic illnesses often includes the long-term use of pharmacotherapy, but although these medications are effective in treating chronic diseases, their full benefits are often not realized because ~50% of patients do not take their medications as prescribed. Therefore, is widely recognized that suffering from one or multiple chronic conditions with a corresponding increase in medication utilization are at an increased risk of medication nonadherence.

Despite the central importance of medication adherence in clinical practice and policy, medication adherence is difficult to define and measure. One of the possible reasons for the difficulty in uniquely assessing, predicting, and measuring adherence to drug therapies is the lack of a harmonized process for measuring adherence and the use of routine measures of adherence in clinical practice. Hence, indicators to measure adherence though pharmacy claims databases generally return a static and dichotomous measure of MA (Adherent/Not-Adherent). This problem stems from an underlying misconception about the nature of adherence, as the idea that adherence is a single stable behavior, instead of the reality that adherence encompasses a set of different and dynamic behaviors.

While definitions have evolved over time (e.g. from compliance to adherence and persistence), the more recent developments on the EMERGE Guidelines have moved towards defining separate elements of adherence (initiation, implementation, and persistence) that are thought to describe the processes involved in medication taking, treating the term “adherence” as an overarching term. Therefore, in addition to the definition, the measurement of adherence through the use of both direct and indirect methods is also reaching a new frontier: Medication adherence is a process divided into three operational and quantifiable phases.

In this scenario, this dissertation has explored and faced challenges in medication adherence research and its relation with patient complexity in terms of multimorbidity and polypharmacy by implementing an innovative drug-utilization (DU) models based on longitudinal calculation of medication adherence by exploiting the crasis between: DU research, ML/AI models (Data science applications) and medication adherence to major chronic diseases. Main findings of this PhD thesis address all the developments and discoveries observed to date regarding the measurement of medication adherence through indirect methods, namely the use of Big Data. Such joining tract between disciplines has enabled the implementation of a recently developed algorithm by Dima A. and colleagues, allowing measurement and visualization of all adherence profiles of patients treated with specific drug therapies throughout the entire pharmacological treatment period. The algorithm was implemented by characterizing patients with similar medication adherence estimates and evaluating their baseline and clinical characteristics as potential determinants of nonadherence.

Thus, findings address that medication nonadherence is a complex problem rooted in a multitude of interconnected factors some of them modifiable and predictable upstream. Future studies are needed to understand the underlying complexity and guide future interventions in real clinical practice.

CHAPTER 1

Drug Utilization Research and Medication Adherence

1.1 Introduction to Drug Utilization Research

Over the past three decades, research in the field of Drug utilization has developed rapidly in the rest of Europe [1]. The main purpose of Drug utilization is to facilitate the rational use of drugs across populations [1,2]. For the individual patient, rational use of a drug involves prescribing a drug that is well documented, at an optimal dose, with correct information, at an affordable price. Inappropriate use of drug therapies can cause adverse events, drain financial resources unduly, and compromise quality of care [3].

Drug utilization does not necessarily provide answers, but it helps to produce information that is useful for the rational use of medicines and for developing a set of indicators that, in the face of improving the quality of care, are able to rationalize treatment outcomes in clinical and economic terms. This discipline is, therefore, of extreme interest both to policy makers, who must implement and evaluate public health programs, and to physicians, who can compare data of clinical relevance with those related to their daily practice [3-5].

This research discipline investigates the appropriateness of drug use. This branch, which is characterized by an interdisciplinary approach that is open to contributions from clinicians, pharmacologists, pharmacists, and epidemiologists, can be divided into two major strands: that relating to studies on the appropriateness of use of specific groups of drugs and that relating to statistics on drug use [6,7].

Therefore, as discussed extensively to date, the drug utilization framework plays a key role in enabling continuous analysis of drug utilization and spending to support health governance [6-8]. The best way to do this is to establish a unit dedicated to drug utilization analysis within the agency responsible for the program that supports access to medicines [8]. The process is simplified in **Figure 1**.

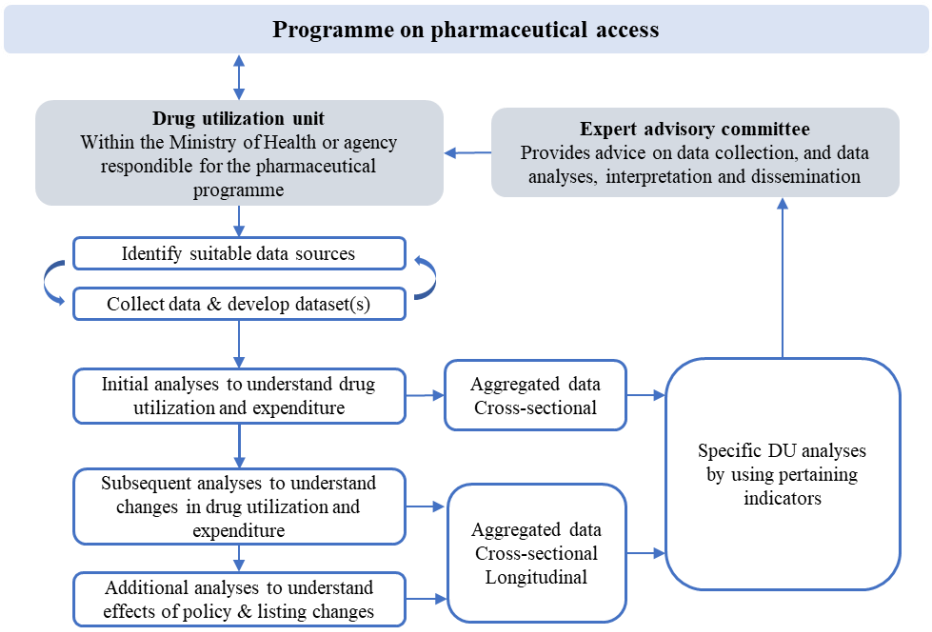

Figure 1. Process for analysis of Drug utilization to support programmes within pharmaceutical access.

Adapted from World Health Organization. (2018). Methods to analyse medicine utilization and expenditure to support pharmaceutical policy implementation [8]

Drug utilization can be distinguished into **two types of studies**, the ***descriptive*** and the ***analytical***. The former outline patterns of Drug utilization and identify issues that need more detailed investigation; the latter, on the other hand, seek to correlate data on drug use with data on morbidity, treatment outcomes, and quality of care, with the ultimate goal of assessing whether drug therapy is rational or not. Both types of studies may focus on the drug (e.g., dose-effect and concentration-effect relationships), the prescribing physician (e.g., prescription quality indices), or the patient (e.g., drug and dose choice in relation to pathological conditions, age, and metabolic abilities). Specifically, types of Drug utilization studies are:

i) Cross-sectional studies: Cross-sectional data provide a snapshot of drug use at a particular time (e.g. over a year, a month or a day). Such studies might be used for making comparisons with similar data collected over the same period in a different country, health facility or ward, and could be drug-, problem-, indication, prescriber- or patient-based.

Alternatively, a cross-sectional study can be carried out before and after an educational or other intervention. Studies can simply measure drug use, or can be criterion-based to assess drug use in relation to guidelines or restrictions. [3,8]

ii) Longitudinal studies: Drug-based longitudinal data can be on total drug use as obtained through a claims database, or the data may be based on a statistically valid sample of pharmacies or medical practices. Longitudinal data are often obtained from repeated cross-sectional surveys. Data collection is continuous, but the practitioners surveyed, and therefore the patients, are continually changing. Such data give information about overall trends, but not about prescribing trends for individual practitioners or practices. [3,8]

iii) Continuous longitudinal studies: These data can provide information about concordance with treatment based on the period between prescriptions, coprescribing, duration of treatment. As electronic prescribing becomes more common, databases are being developed to provide continuous longitudinal data comprising full medical and prescribing information at the individual patient level. Such databases are very powerful, and can address a range of issues including reasons for changes in therapy, adverse effects and health outcomes. [3,8]

Across the numerous applications and methods of DU Research (such as estimation of number of patients exposed to the use of specific drugs in a given time period; estimation of appropriateness of drugs' prescription; estimation of drug utilization patterns with the most recent recommendations of best clinical practice or guidelines related to a given condition; evaluation of the impact that regulatory measures) [9], the availability of retrospective data on medication use allow the discipline to assess and evaluate adherence to a specific chronic medication in a selected population. Application of DU research for medication adherence assessment also allow comparison of adherence level across several setting or areas (regional, national, international) [8]. Hence, Drug utilization methods applied to medication adherence assessment can be a useful feedback to healthcare providers and decision makers to implement appropriate interventions to improve medication adherence in selected populations.

1.2 Medication adherence: Definition and domains

Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies to improve adherence. An enormous amount of research has resulted in the development of medications with proven efficacy and positive benefit-to-risk profiles. This drug treatment benefit-to-risk profile has a resultant in clinical outcomes, however, between the former and the latter lies medication adherence: *Drug Treatment → Medication Adherence → Health Outcomes* [10].

The World Health Organization (WHO) defines adherence to long-term therapy as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" [11]. Often, the terms *adherence* and *compliance* are used interchangeably. Albeit this, their connotations are different: adherence presumes the patient's agreement with the recommendations, whereas compliance implies patient passivity. Also, a number of other common definitions are scientifically used: to define the act of seeking medical attention, filling prescriptions and taking medicines appropriately such as *persistence*, and *concordance* [11-14]. Hence, medication persistence refers to the act of continuing the treatment for the prescribed duration and it may be defined as "the duration of time from initiation to discontinuation of therapy" [10]. These definitions are sometimes used interchangeably, though they impose different views about the patient medication-taking behavior [13,14]. The definitions that are currently used in the literature do not support quantitative assessment, thus compromising any sound analysis aimed at describing or comparing patients' adherence to prescribed drug dosing regimens. Those limitations preclude the finding of useful methods to enhance patient adherence with prescribed therapies in daily practice. In response to the proliferation of ambiguous or unquantifiable terms and definition in the literature on medication adherence so far, new scientific researches has resulted in a new conceptual foundation for a transparent taxonomy to address the issue to promote consistency and quantification in terminology and methods to aid in the conduct, analysis, and interpretation of scientific studies of medication adherence [15].

For this purpose, the European project Ascertaining Barriers for Compliance (ABC) has proposed a new taxonomy of adherence [15] addressed in the new developed guidelines for reporting of medication adherence research studies: the ESPACOMP Medication Adherence Reporting Guidelines (**EMERGE**) [16]. The taxonomy defines adherence as the process by which patients take prescribed medications and consists of three essential components: (i) *initiation*; (ii) *implementation*; and (iii) *discontinuation*. The process begins with initiation, when the patient takes the first dose of a prescribed medication [15]. The process continues with implementation of the dosing regimen, defined as the extent to which the patient's actual dosage matches the prescribed dosing regimen, from initiation until the last dose is taken. Discontinuation marks the end of therapy, when the next dose to be taken is omitted and no further doses are taken. Third phase of taxonomy defines persistence as the period of time between initiation and the last dose, which immediately precedes discontinuation. After discontinuation, there may be a period of non-persistence until the prescription period ends (**Figure 2**).

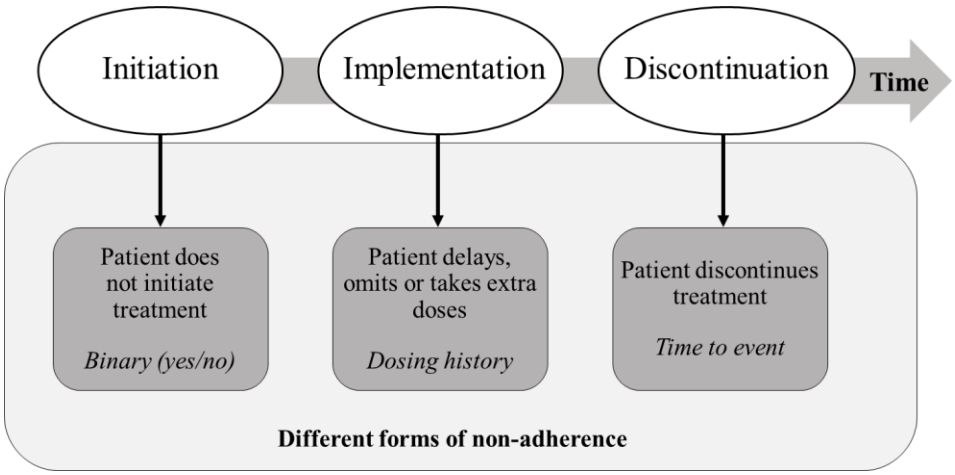

Figure 2. Phases of Medication Adherence according to the ABC Taxonomy

Adapted from Vrijens et al, Br J Clin Pharmacol 2012;73:691-705. [15]

1.3 Determinants of Medication Adherence

In 2005, Osterberg and Blaschke [16] proposed an expanded view of barriers to medication adherence that considers wider contextual issues and the interplay between them as shown in **Figure 3**.

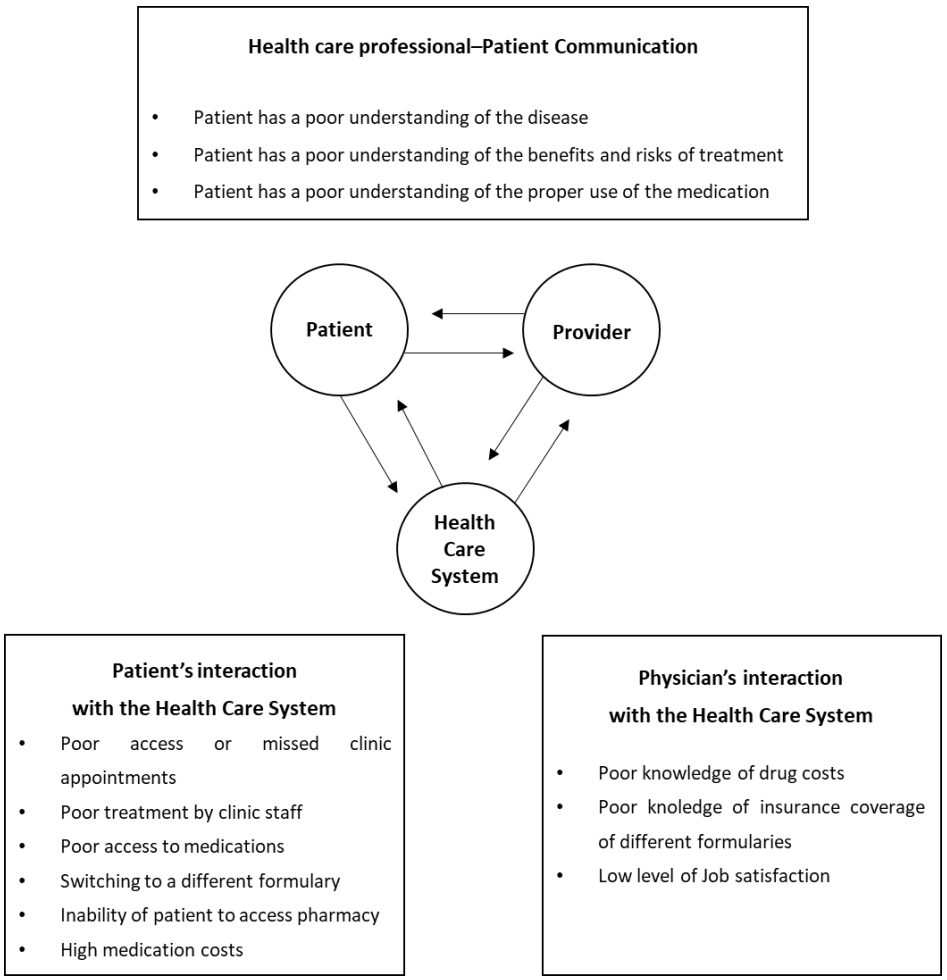

Figure 3. Medication Adherence related barriers.
Source: Osterberg L, Blaschke T. N Engl J Med. 2005; 353(5):487-97. [16]

Hence, as also recognized by the WHO, medication adherence is not only affected by patient-provider relationship and/or systemic and organizational factors associated with health care system but also the nature of condition, complexity and duration of the treatment regimen, adverse drug reactions. According to the WHO these determinants of non-adherence can be aggregated into five dimensions:

- social and economic;
- health system related;
- therapy-related;
- condition-related;
- patient related.

In **Table 1** lists all the factors relating to each dimensions [17].

Table 1. Five dimension of poor medication adherence

1st SOCIAL AND ECONOMIC DIMENSION
Limited English language proficiency
Low health literacy
Lack of family or social support network
Unstable living conditions; homelessness
Burdensome schedule
Limited access to health care facilities
Lack of health care insurance
Inability or difficult accessing pharmacy
Medication cost
Cultural and lay beliefs about illness and treatment
Elder abuse
2nd HEALTH CARE SYSTEM DIMENSION
Provider-patient relationship
Provider communication skills (contributing to lack of patient knowledge or understanding of the treatment regimen)
Disparity between the health beliefs of the heath care provider and those of the patient
Lack of positive reinforcement from the health care provider
Weak capacity of the system to educate patients and provide follow-up
Lack of knowledge on adherence and of effective interventions for improving it
Patient information materials written at too high literacy level
Restricted formularies; changing medications covered on formularies
High drug costs, copayments, or both
Poor access or missed appointments
Long wait times
Lack of continuity of care

3rd CONDITION-RELATED DIMENSION
Chronic conditions
Lack of symptoms
Severity of symptoms
Depression
Psychotic disorders
Mental retardation/developmental disability
4th THERAPY-RELATED DIMENSION
Complexity of medication regimen (number of daily doses; number of concurrent medications)
Treatment requires mastery of certain techniques (injections, inhalers)
Drug-formulation
Duration of therapy
Frequent changes in medication regimen
Lack of immediate benefit of therapy
Medications with social stigma attached to use
Actual or perceived unpleasant side effects
Treatment interferes with lifestyle or requires significant behavioral changes
5th PATIENT-RELATED DIMENSION
Physical Factors
Visual impairment
Hearing impairment
Cognitive impairment
Impaired mobility or dexterity
Swallowing problems
Psychological/Behavioral Factors
Knowledge about disease
Perceived risk/susceptibility to disease
Understanding reason medication is needed
Expectations or attitudes toward treatment
Perceived benefit of treatment
Confidence in ability to follow treatment regimen
Motivation
Fear of possible adverse effects
Fear of dependence
Feeling stigmatized by the disease
Frustration with health care providers
Psychosocial stress, anxiety, anger
Alcohol or substance abuse

1.4 Medication adherence across multimorbidity and polypharmacy

Medication adherence is a key factor associated with the effectiveness of all pharmacological therapies but is particularly critical for medications used for chronic conditions. The treatment of chronic illnesses often includes the long-term use of pharmacotherapy, but although these medications are effective in treating chronic diseases, their full benefits are often not realized because ~50% of patients do not take their medications as prescribed [11,18]. As, it is widely recognized that medication adherence is often poor and perceived as a major public health issue worldwide because it decreases the efficacy of pharmacological therapies, and increases direct and indirect related costs, this phenomenon was widely studied especially among more complex patients [19,20]. Hence, poor adherence was resulted to be more prevalent in specific groups of patients with some recognized characteristics: age, multimorbidity and polypharmacy regimen. Therefore, people suffering from one or multiple chronic conditions with a corresponding increase in medication utilization are at an increased risk of medication nonadherence.

Multimorbidity is defined by the World Health Organization as the co-occurrence of two or more chronic medical conditions in one person. Patients with multimorbidity may require medicines to treat each condition, which can lead to polypharmacy. Currently, an estimated 50 million EU citizens are affected by multimorbidity, and most of them are over 65 years old [19,20]. According to the European community, it has been found that most people with two chronic diseases take four to nine medications a day, and the patients who take the most are the older ones [20]. It is also estimated that the burden of multiple diseases can have a combined effect on physical health, quality of daily life and mental health. The burden of multiple treatments, termed **polypharmacy**, can be equally problematic, causing frequent contact with health care facilities and a greater likelihood of side effects, adverse drug reactions and interactions [20]. There are a number of different definitions of polypharmacy but it is generally understood as the concurrent use of multiple medicines by one individual. It can be therapeutically beneficial when appropriate or inappropriate when not.

- *Appropriate polypharmacy* is defined as prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best evidence [20].
- *Inappropriate polypharmacy* is defined as the prescribing of multiple medicines inappropriately, or where the intended benefit of the medication is not realized [20].

Thus, it is noteworthy that polypharmacy management is a whole systems approach which optimizes the care of multimorbid patients through maximizing benefit while reducing the risks of inappropriate polypharmacy and related medication non-adherence. Therefore, as polypharmacy is known to be associated with non-adherence to medication due to the greater number of drugs that may be missed on a daily basis, assessment of adherence to the entire polypharmacy regimen is essential. Furthermore, as irregular and inconsistent intake of one or more drugs in a polypharmacy regimen is common and may impact clinical outcomes, assessment of polypharmacy adherence is clinically relevant [21]. However, polypharmacy estimation, especially in older populations, requires a composite measure to assess adherence to multiple drugs as a whole and to evaluate the overall effect of drug adherence on a patient's clinical outcomes, providing reliable and unbiased results. The methodology for conducting these estimates strictly depends on the health data sources available [22]. Indeed, a common theme throughout the main findings of this dissertation is the investigation of specific patient populations at risk of complex drug regimens and impaired adherence. The actual unsolved challenge arising from the polypharmacy-poor adherence linkage is caused by the uneasy identification of the index chronic condition from which the patient's clinical pattern begins to complicate with the onset of comorbidities and polypharmacy. Therefore, this thesis is based on the assumption that investing in identifying and implementing medication adherence to a complex chronic disease can reduce the risk of onset and/or worsening of multimorbidity and polypharmacy.

1.5 Medication adherence: clinical and economic outcomes

Nonadherence to prescribed medications is an important public health problem, intrinsically linked to multimorbidity and polypharmacy. Research to date suggests that between 50% and 80% of patients with chronic conditions may be nonadherent, depending on the clinical condition studied [23]. Specifically, in fact, various studies estimate that non-adherence is responsible for 48% of deaths from asthma, an 80% increase in the risk of death from diabetes, and a 3.8-fold increase in the risk of death from heart attack [24]. Overall, it is noteworthy that non-adherence to drug therapies costs the European Union 125 billion euros annually [3,11,24]. Therefore, in light of the pressure to reduce unnecessary healthcare expenditure in the current economic scenario, the literature stressed and studied evidences of cost effectiveness of adherence-enhancing interventions [23-25].

Strategies to enhance adherence should consider the impact on overall health care costs, weighing increased drug expenditures against savings from improved outcomes [23-25]. The majority of the costs attributed to medication nonadherence result from avoidable hospitalization [26]. Additional **direct costs** are incurred by progression of controllable disease with: 1) increased service utilization at physician offices, emergency rooms, and urgent care and treatment facilities such as nursing homes, hospice, or dialysis centers; 2) avoidable pharmacy costs related to therapy intensification as comorbid conditions develop; and 3) diagnostic testing that could be avoided by controlling the primary illness [23-25]. The relationship between non-adherence and associated health care costs is shown in **Figure 4**. Medication nonadherence leads to poor outcomes, which then increase health care service utilization and overall health care costs. The financial pressure is passed to patients by payers through higher copayments, or via higher costs to employers for coverage. Increased patient cost sharing beyond a threshold negatively impacts the level of medication adherence [27].

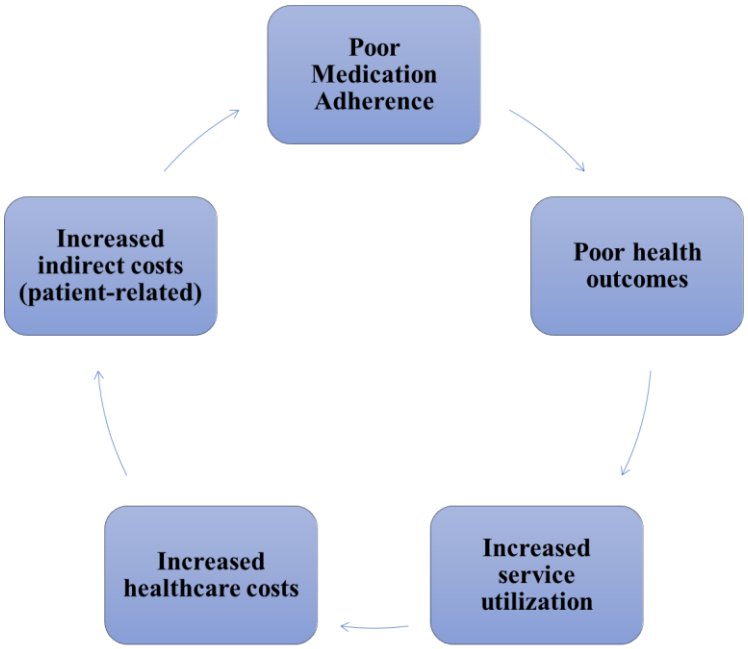

Figure 4. Relation between medication adherence and healthcare costs
Adapted from Iuga AO et al, Risk Manag Healthc Policy. 2014;7:35-44. [25]

1.6 Medication adherence and patient-health care professionals communication strategy

Literature so far suggests that between 50% and 80% of patients with chronic diseases may be non-adherent, depending on the clinical condition studied [20]. As discussed above, non-adherence to prescribed drugs is a major public health problem, closely linked to multimorbidity and polypharmacy. Although there are promising interventions that improve medication adherence, most interventions are developed and tested in tightly controlled research environments that are dissimilar from the real-world settings where the majority of patients receive health care [28]. Thus, different strategies to implement adherence into real setting were developed and investigated so far [29-31]. Results from literature already confirmed that patients' – and their caregivers – involvement in decision-making about their medication would lead to co-production in a better management of medication adherence [20]. As already discussed, several factors can predict patient medication adherence, these factors includes the relationship between health care professional (HCP)-patient communication and medication adherence. Several research studies have already examined how HCP-patient communication can improve patient adherence and illustrated how interventions to improve communication can effectively improve adherence [32]. Therefore, it is essential to raise patients' awareness of the challenges of non-adherence and ways to prevent harm from medication side effects. Patients should be provided with information and tools developed to enable them to ask questions and understand how to make decisions about the management of their long-term conditions, and, this information must be consistent across all sectors of the healthcare system [20]. Several tools to assess patient perceptions of HCP' interpersonal and communication skills were already considered to be useful in supporting development of this professional skill in order to finally improve patient involvement in resulting in better adherence [29-31, 33, 34]. In this scenario, pharmacists are in an ideal position to facilitate communication between physicians and patients since they have frequent contact with patients, have extensive knowledge about drug therapy, and are equipped to provide information, monitor patients' experiences and adherence, and co- ordinate care between different healthcare professionals.

the World Health Organization (WHO) already recognized the role of "communicator" as one of the essential functions attributed to pharmacists [35] by proposing the concept of the "Seven-star pharmacist" in 1997, which evolved and was taken up by the International Pharmaceutical Federation and covered the following roles: Caregiver, decision-maker, communicator, manager, lifelong learner, teacher, and leader [36, 37].

Hence, this dissertation will support and prove that ad-hoc validated communication tools can help pharmacists to reflect on their interpersonal and communication skills with the goal of reinforcing strengths and identifying areas that would require more attention to improve patient medication adherence.

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CHAPTER 2

Measuring Medication Adherence through computational methods of DU

2.1 Measurements of medication adherence

WHO classifies adherence assessment methods by dividing them into two macro-areas: subjective and objective methods [1]. Subjective methods involve the patient's assessment of his or her own medication-taking behavior or that of the health care provider (survey/questionnaries-related methods) and definitely have bias as there is a very subjective component [2]. Objective methods, on the other hand, (such as clinical outcome measurement, dose counts, pharmacy records, electronic monitoring of medication administration) have the obvious potential to not suffer from such biases but to provide objective data with respect to actual medication adherence. A further classification, however, refers to direct and indirect assessment methods [3] (**Table 2**).

Table 2. Direct and Indirect methods to measure Medication Adherence

MA Assessment method	*Pros*	*Cons*	Indicator
Direct Methods			
Measurement of drug/ metabolite levels	Objective Accurate Evidence drug administration	Costly Invasive Inter individual differences	Concentration of the drug/metabolite
Indirect Methods			
Pill counts	Simple Used in clinical trials	No evidence drug administration	Number of doses missed
Self-reports	Simple Not-expensive	Overestimate Individual-dependent	Score with a cut-off point
Electronic monitoring systems	Objective Accurate Used in clinical trials	Costly No evidence drug administration	Dosing regime
Electronic databases	Simple Not-expensive Non-invasive Level of adherence	No evidence drug administration	Medication possession ration (MPR) Proportion of days covered (PDC) Persistence thought Gap Method Daily Patient Possession Ratio (DPPR)

Every method of assessing medication adherence presents advantages and disadvantages, and there is no agreement on a single gold standard approach. Particularly, **direct methods** of measuring adherence include [1,4,5]:

i) **Measurement of concentrations of a drug or its metabolite** in blood or urine and detection or measurement in blood of a biologic marker added to the drug formulation are examples of direct methods of measures of adherence. For instance, the serum concentration of antiepileptic drugs such as phenytoin or valproic acid will probably reflect adherence to regimens with these medications, and subtherapeutic levels will probably reflect poor adherence or suboptimal dose strengths. This direct method is appropriate for the measurement of adherence to one drug therapy regimen only and it offers no supplementary data on the additional causes of non-adherence and does not report on any patterns of non-adherence.

While, **indirect methods** of measuring adherence include [1,2]:

i) **Pill counts** to be more precise counting the number of pills remaining in a patient's supply and calculating the number of pills that the patient has taken since filling the prescription is the easiest method for calculating patient medication adherence. Pill counts method can assess an average adherence level, not giving specific information about daily adherence or patterns of adherence. It is based on the assumption that removing the correct number of tablets from the dosing unit is equivalent with taking the medicine as recommended, and this is especially feasible for the assessment of adherence to a single drug therapy.

ii) **Self-reports** to assess the knowledge of patient about the medications prescribed and the dosing schedule. This provide information as to whether the patient is adherent with the actual dosing schedule. Subjective assessments by interviewers can bias adherence estimates. Using the self-report method, it is possible to have information regarding adherence determinants such as understanding of the medication regimen, reasons for nonadherence, attitudes and beliefs toward medicines, and other psychosocial factors directly from the patient [6]. Therefore, an evaluation of the adherence to more than one drug therapy can be assessed with this method but strictly dependent to the patient perspective.

iii) **Electronic monitoring systems** such as Medication Event Monitoring System (MEMS) which consists of a monitoring system, applied to the

packages delivered to the patient. consisting in electronic detection of package entry by incorporating micro- circuitry into pharmaceutical packages of various design, which detects, time-stamps and stores the manoeuvresneeded to remove a dose of the drug. This automatic compilation of times of medication intake (dosing history) provides athorough characterization of medication adherence, with clear distinctions between initiation, implementation and discontinuation. This method is still considered the golden standard for the verification of the adherence to treatment in clinical trials [7,8] but is focused on the evaluation of adherence to a single drug therapy.

iv) **Electronic databases** such as pharmacy records based on pharmacy refills are the more frequently used methods in the literature. The advance of computerized pharmacy records enabled to assess medication adherence to an index medication based on refill patterns. This source allows to obtain pharmacy refills and the frequency with which the refills are acquired reflect different aspects of a patient's adherence behavior, also, allowing to check the number and type of treatments withdrawn from the patient and also any interruptions occurring after the first prescription. Using administrative claims data, several measures are proposed and used so far to calculate adherence to a single drug therapy and the most frequently used are the medication possession ratio (MPR), the proportion of days covered (PDC), which provide almost the same results and are usually recommended for their simplicity and the small number of data required [9, 10]. These indicators will be described more in depth in the Chapter 2.3.1. Estimates of adherence to single-medications obtained from MPR/PDC-based methods may vary because of differences in calculation methods.

Moreover, using administrative claims data is possible to assess adherence to polypharmacy. Because adherence to multiple medications has been assessed with methods developed for single-medication use, results have so far proved divergent [9, 10]. Despite this, to date there is no gold standard for assessing adherence to multiple medications as it is not easy to estimate the correct levels of adherence which might be true for one chronic treatment per specific but underestimated or overestimated for a different chronic treatment. To date, one indicator has enabled the assessment of adherence to polypharmacy, the Daily Patient Possession

Ratio (DPPR) which seems to avoids the overestimation inherent to using single-medication records [9].

Finally, a large part of the present thesis' results are based on the use of electronic health databases evaluating adherence to single-medication for the treatment of certain chronic diseases considering and identifying polypharmacy as one of the major determinants of overall non-adherence.

2.2 Data sources for MA measurement through health-related databases

It is widely recognised that application of DU methods to health-related databases can be useful in assessing medication adherence. One of the most long-standing challenges in Drug utilization studies concerns the choice of sources from which to extract data to develop the research to be conducted [11-13]. Different types of information related to drug consumption can be queried depending on the research question to be assessed. The growing interest in the appropriateness of health care resource use has led to the establishment of databases dedicated to Drug utilization studies [12]. These databases are derived from several types of sources:

i) Administrative databases. These databases are created independently for administrative purposes. However, such archives often have the necessary requirements to be able to share and integrate the information they hold. Through the patient identifier, in fact, links can be made to create a population database. This makes it possible to reconstruct, for each patient, the analytical and chronological profile of the treatments performed and resources absorbed and, at the same time, how the patient used healthcare resources. This type of database is a suitable source for the evaluation of drug utilization patterns. The integration of the different archives results in the attribution to the individual patient of the set of factors (date of birth, sex, any drug prescriptions, any hospitalizations) and the distribution of these data along an unfinite time interval. The end result of this procedure is, at the level of the individual patient, the definition of a clinical, analytical and chronological profile and, at the aggregate level, the creation of a population epidemiological database. These databases contains several information as: personal data of patients/doctors, pharmaceutical prescriptions, outpatient prescriptions, exemption codes and hospital discharge forms [11-13].

ii) Clinical databases. The main constraint of administrative databases is the lack of clinical data. Such databases, in fact, being created, as mentioned, for administrative and accounting purposes, leave out all aspects pertaining to the patient's lifestyle habits (e.g., being a smoker or alcohol consumption), symptoms and diagnoses (diagnosis of

hypertension, hypercholesterolemia, or diabetes), staging of the disease (absolute cardiovascular risk), and intermediate outcome indicators (blood pressure, cholesterol, blood glucose values). In order to complete the information contribution provided by an administrative database, a clinical database can be activated. This tool offers the possibility of collecting the remaining information for the completeness of patient characterization, definition of interventions, and evaluation of outcomes. Clinical databases, however, involve some management problems such as the need for user collaboration for data quality and completeness, difficulties in training in the proper and constant use of data collection tools, and the costs of implementation and maintenance. These databases are derived from the health care provider's routine electronic medical record system containing various information including: patient's medical history, diagnoses, medications, treatment plans, laboratory and test results [11-13].

The data contained in the databases described above are organized in tables assuming greater relevance when linked together. This operation is defined as ***record linkage*** which can be extended between tables if they contains a shared key, thus performing a cross database record linkage operation [14,15]. By linking the various tables based on the key "patient code," it is possible to reconstruct the position of each patient within the administrative database. Where there are keys shared by several databases, in fact, it is possible to extend record linkage operations between tables belonging to different databases, thus performing a ***cross database record linkage*** operation [16] (**Figure 5**). In conclusion, the strategy of implementing an information system accessible to carry out Drug utilization studies, can be stepwise (first the administrative database then the clinical database) or partial (only one between the two databases).

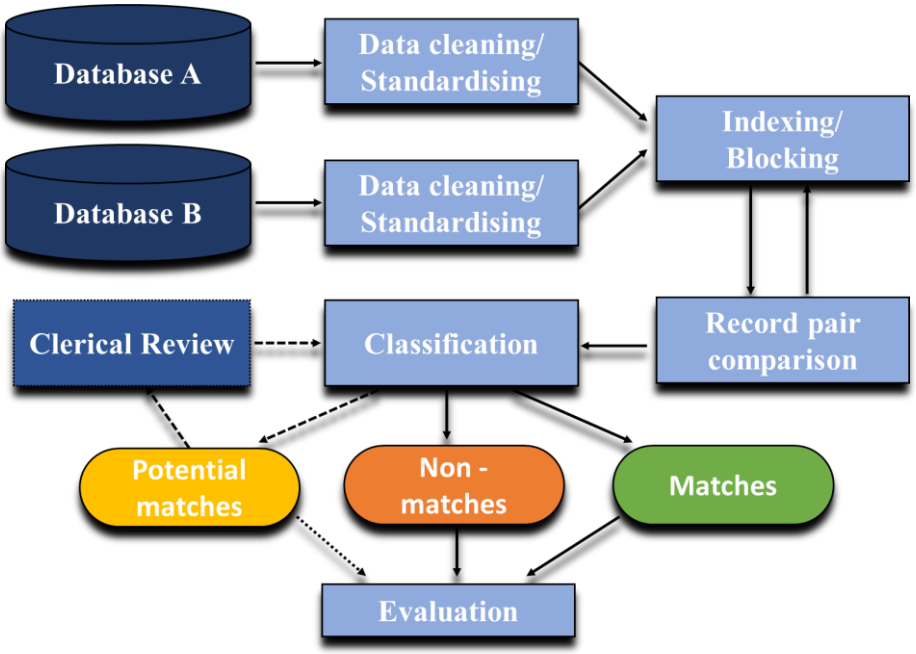

Figure 5. Cross database record linkage operation

2.3 Measurement of MA in health-related databases

Health-related databases such as pharmacy claims data, patients' health records and laboratory files provide a non-invasive, objective and relatively inexpensive method to estimate medication adherence at the population level in real-world settings [17-20]. Albeit this, it is critical to identify upstream the theology of drug utilization study to be conducted in order to query the database(s) that contain the necessary information to assess MA, since, different databases provide different types of data. The characteristics, advantages and disadvantages of using different types of data are outlined below (**Table 3**).

Table 3. Most common data types carrying out DU studies to assess MA: Pros and cons

Data Types	Main Information available	*Pros*	*Cons*
Procurement data	• drug name • dosage form • strength • quantity • cost	**i)** Information about changes in aggregated drug utilization. **ii)** Include over-the-counter drugs. **iii)** Describe total quantities of specific medicines or medicine classes for defined periods **iv)** Most used in low and middle-income countries.	**i)** May not be comprehensive **ii)** May be subject to fluctuations in capturing products with changing procurement practices. **iii)** Include stock purchased but never supplied. **iv)** May include parallel trade stock movements.
Sales data	• drug name • dosage form • strength • quantity • cost	**i)** Information about changes in aggregated drug utilization. **ii)** Include over-the-counter drugs. **iii)** Describe total quantities of specific medicines or medicine classes for defined periods. **iv)** Most used in low and middle-income countries.	**i)** May not be comprehensive **ii)** May be subject to fluctuations in capturing products with changing procurement practices. **iii)** Include stock purchased but never supplied. **iv)** May include parallel trade stock movements.
Dispensing data	• patient identifier • drug name • dosage form • strength • quantity • cost	**i)** Recorded at the patient level. **ii)** Include over the-counter medicines. **iii)** Include a routine audit of all drug dispensed.	**i)** Subject to drugs availability **ii)** No information about the condition or diagnosis for which drugs are dispensed **iii)** Data may or may not be able to be linked to a prescriber **iv)** No information on medication adherence **v)** No clinical data available

Data Types	Main Information available	*Pros*	*Cons*
Prescribing data	• patient identifier • patient demographics • drug name • dosage form • strength • dose prescribed • frequency of administration • reasons for prescribing • type of prescriber	**i)** Disease-specific prescribing. **ii)** Identify relevant characteristics of patients and general practitioners. **iii)** Duration of use, comorbidities, adverse events or reason for interruption.	**i)** Drugs prescribed might not be dispensed or used. **ii)** May not include a representative sample of prescribers; **iii)** Not always suitable for monitoring drug utilization at national level.
Health claims data	• drug name • dosage form • strength • quantity • cost	**i)** Information about aggregated drug utilization for the insured population. **ii)** May allow analyses at different levels of the health system (e.g. regional, national or individual). **iii)** Some contain unique patient identifiers enabling patient-level analyses.	**i)** May not include all relevant information for DU studies. **ii)** Data do not usually include over-the-counter drugs. **iii)** No data on drugs prescribed but never dispensed. **iv)** No information on drugs not covered by the reimbursement programme.
Survey data	• drug name • dosage form • strength • dose used • frequency of administration • duration of use • reason for use	**i)** Patient-level data **ii)** could be aggregated for a defined population. **iii)** Repeated surveys over time to enable longitudinal analyses.	**i)** Time-consuming and labour-intensive. **ii)** Subject to reporting bias and low response rates. **iii)** Limited capacity for valid longitudinal analysis.

When assessing MA through administrative data, firstly it's crucial to assess upstream the type of data to be used: **prescription data** or **dispensation data**.

By using prescription data, one of the main limitation is the assumption that prescriptions are filled by patients on the same day they are issued and that treatments are taken as prescribed. On the other hand, dispensing data provide information on prescribed drugs once patients get it. Hence, If the research focus is on quality of prescribing, dispending data are less informative than prescription data. However, dispensing data are particularly useful for measuring MA, if the administrative database provides information on number of days supplied but they also have their limitations as they do not contain information on whether a drug is still being prescribed [12] (**Table 4**).

Table 4. Source of administrative data used to measure adherence [12]

Source	Construct	Advantages	Limitations
Prescription Data	Initiation	Allows initiation to be measured, if linked with dispensing data	Initiation cannot be measured unless linked with dispensing data
	Implementation	Provides information on dosing history	Requires one to assume that the prescription is filled the same day it is issued, that patients fill all prescribed renewals and that the drug is taken according to the prescribed dosage regimen
	Persistence	Confirms the drug is still being prescribed	Requires one to assume that the prescription is filled the same day it is issued and that patients fill all prescribed renewals
Dispensing Data	Initiation	Allows initiation to be measured, if linked with prescribing data	- Initiation cannot be measured unless linked with prescribing data - Sensitive to reimbursement rules
	Implementation	Provides information on dosing history	- Requires one to assume that drugs in a patient's possession will be taken and that such drugs are still being prescribed - Cannot measure the adequacy of the drug schedule - Sensitive to reimbursement rules
	Persistence	Provides information on drug possession	- Requires one to assume that drugs in patient's possession will be taken and that the patient is still on treatment all such drugs - Sensitive to reimbursement rules

There is no golden standard of medication adherence measurement using administrative data. As already discussed, all methods have their advantages and limitations in assessing adherence levels. Measurement selection should therefore be be guided by the specific adherence phase to be assessed [12] (**Table 5**).

Table 5. Measures of adherence constructs using health related DB [12].

Adherence construct	Measure	Type of administrative data
Initiation (*acceptance or primary adherence*)	Drug is filled within an acceptable period after the prescription is issued (*yes/no*)	Prescription and dispensing
Implementation (*dosing history*)	1. Proportion of days covered (PDC) 2. Proportion of prescribed doses taken 3.Calculated proportion is higher than a predetermined threshold value (*yes/no*)	Dispensing
Persistence (*discontinuation*)	1. Time between filling of first prescription and discontinuation 2. Initiated drug is refilled: - within the no. Of days of supply (plus a permissible gap) (*yes/no*) - sufficiently close to a given initiation anniversary date (based on no. of days of supply plus permissible gap) (*yes/no*)	Dispensing

2.3.1 Static measures to assess MA through health-related databases

By using administrative databases, dicotomous measures of medication adherence can be assessed and were used for decades by using specific indicators [3,13,21], as follow:

- **Medication Possession Ratio (MPR)** defined as the proportion of days supply obtained during a specified time period or over a period of refill intervals.

- **Proportion of Days Covered (PDC)** defined as the number of days when the drug was available divided by the number of days in the study period.

The numerator of the PDC is not merely a sum of the 'days supplied' by all prescriptions filled during the period. Rather, filled prescriptions are evaluated using a set of rules to avoid double-counting covered days. Thus, the PDC is always a value between 0 and 1.
PDC differs from MPR in that it credits the patient with finishing the current fill of medication before starting the next refill. Some believe compliance can be overestimated by simply summing the days' supply because patients usually refill their medication before completing the current fill.
The main limit of these methodologies is that multiple periods of non-exposure in the short term can result in the same MPR/PDC as few periods of non-exposure in the long term and duration of treatment needs to be considered [22].
These measures are often *dichotomized* and patients with a PDC or MPR≥ 80% are generally classified as adherent to their treatment (< 80% non-adherent). However unless an appropriate threshold can be justified these measures should be analyzed as continuous variables [22, 23].

- **Persistence** defined as the duration of time from initiation to discontinuation of therapy.

This is usually the time, measured in days, from first claim to last claim (plus the days' supply of the last claim) considering the days between refills. Continuing to take any amount of the medication is consistent with the definition of persistence. This definition can be operationalized in both prospective and retrospective assessments by determining the initiation of

treatment, or a point in time during chronic treatment, to a point in time defined as the end of the observation period. Persistence analyses must include a prespecified limit on the number of days allowed between refills, considered the *permissible gap* [21,22].

Methods for gap determination should be based on the pharmacologic properties of the drug and the treatment situation (**Figure 6**). Persistence is generally reported as a *dichotomous* variable measured at the end of a predefined time period, considering patients as being "persistent" or "non-persistent" [22,23]

The most relevant issue about this methodology is that periods of non-exposure that are shorter than the gap are not taken in account. This limitation derives from the fact that in pharmacy databases it is very difficult to estimate exactly the effective daily dose taken by the patient. In order to overcome this issue it is necessary to adjust the persistence analysis model to take into account information about the pharmacological characteristics of the drug being studied as well as the specific objectives of the study.

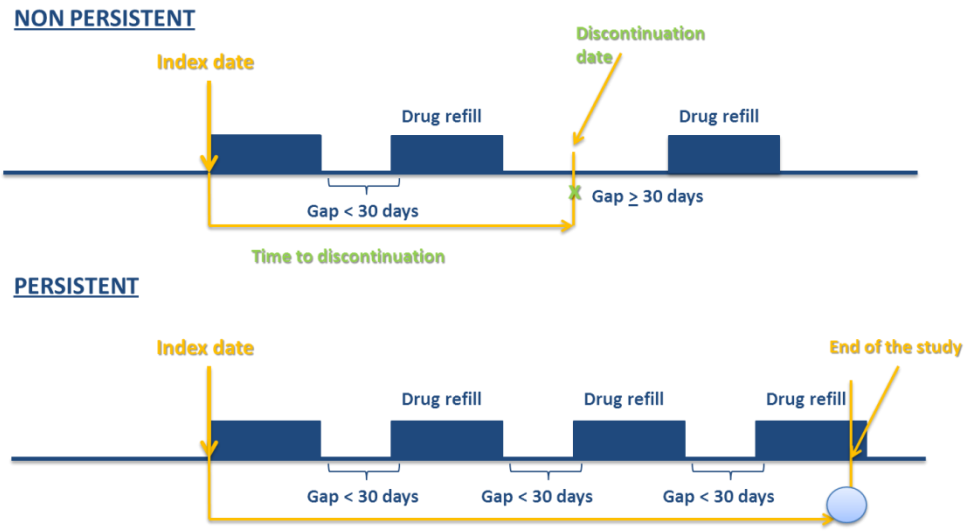

Figure 6: Methods for gap determination

2.3.2 Dynamic measures to assess MA through health-related databases

Despite the central importance of medication adherence in clinical practice and policy, medication adherence is difficult to define and measure. Hence, indicators to measure adherence though pharmacy claims databases gave generally a static and dichotomous measure of MA (Adherent/Not-Adherent) [22]. This problem stems from an underlying misconception about the nature of adherence, as the idea that adherence is a single stable behavior, instead of the reality that adherence encompasses a set of different and dynamic behaviors [22]. According to the EMERGE guidelines [23], there are many ways in which patients can be non-adherent to a pharmacological treatment: not starting medications that have been prescribed (*non-initiation*); delaying prescriptions (*refill adherence gaps*); stopping medications altogether (*non-persistence* or *discontinuation*); taking a lower dose than prescribed (eg, *pill-splitting*); refilling prescriptions more often than required (eg, *stockpiling*); and improperly administering medications (eg, errors in posology coverage) [24].

Corroborating this concept, Gellad W.F. and colleagues [24] in a commentary published on 2017, identified and discussed the four myths of medication adherence measurement, each of which originates from the misconception of adherence as an unidimensional, static construct. Hence, it widely recognized that the measure of medication adherence by using direct or indirect methods comprises significant methodological challenges. Variation in the literature regarding the quantification and conceptualisation of adherence has led to confusion, ambiguity, and inconsistent reporting [24]. While definitions have evolved over time (e.g. from compliance to adherence, concordance, and persistence), the more recent developments on the EMERGE Guidelines have moved towards defining separate elements of adherence (*initiation*, *implementation*, and *persistence*) that are thought to describe the processes involved in medication taking, treating the term “adherence” as an overarching term [21,22]. Therefore, in addition to the definition, the measurement of adherence through the use of both direct and indirect methods is also reaching a new frontier: Medication adherence is a *Process* divided into

three operational and quantifiable phases [22]. These phases, therefore, should be analyzed and measured separately and properly (**Figure 7**).

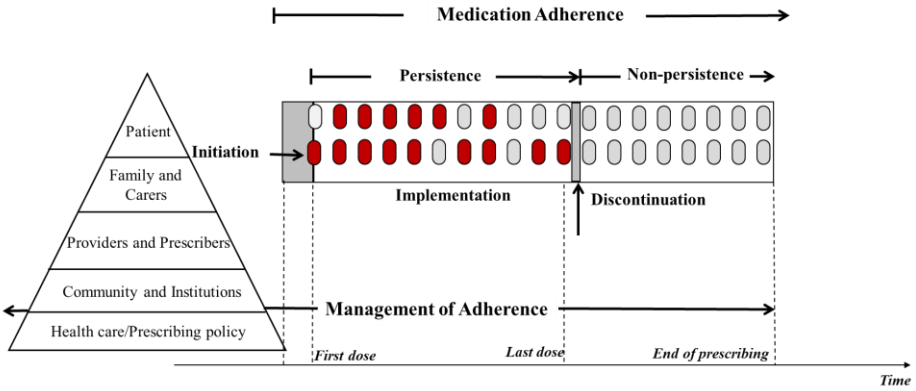

Figure 7. The ABC Taxonomy on Medication Adherence
Adapted from Vrijens et al., Br J Clin Pharmacol 2012;73:691-705. [22]

One of the possible reasons for the difficulty in uniquely assessing, predicting, and measuring adherence to drug therapies is the lack of a harmonized process for measuring adherence and the use of routine measures of adherence in clinical practice [25]. Sound scientific knowledge – agreed upon by multiple countries – could be an essential tool to guide policy-making in implementing strategies to improve adherence. In this regard, drug-utilization studies so far have applied different methods of measurement of adherence across a range of different data sources and populations, making comparisons of the results of these studies difficult. Pharmacy refill data provide an important, valid, and relatively efficient method of assessing retrospective medication adherence in large population-based research, however, few studies have undertaken cross-country comparisons of adherence that was measured this way. Although cross-country comparisons of administrative databases are essential to harmonize the analysis of medication adherence estimates and encourage reproducible science, using multiple sources is not an effortless task, as it involves multiple actions to be taken, such as data and metadata analysis, identification of common datasets [21] (**Figure 8**).

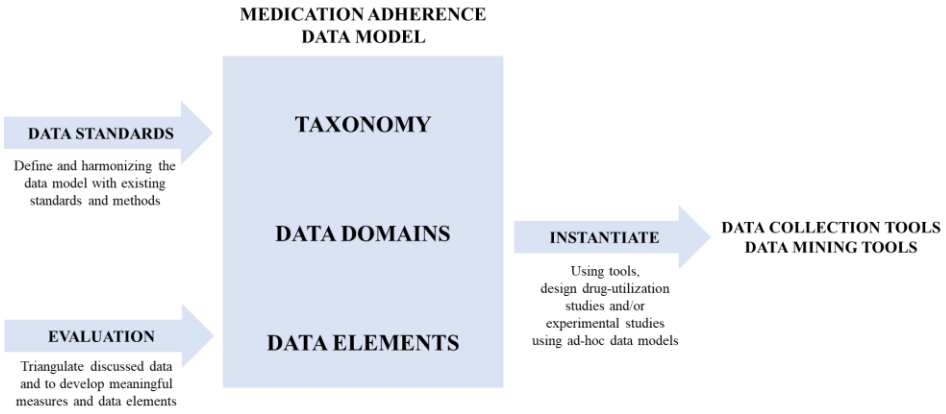

Figure 8. Roadmap to quality on standardized measurement of medication adherence

Adapted from Granger BB et al, Front Pharmacol. 2013;4:139. [25]

2.4 Data Science in DU to assess medication adherence

Over the past decade, artificial intelligence (AI) and machine learning (ML) have become the breakthrough technology most anticipated to have a transformative effect on pharmaceutical research and development. This is partially driven by revolutionary advances in computational technology and the parallel dissipation of previous constraints to the collection/processing of large volumes of data [26].

Machine Learning (ML), or an application of AI, is the link that connects Data Science and AI. Hence, thanks to Data Science, it is possible to manage the information assets of Big Data in the healthcare sector by applying ML-based statistical models and make the resulting information usable for the application in real practice. An example of the use of Big Data though the application of Data Science is shown in **Figure 9.**

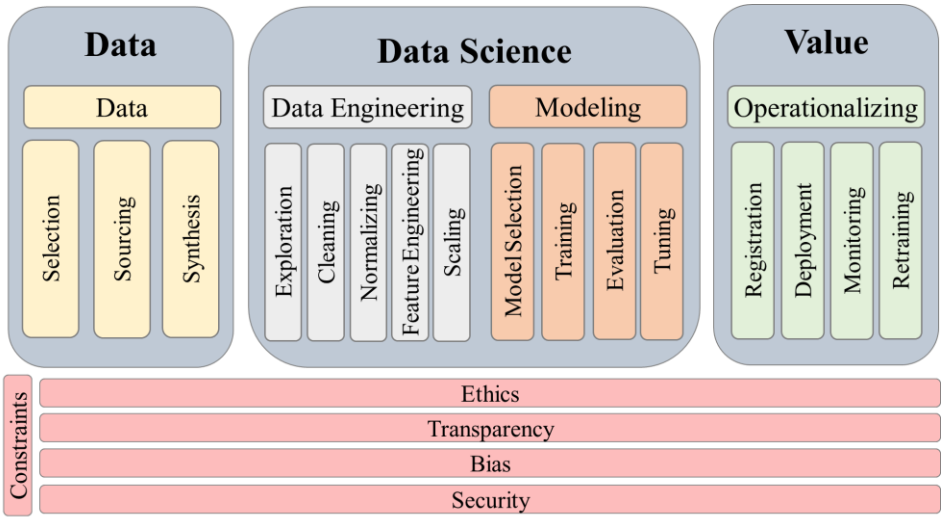

Figure 9. Application of Data Science
Image credits to Andy Scherpenberg, Data Scientist

Specifically, Machine Learning (ML), uses statistical methods to find patterns in data, such as behaviors common to groups of subjects, where the data can be text, images or whatever is stored digitally. ML methods are typically classified as supervised learning, unsupervised learning, and reinforcement learning. Within unsupervised learning is clustering or group analysis. Clustering is a set of multivariate data analysis techniques aimed at selecting and grouping homogeneous items in a data set. Clustering techniques are based on measures of similarity between items. (**Figure 10** gives an overview of what has been summarized). In drug utilization, cluster analysis allows the identification of groups of patients and/or selected populations (e.g., subjects with a chronic condition, subjects on the same drug therapy, subjects taking the same medications) with common characteristics (e.g., potential determinants or predictors of risk). Therefore, the crasis of ML/AI and drug utilization research may represent a new frontier of identifying determinants of medication adherence levels by allowing upstream corrective strategies to be implemented [26] (**Figure 10**).

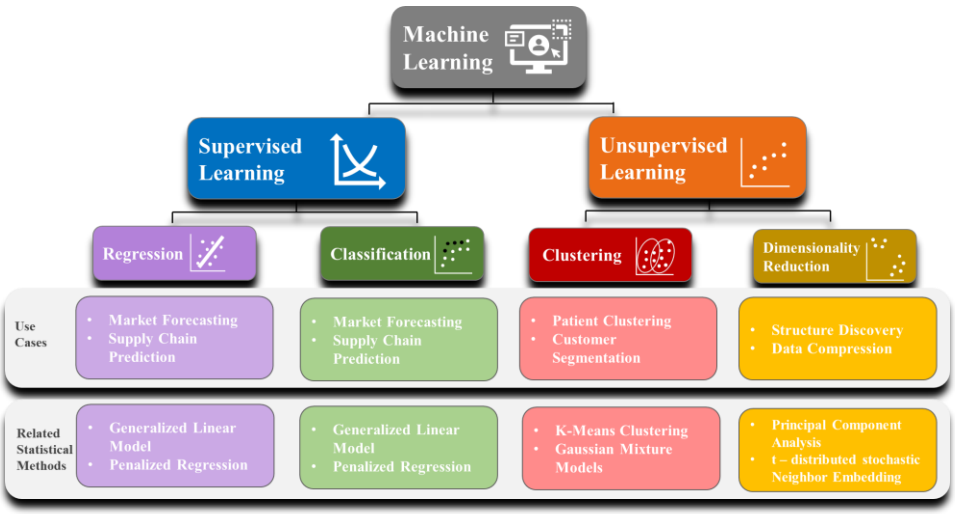

Figure 10. An overview of Machine Learning in DU studies
Source Kolluri S et al, AAPS J. 2022 Jan 4;24(1):19 [26]

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CHAPTER 3

Main goal of the project

3.1 General Aim

The main goal of the research project is to deeply investigate on challenges in medication adherence research and its relation with patient complexity in terms of multimorbidity and polypharmacy by using innovative drug-utilization models, generating new evidence that will advance the field, and indicating areas of unmet needs for further developments.

3.2 Thesis synopsis: The Stepwise approach

To reach the aim of these thesis a *Stepwise Approach* was followed for the whole PhD Project. The *Stepwise Approach* consisted in **4 Stages** carried out with the collaboration of diverse national and international Universities, Research Centers, Research Groups, Health Entities. The remainder of this thesis will be structured following these 4 Stages as showed in **Table 6**.

Therefore, Chapter 4 will summarise the published results on specific methodological issues of medication adherence in the field of Drug utilization research and how patient complexity can be related to it. Chapter 4.1 will report findings emerged from the DU studies carried out thought the conduction of retrospective analyses of chronic patients' complexity in terms of patterns of multimorbidity and polypharmacy in order to assess in subsequent stages where these covariates are determinants of scares medication adherence. Particularly, Chapter 4.1. reports findings of Drug utilization profiles to assess pattern and determinants of medication use in selected chronic diseases (**Stage 1**). *Appendix of Chapter 4.1* contains the supplementary material published within this Stage.

Chapter 4.2 will focus on the description of a new paradigm to define and measure medication adherence (**Stage 2**) and its implementation among different countries carried out in collaboration with the International Society for Medication Adherence (ESPACOMP). *Appendix of Chapter 4.2* contains the supplementary material published within this Stage.

Then, Chapter 4.3 will show process used for the development and validation of a tool to assess medication adherence in real practice (**Stage 3**). This stage was carried out with the collaboration of University of Malta (Department of Pharmacy) and The Italian Society of Clinical Pharmacy

(SIFAC). *Appendix of Chapter 4.3* contains the supplementary material published within this Stage.
Chapter 4.4 will end with the results emerged from the **Stage 4** which consisted in the implementation of an innovative DU-model to measure medication adherence in chronic patients by using EHD and the validation of the tool in a different database in collaboration with the Netherlands Institute for Health Services Research-Nivel (Utrecht, NL). *Appendix of Chapter 4.4* contains the supplementary material published within this Stage.
Finally, the dissertation will provides an overall discussion of main findings and recommendations for future research and practice in the general consideration section.

Table 6. The Stepwise approach.

STAGE	PARTNERS	AIMS
STAGE 1 Drug utilization profiles to assess pattern and determinants of medication use in chronic diseases	**UNINA** (Naples, IT) **EpiChron** (Zaragoza, ES)	To perform retrospective analyses of the complexity of patients with chronic diseases, in terms of patterns of multimorbidity and polypharmacy.
STAGE 2 Implementation of new paradigm to define and measure medication adherence	**UNINA** (Naples, IT) **ESPACOMP** (International Society for MA) **RCSI** (Dublin IE)	To implement the new medication adherence taxonomy in the Italian setting.
STAGE 3 Development and validation of a tool to assess medication adherence in real practice	**UNINA** (Naples, IT) **University of Malta** (Malta) **SIFAC** (Italian Society of Clinical Pharmacy)	**i)** To provide a specific tool for pharmacist use in order to benefit from patient's assessment and to develop and deliver tailored guidance and services reducing identified barriers. **ii)** To assess medication adherence in real practice by new developed and adapted assessment to identify adherence barriers.
STAGE 4 Innovative DU-model to measure medication adherence in chronic diseases	**UNINA** (Naples, IT) **Nivel** (Utrecht, NL)	**i)** To implement the ML/AI algorithm on the library AdhereR of R and tested to Big Data health in the Italian context **ii)** To test and validate the ML/AI algorithm among different health related databases across EU.

CHAPTER 4

Results

4.1 STAGE 1 Drug utilization profiles to assess pattern and determinants of medication use in chronic diseases

The outlining of drug utilization profiles in people with multimorbidity, receiving multiple drugs prescriptions (polypharmacy), are imperative in order to predict and identify patients at increased risk of potentially preventable drug-related problems. Therefore, it's globally recognized that multimorbidity in combination with inappropriate polypharmacy increases the potential for clinical and economic harm [1-3]. This is compounded by the risks of non-adherence to complex treatment regimens [4]. These factors combine to increase the likelihood of morbidity, unplanned hospitalization, readmission, and prolonged hospital stay [5].

Therefore, assessment of patient complexity is carried out through a series of complexity indices which, ideally, in any given individual, is based on complete information on clinical and demographic profile. As patients suffering from one or more chronic conditions are likely to receive a complex pharmacotherapy regimen, medication-based scores offer an alternative tool for measuring comorbidities [6]. Accordingly, in the field of measuring a complexity score for large populations cohorts, attention has been directed to measures that make use of data available via computerized information systems [7]. Some of the score used are:

The Charlson Comorbidity Score [8]: a validated method of classifying comorbidities to predict short- and long-term mortality from medical records. The score replaces direct measures of disease severity, which require prospective data collection. This index assigns weights for a number of major conditions included in secondary diagnoses. The Charlson score appears as the total value of the assigned weights and pertaining measure of the weight of each comorbidity. This final measure at patient level incorporating 19 different medical categories, each weighted according to its potential impact on mortality. Comorbidities with a relative risk of less than 1.5 were given a weight of 1; Comorbidities with a risk between 1.5 and <2.5 were given a weight of 2; Comorbidities with a risk between 2.5 and <3.5 were given a weight of 3; metastatic cancers and AIDS were given a weight of 6. The final score was calculated for each patient taking into account all comorbid conditions present at the time the index was applied. A complete overview of comorbidities

assessed with their relative weight in the scoring system and pertaining ICD-9 codes are listed in Supplementary Table 1 of the *Appendix of Chapter 4.1*.

Adjusted Charlson Comorbidity Index (ACCI) scores [9]: calculated for each patient by taking into account all comorbidity conditions present with additional points added for age. This modification of the Charlson index included the patient's age as a corrective variable in the final score. For each decade after the age of 40, one point is added: 1 point for the age group 41-50 years, 2 points for the age group 51-60 years, 3 points for 61-70 years and 4 points for 71 years or older. The overall score represents the weighted sum of the patients' medical conditions, with a high score representing greater medical comorbidity. Patients are dichotomized into three groups according to ACCI score: low score (0-1), mild score (2-3), severe score (≥4).

Multisource comorbidity score (MCS) [6,10]: a novel comorbidity score predictive of mortality, hospital admissions and healthcare costs using multiple source information from the administrative Italian National Health System (NHS) databases. It combines data from administrative health sources currently available in all Italian regions into a tool able to measure comorbidity, and to predict 1-year mortality, and even other adverse outcomes.

Albeit all these scores were considered in defining chronic patients' DU-profiles in the following results, additionally, a standardized criterion was developed to query dispensing and prescriptions sources of EHD and identify patients' complexity. The algorithm developed is showed in Supplementary Table 2 of the *Appendix of Chapter 4.1*. This algorithm was useful in identifying the degree of complexity of patients and then considering it in subsequent Stages as a determinant of poor medication adherence.

Considering the abovementioned challenging in the correct management of medication adherence in real clinical practice with patients with a chronic health condition or, especially, multimorbidity, a patient-goal-oriented approach can thus be beneficial. To make this happen, it is necessary to know the specific profiles of patients suffering from certain chronic diseases and to identify upstream the risk to which they are most

subject, i.e. health complications with the appearance of new chronic conditions that add up to the main condition, outlining a framework of multimorbidity and consequently polypharmacy. Real world data (RWD) from healthcare-related databases served for the application of prevention models in order to address the complexity associated with the most chronically concomitant subjects and to prevent medication non-adherence phenomenon.

Therefore, main goals of the scientific production carried out across the **Stage 1** were:

i) To perform retrospective analyses of the complexity of patients with chronic diseases, in terms of patterns of multimorbidity and polypharmacy.

4.1.1 Changes in Multimorbidity and Polypharmacy Patterns in Young and Adult Population over a 4-Year Period: A 2011-2015 Comparison Using Real-World Data.

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Abstract: The pressing problem of multimorbidity and polypharmacy is aggravated by the lack of specific care models for this population. We aimed to investigate the evolution of multimorbidity and polypharmacy patterns in a given population over a 4-year period (2011–2015). A cross-sectional, observational study among the EpiChron Cohort, including anonymized demographic, clinical and drug dispensation information of all users of the public health system ≥65 years in Aragon (Spain), was performed. An exploratory factor analysis, stratified by age and sex, using an open cohort was carried out based on the tetra-choric correlations among chronic diseases and dispensed drugs during 2011 and compared with 2015. Seven baseline patterns were identified during 2011 named as: mental health, respiratory, allergic, mechanical pain, cardiometabolic, osteometabolic, and allergic/derma. Of the epidemiological patterns identified in 2015, six were already present in 2011 but a new allergic/derma one appeared. Patterns identified in 2011 were more complex in terms of both disease and drugs. Results confirmed the existing association between age and clinical complexity. The systematic associations between diseases and drugs remain similar regarding their clinical nature over time, helping in early identification of potential interactions in multimorbid patients with a high risk of negative health outcomes due to polypharmacy.

Keywords: multimorbidity; polypharmacy; chronic diseases; real-world data; epidemiology

Introduction

Polypharmacy is referred to as the concurrent use of multiple drugs, and it can be the natural consequence of multimorbidity, more often intended as the coexistence of two or more chronic diseases [1]. However, inappropriate polypharmacy increases the risk of unnecessary drug use, potential drug–drug and drug–disease interactions, and adverse drug reactions (ADRs) [2,3], representing an economic and public health issue related to the quality and efficiency of health care [4,5]. The lack of development of specific care models for this population aggravates multimorbidity and polypharmacy [6].

Large-scale population studies based on real-world data represent an excellent opportunity to analyze the complexity of drug prescribing and clinical conditions and allow us to investigate the existence of systematic associations among drugs and diseases [7–10]. Factor analysis can improve the understanding of multimorbidity and polypharmacy in a real-world context. In 2015, we conducted a study that revealed the existence of systematic associations among chronic diseases and dispensed drugs, identifying up to six patterns of multimorbidity and polypharmacy [11]. Hence, this study aims to compare the baseline epidemiological patterns of multimorbidity and polypharmacy of the EpiChron Cohort in 2011 with those published in 2015 and to describe the clinical evolution of the clinical clusters identified.

Materials and Methods

Design, Study Population, and Variables

We performed an observational, cross-sectional study in the EpiChron Cohort [12]. This cohort includes the anonymized demographic, drug dispensation and clinical information of 98% of users of the public health system in Aragon, Spain (about 1.3 million inhabitants). We collected data from 2011 and compared them with previously published data from 2015 [11] in order to make a 4-year comparison.

The study population included all the subjects living in the Aragon region up to 65 years of age who were users of the public health system. Patients aged 65 and older were excluded from the study to allow for focus on young and adult populations for reasons already explained [11]. We stratified the population by sex and into three age groups: 0–14, 15–44,

and 45–65 years, as for the previous analysis to compare the same age groups. For each subject, we analyzed all the diagnoses of chronic diseases from primary care and hospital electronic health records and all dispensed drugs from pharmacy billing records during 2011.

Diagnoses were coded initially based, first on the International Classification of Primary Care (ICPC) and then converted to codes of the International Classification of Diseases 9th Revision (ICD-9). Finally, they were grouped in the Expanded Diagnostic Clusters (EDC) of the ACG System (version 11.0, The Johns Hopkins University, Baltimore, MD, United States). We included in the analysis all 114 diseases classified as chronic by Salisbury et al. [13] and coded in binary format (i.e., presence/absence of the disease). As in the 2015 study, we also included rhinitis, following the World Health Organization (WHO) indications [14], and acute lower respiratory tract infection, as it can generate chronic sequelae. We classified dispensed drugs according to their Anatomical Therapeutic Chemical (ATC) code at the third level and included chronic and acute drug dispensation with a prevalence of at least 3% in 2015. The Clinical Research Ethics Committee of Aragón (CEICA) approved the study (ethical approval code: PI18/041) and waived the requirement for patient consent, since data of the EpiChron Cohort are anonymized, and no interventions on individuals were performed.

Statistical Analyses

As we used an open cohort, we performed a descriptive analysis of both 2011 and 2015 populations by describing demographic and clinical information expressed as frequencies, means, standard deviations (SD), and medians. We compared differences between patient characteristics using the chi-squared test for categorical variables or the unpaired t-test for numerical variables, as appropriate, considering statistically significant a p value <0.05. Patients' characteristics compared were age, area of living, immigrant status, deprivation index and number of chronic diseases, multimorbidity, and number of drugs related to the reference year. The deprivation index is strictly related to the census section of subjects, which represents the degree of deprivation from the lowest (Q1) to the highest (Q4) of the administrative health area to which it belongs.

An exploratory factor analysis was performed to identify multimorbidity and polypharmacy patterns according to a correlation matrix to decide which diagnoses and dispensed drugs comprised each pattern. Tetra-choric correlation matrices were used due to the dichotomous nature of both chronic diagnoses and administrated medicines. We performed factor extraction based on the principal factor method. We also applied an oblique rotation (Oblimin) to facilitate factor interpretation.

Scree plots were used to decide the number of factors to extract in each group. To determine which codes formed each pattern, we included those with scores >0.30 for each factor. This is the threshold factor loading traditionally used when deciding whether to accept a variable as belonging to a factor [11]. Nonetheless, as done in the previous study, EDCs and ATC codes with scores between 0.25 and 0.30 were included in a factor if considered relevant in the clinical explanation of the pattern.

As done in the previous work [11], we included EDCs with a prevalence >1–2% and ATC codes with a prevalence >3–5% in each age and sex group. Some ATCs with lower prevalence were also covered based on their potential relevance for interactions or side effects. The inclusion and exclusion criteria of EDCs and ATC codes used for each sex and age group were the same, explicitly explained in the 2015 study [11]. We used this prevalence threshold to increase the epidemiological interest of the study, and for statistical reasons regarding collinearity amongst some of the studied variables. The order of factors depends on the prevalence of its components. ATCs and EDCs with higher prevalence values will be identified in the first factors.

We evaluated sample adequacy using the Kaiser–Meyer–Olkin (KMO) test. We only considered values >0.60 as acceptable. Moreover, we calculated the proportion of cumulative variance as a measure of the model's goodness-of-fit. This measurement describes the data variability explained by the patterns. We conducted all statistical analyses in STATA (version 12.0, StataCorp LLC, College Station, TX, USA).

2.3. Differences in the Clinical Patterns Evaluation Process

Once we obtained the data, the clinical nature of the patterns identified, and the comparability of the patterns over the 4-year period analyzed, we identified the presence of potential interactions between diseases and drugs within the patterns and the substantial differences observed. The

associations found in each pattern were independently reviewed by three pharmacists (E.M., V.O., and S.M.) and seven physicians (F.G.R., M.A.S., A.M.J., A.J.M., I.I.S., J.C.P., and A.P.T.) from the research team. Subsequently, a consensus meeting was held to discuss and analyze the differences that existed at the turn of four years. We retained the names of the clusters given in the previous published study with 2015 data, wherever possible, to ensure a better reading of the difference over the years. Finally, the differences observed between 2011 and 2015 were compared with existing literature.

Results

Subjects identified up to 65 years old in the Aragon region were 1,000,390 during 2011 and 887,572 during 2015. Comparison and description of demographic and clinical characteristics of the two study populations are shown in Table 1 for women and Table 2 for men. Firstly, for both the years 2011 and 2015, we detected a statistically significant increase in the number of drugs and chronic conditions for both sexes as age increases.

Table 1. Demographic and clinical characteristics of women in 2011 and 2015.

Subjects' characteristics	0–14 Years			15–44 Years			45–65 Years		
Women	**2011**	**2015**	***p* Value**	**2011**	**2015**	***p* Value**	**2011**	**2015**	***p* Value**
DEMOGRAPHIC									
Population (N)	72,940	78,534		245,171	205,122		170,584	168,587	
Age (mean (SD))	7.79 (3.71)	7.03 (4.21)	<0.001	31.57 (8.21)	31.71 (8.45)	<0.001	54.23 (6.03)	54.43 (5.96)	<0.001
Area of living (n (%))			0.001 [a]			<0.001[a]			<0.001 [a]
Urban	43,911 (60.20%)	46,649 (59.40%)		155,773 (63.54%)	127,450 (62.13%)		109,249 (64.04%)	106,244 (63.02%)	
Rural	29,008 (39.77%)	31,885 (40.60%)		89,252 (36.40%)	77,672 (37.87%)		61,279 (35.92%)	62,343 (36.98%)	
Unknown	21 (0.03%)	-		146 (0.06%)	-		56 (0.03%)		
Immigrant status (n (%))			0.032 [a]			<0.001[a]			<0.001 [a]
Native	61,997 (85.00%)	67,740 (86.26%)		199,026 (81.18%)	168,839 (82.31%)		159,239 (93.35%)	156,311 (92.72%)	
Immigrant	10,168 (13.94%)	10,761 (13.70%)		46,100 (18.80%)	36,277 (17.69%)		11,331 (6.64%)	12,275 (7.28%)	
Unknown	775 (1.06%)	33 (0.04%)		45 (0.02%)	6 (0.00%)		14 (0.01%)	1 (0.00%)	
Deprivation index (n (%)) [b]			<0.001 [a]			<0.001 [a]			0.007 [a]
Q_1	20,305 (27.84%)	22,448 (28.58%)		69,079 (28.18%)	55,733 (27.17%)		44,754 (26.24%)	43,546 (25.83%)	
Q_2	18,719 (25.66%)	19,019 (24.22%)		60,847 (24.82%)	50,671 (24.70%)		43,587 (25.55%)	43,732 (25.94%)	
Q_3	14,137 (19.38%)	15,556 (19.81%)		48,256 (19.68%)	41,415 (20.19%)		35,696 (20.93%)	35,040 (20.78%)	
Q_4	19,743 (27.07%)	21,511 (27.39%)		66,913 (27.29%)	57,303 (27.94%)		46,512 (27.27%)	46,269 (27.45%)	
Unknown	36 (0.05%)	-		76 (0.03%)	-		35 (0.02%)	-	
CLINICAL									
Number of chronic diseases [e]			<0.001			<0.001			<0.001
mean (SD)	0.67 (0.92)	1.00 (1.05)		0.89 (1.24)	1.47 (1.47)		2.28 (2.18)	3.06 (2.34)	
median (P_{25}; P_{75})	0 (0; 1)	1 (0; 2)		0 (0; 1)	1 (0; 2)		2 (1; 3)	3 (1; 4)	
Multimorbidity (n (%))[c]	11,525 (15.80%)	20,022 (25.49%)	<0.001	56,798 (23.17%)	80,521 (39.26%)	<0.001	95,722 (56.11%)	120,101 (71.24%)	<0.001
Number of drugs [d,e]			<0.001			<0.001			<0.001
mean (SD)	2.40 (2.42)	2.16 (2.09)		2.80 (3.12)	2.67 (2.71)		5.13 (4.66)	4.34 (3.75)	
median (P_{25}; P_{75})	2 (0; 4)	2 (0; 3)		2 (0; 4)	2 (0; 4)		4 (1; 8)	4 (1; 6)	

[a] Missing values were not considered when performing test and *p* value. [b] Deprivation index: degree of deprivation from the lowest (Q1) to the highest (Q4) of the administrative health area to which it belongs. [c] Defined as the coexistence of 2 or more chronic diseases. [d] Refers to different drugs dispensed at the third level of the anatomical, therapeutic, chemical (ATC) classification system. [e] Non-parametric test.

Table 2. Demographic and clinical characteristics of men in 2011 and 2015.

Subjects' Characteristics	0–14 Years			15–44 Years			45–65 Years		
Men	2011	2015	*p* Value	2011	2015	*p* Value	2011	2015	*p* Value
DEMOGRAPHIC									
Population (N)	77,391	82,893		260,915	190,658		173,389	161,778	
Age (mean (SD))	7.82 (3.72)	7.04 (4.21)	<0.001	31.68 (8.18)	31.54 (8.67)	0,768	54.00 (6.01)	54.36 (5.93)	<0.001
Area of living (n (%))			<0.001 [a]			<0.001 [a]			<0.001 [a]
Urban	46,346 (59.89%)	48,943 (59.04%)		160,106 (61.36%)	113,262 (59.41%)		102,994 (59.40%)	94,223 (58.24%)	
Rural	31,022 (40.08%)	33,950 (40.96%)		100,728 (38.61%)	77,396 (40.59%)		70,349 (40.57%)	67,555 (41.76%)	
Unknown	23 (0.03%)	-		81 (0.03%)	-		46 (0.03%)		
Immigrant status (n (%))			<0.001 [a]			<0.001 [a]			<0.001 [a]
Native	65,525 (84.67%)	71,506 (86.26%)		206,631 (79.19%)	160,073 (83.96%)		159,095 (91.76%)	149,258 (92.26%)	
Immigrant	11,040 (14.27%)	11,357 (13.70%)		54,219 (20.78%)	30,577 (16.04%)		14,292 (8.24%)	12,519 (7.74%)	
Unknown	826 (1.07%)	30 (0.04%)		65 (0.02%)	8 (0.00%)		2 (0.00%)	1 (0.00%)	
Deprivation index (n (%)) [b]			<0.001 [a]			<0.001 [a]			0.011 [a]
Q_1	21,455 (27.72%)	23,695 (28.59%)		69,997 (26.83%)	49,759 (26.10%)		43,513 (25.10%)	40,042 (24.75%)	
Q_2	19,695 (25.45%)	19,725 (23.80%)		64,037 (24.54%)	46,709 (24.50%)		44,237 (25.51%)	41,522 (25.67%)	
Q_3	15,168 (19.60%)	16,465 (19.86%)		52,872 (20.26%)	39,962 (20.96%)		37,330 (21.53%)	34,511 (21.33%)	
Q_4	21,052 (27.20%)	23,008 (27.76%)		73,953 (28.34%)	54,228 (28.44%)		48,285 (27.85%)	45,703 (28.25%)	
Unknown	21 (0.03%)	-		56 (0.02%)	-		24 (0.01%)	-	
CLINICAL									
Number of chronic diseases [e]			<0.001			<0.001			<0.001
mean (SD)	0.76 (0.99)	1.12 (1.11)		0.62 (1.01)	1.14 (1.24)		1.70 (1.94)	2.48 (2.12)	
median (P_{25}; P_{75})	0 (0; 1)	1 (0; 2)		0 (0; 1)	1 (0; 2)		1 (0; 3)	2 (1; 3)	
Multimorbidity (n (%)) [c]	14,748 (19.06%)	24,386 (29.42%)	<0.001	38,788 (14.87%)	55,704 (29.22%)	<0.001	75,251 (43.40%)	99,176 (61.30%)	<0.001
Number of drugs [d,e]			<0.001			<0.001			<0.001
mean (SD)	2.50 (2.50)	2.27 (2.20)		1.71 (2.34)	1.78 (2.10)		3.53 (3.88)	3.42 (3.32)	
median (P_{25}; P_{75})	2 (0; 4)	2 (0; 3)		1 (0; 3)	1 (0; 3)		2 (0; 5)	3 (1; 5)	

[a] Missing values were not considered when performing test and *p* value. [b] Deprivation index: degree of deprivation from the lowest (Q1) to the highest (Q4) of the administrative health area to which it belongs. [c] Defined as the coexistence of 2 or more chronic diseases. [d] Refers to different drugs dispensed at the third level of the anatomical, therapeutic, chemical (ATC) classification system. [e] Non-parametric test.

Comparison of Multimorbidity and Polypharmacy Patterns

All the six epidemiological patterns identified in 2015 were also maintained during 2011, named as respiratory, mental health, cardiometabolic, endocrinological, osteometabolic, and mechanical pain. In addition, a new one appeared in 2011 mainly in younger age groups, recognized as an allergic/derma factor. Comparison of multimorbidity and polypharmacy patterns are detailed in Table 3.

Table 3. Comparison of multimorbidity and polypharmacy patterns identified in each age and sex group in 2011 and 2015.

Gender	0–14 Years		15–44 Years		45–65 Years	
	2011	2015	2011	2015	2011	2015
Women	Allergic–Derma	Respiratory–Acute Infection	Mechanical Pain	Mental Health	Mental Health	Mental Health
	Respiratory-Asthma–Acute Infection	Respiratory–Asthma–Allergic	Respiratory	Respiratory	Respiratory	Respiratory
	Allergic	Mental Health	Mental Health	Endocrinological	Cardiometabolic	Cardiometabolic
	Mental Health		Endocrinological		Osteometabolic	Osteometabolic
Men	Allergic–Derma	Respiratory–Acute Infection	Mental Health–Pain	Mental Health	Respiratory	Mental Health
	Respiratory–Asthma–Acute Infection	Respiratory–Asthma–Allergic	Respiratory–Allergic	Mechanical Pain	Cardiometabolic	Cardiometabolic
	Allergic	Mental Health	Cardiometabolic	Respiratory	Mental Health	Respiratory
	Mental Health		Derma			

Girls Aged 0–14 Years

Scree plot identified four factors during 2011 versus three during 2015 (Table 4). Factors identified in 2015 in girls in this age group were generally already present in 2011, but with the addition of an allergic/derma component recognized in 2011 and not maintained in 2015. In contrast, the first factor of 2015 was identified as respiratory/acute infection due to the presence of acute lower respiratory tract infection conditions and anti-infectives, corticosteroids, antifungals, and antibiotics. Second factors were similar in both years, having respiratory/asthmatic character due to the equal presence of asthma but differed for drugs-related such as adrenergics and corticosteroids for 2011 and antihistamines and decongestants for 2015. The third factor, the allergic one, with allergic rhinitis and antihistamines and decongestants, appeared only in 2011 in the pediatric population. The last factor identified as mental health remained unchanged over the years due to the presence of developmental disorders and psychosocial disorders of childhood as frequent childhood mental conditions. The KMO sampling adequacy index was 0.72 in 2011 and 0.73 in 2015, while a cumulative variance percentage was of 34.0% in 2011 and 33.2% in 2015.

Table 4. Patterns of chronic diseases (EDC codes) and drugs (ATC codes) and actor loading scores in women. Diseases are highlighted in bold.

	Year 2011	Prev	Values		Year 2015	Prev	Values
0–14 years							
FACTOR 1: ALLERGIC/DERMA		**Prev (%)**	**Values**	**FACTOR 1: RESPIRATORY/ACUTE INFECTION**		**Prev (%)**	**Values**
M01A	Anti-inflammatory and antirheumatic products, non-steroids	38.65	0.6462	H02A	Corticosteroids for systemic use, pain	9.40	0.6427
J01C	Beta-lactam antibacterials, penicillins	34.11	0.6454	RES02	Acute lower respiratory tract infection	11.06	0.6355
N02B	Other analgesics and antipyretics	17.85	0.5855	R03A	Adrenergics, inhalants	10.68	0.6224
R05C	Expectorants, excl. combinations with cough suppressants	22.57	0.5845	J01C	Beta-lactam antibacterials, penicillins	33.57	0.5882
R05D	Cough suppressants, excl, combinations with expectorants	22.14	0.5616	N02B	Other analgesics and antipyretics	22.57	0.5116
J01D	Other beta-lactam antibacterials	5.30	0.4862	J01F	Macrolides, lincosamides, and streptogramins	8.76	0.4816
S01A	Anti-infectives	6.86	0.4411	N05B	Anxiolytics	3.64	0.4570
J01F	Macrolides, lincosamides and streptogramins	8.24	0.4225	S01A	Anti-infectives	9.63	0.4271
D07A	Corticosteroids, plain	7.87	0.4198	M01A	Anti-inflammatory and antirheumatic products, non-steroids	34.45	0.4174
A03F	Propulsives	2.04	0.3905	D07A	Corticosteroids, plain	8.05	0.4097
D01A	Antifungals for topical use	3.44	0.3817	D01A	Antifungals for topical use	3.97	0.3684
N05B	Anxiolytics	3.71	0.3750	A07C	Electrolytes with carbohydrates	4.15	0.3648
D06A	Antibiotics for topical use	4.34	0.3681	D06A	Antibiotics for topical use	5.07	0.3583
SKN02	Dermatitis and eczema	18.13	0.2929				
FACTOR 2: RESPIRATORY/ASTHMA/ ACUTE INFECTION		**Prev (%)**	**Values**	**FACTOR 2: RESPIRATORY/ASTHMA/ ALLERGIC**		**Prev (%)**	**Values**
H02A	Corticosteroids for systemic use, plain	6.93	0.4682	R06A	Antihistamines for systemic use	13.63	0.6105
R03A	Adrenergics, inhalants	7.50	0.8946	ALL03	Allergic rhinitis	4.23	0.7546
RES02	Acute lower respiratory tract infection	8.21	0.7506	S01G	Decongestants and antiallergics	2.68	0.7419
ASMA	Asthma	6.25	0.6038	R01A	Decongestants and other nasal preparations for topical use	3.90	0.6744
				ASMA	Asthma	7.18	0.3489
FACTOR 3: ALLERGIC		**Prev (%)**	**Values**				
R06A	Antihistamines for systemic use	10.50	0.5823				
ALL03	Allergic rhinitis	2.90	0.8316				
S01G	Decongestants and antiallergics	1.92	0.7065				
R01A	Decongestants and other nasal preparations for topical use	3.03	0.6528				
FACTOR 4: MENTAL HEALTH		**Prev (%)**	**Values**	**FACTOR 3: MENTAL HEALTH**		**Prev (%)**	**Values**
N06B	Psychostimulants, agents used for ADHD and nootropics	0.89	0.7123	N03A	Antiepileptics	0.36	0.6693
N03A	Antiepileptics	0.36	0.6379	N06B	Psychostimulants, agents used for ADHD and nootropics	0.74	0.5403
NUR19	Developmental disorder	1.19	0.6150	NUR19	Developmental disorder	2.15	0.3793
PSY14	Psychosocial disorders of childhood	3.40	0.3113	A02B	Drugs for peptic ulcers and GERD	0.69	0.3761
				PSY14	Psychosocial disorders of childhood	5.36	0.3287
END02	Osteoporosis	9.45	0.8609				

Year 2011		Prev	Values	Year 2015		Prev	Values
15–44 years							
FACTOR 1: MECHANICAL PAIN		**Prev (%)**	**Values**				
M01A	Anti-inflammatory and antirheumatic products, non-steroids	30.97	0.7664				
M03B	Muscle relaxants, centrally acting agents	4.08	0.5416				
A02B	Drugs for peptic ulcer and GERD	10.67	0.5046				
N02B	Other analgesics and antipyretics	19.65	0.5007				
M02A	Topical products for joint and muscular pain	3.80	0.4578				
N02A	Opioids	2.68	0.4304				
J01C	Beta-lactam antibacterials, penicillins	19.96	0.3998				
MUS14	Low back pain	4.20	0.3607				
R05D	Cough suppressants, excl. combinations with expectorants	9.30	0.3497				
A03F	Propulsives	4.27	0.3157				
FACTOR 2: RESPIRATORY		**Prev (%)**	**Values**	**FACTOR 1: RESPIRATORY**		**Prev (%)**	**Values**
R05C	Expectorants, excl. combinations with cough suppressants	14.62	0.4734	M01A	Anti-inflammatory and antirheumatic products, non-steroids	30.85	0.3224
J01F	Macrolides. lincosamides and streptogramins	7.94	0.3563	R06A	Antihistamines for systemic use	14.83	0.8167
S01C	Anti-inflammatory agents and anti-infectives in combination	2.15	0.9123	R03A	Adrenergics, inhalants	5.24	0.7087
R03A	Adrenergics, inhalants	3.95	0.8991	R01A	Decongestants and other nasal reparations for topical use	8.50	0.6800
ASMA	Asthma	4.15	0.6915	S01G	Decongestants and antiallergics	3.10	0.6329
R06A	Antihistamines for systemic use	11.12	0.6647	ASMA	Asthma	6.67	0.4935
R01A	Decongestants and other nasal preparations for topical use	6.37	0.5650	RES02	Acute lower respiratory tract infection	2.38	0.4617
RES02	Acute lower respiratory tract infection	2.25	0.5564	ALL03	Allergic rhinitis	12.64	0.4243
ALL03	Allergic rhinitis	7.27	0.3956	H02A	Corticosteroids for systemic use. plain	3.30	0.4065
H02A	Corticosteroids for systemic use, plain	2.35	0.3574	J01F	Macrolides, lincosamides and streptogramins	9.55	0.3837
				J01C	Beta-lactam antibacterials, penicillins	21.02	0.3651
				J01M	Quinolone antibacterials	3.64	0.3413
				J01D	Other beta-lactam antibacterials	3.42	0.3320
				N02B	Other analgesics and antipyretics	20.89	0.3169
				D07A	Corticosteroids, plain	5.54	0.3086
FACTOR 3: MENTAL HEALTH		**Prev (%)**	**Values**	**FACTOR 2: MENTAL HEALTH**		**Prev (%)**	**Values**
N06A	Antidepressants	6.10	0.9314	N06A	Antidepressants	6.95	0.8600
N05B	Anxiolytics	8.86	0.7156	N03A	Antiepileptics	2.75	0.7610
N03A	Antiepileptics	2.22	0.6426	N05B	Anxiolytics	11.11	0.7584
PSY09	Depression	4.55	0.6301	N05A	Antipsychotics	2.03	0.5738
N05A	Antipsychotics	1.83	0.5151	PSY09	Depression	6.76	0.5535
PSY01	Anxiety, neuroses	2.65	0.4704	A02B	Drugs for peptic ulcers and GERD	10.42	0.4688
N02C	Antimigraine preparations	1.48	0.2683	N02A	Opioids	3.83	0.4575
				PSY01	Anxiety, neuroses	4.89	0.4333
				PSY19	Sleep disorders of nonorganic origin	3.65	0.3776
				N02C	Antimigraine preparations	1.74	0.3742
				NUR21	Neurologic disorders, other	2.33	0.3556
				NUR03	Peripheral neuropathy, neuritis	2.60	0.3093
FACTOR 4: ENDOCRINOLOGICAL		**Prev (%)**	**Values**	**FACTOR 3: ENDOCRINOLOGICAL**		**Prev (%)**	**Values**
B03A	Iron preparations	7.73	0.9181	B03A	Iron preparations	8.97	0.7959
H03C	Iodine therapy	4.24	0.7731	H03C	Iodine therapy	5.61	0.6469
HEM02	Iron deficiency, other deficiency anemias	4.10	0.5908	HEM02	Iron deficiency, other deficiency anemias	6.18	0.5369
B03B	Vitamin B12 and folic acid	3.53	0.5032	B03B	Vitamin B12 and folic acid	3.99	0.4798
G03A	Hormonal contraceptives for systemic use	3.03	0.3399	H03A	Thyroid preparations	4.30	0.4306
C05C	Capillary stabilizing agents	3.02	0.2817	END04	Hypothyroidism	6.29	0.3658

Year 2011		Prev	Values	Year 2015		Prev	Values
45–65 years							
FACTOR 1: MENTAL HEALTH		**Prev (%)**	**Values**	**FACTOR 1: MENTAL HEALTH**		**Prev (%)**	**Values**
N06A	Antidepressants	16.63	0.8254	N06A	Antidepressants	18.21	0.8980
N05B	Anxiolytics	22.35	0.7021	N05B	Anxiolytics	24.67	0.6682
N03A	Antiepileptics	5.70	0.5976	PSY09	Depression	16.81	0.6131
N05C	Hypnotics and sedatives	6.12	0.5944	N05C	Hypnotics and sedatives	6.08	0.5592
PSY09	Depression	12.93	0.5871	N03A	Antiepileptics	7.01	0.5406
N02A	Opioids	8.24	0.4676	PSY01	Anxiety, neuroses	6.70	0.4116
A02B	Drugs for peptic ulcer and GERD	30.90	0.4483	N02A	Opioids	10.24	0.3805
PSY01	Anxiety, neuroses	4.13	0.4187	PSY19	Sleep disorders of nonorganic origin	10.29	0.3618
PSY19	Sleep disorders of nonorganic origin	6.54	0.4111	A02B	Drugs for peptic ulcers and GERD	29.06	0.3379
M01A	Anti-inflammatory and antirheumatic products, non-steroids	46.56	0.4095				
A03F	Propulsives	6.28	0.3674				
M03B	Muscle relaxants, centrally acting agents	7.11	0.3614				
MUS13	Cervical pain syndromes	2.38	0.3128				
MUS14	Low back pain	7.52	0.2733				
NUR21	Neurologic disorders, other	3.57	0.2617				
NUR03	Peripheral neuropathy, neuritis	4.59	0.2524				
FACTOR 2: RESPIRATORY		**Prev (%)**	**Values**	**FACTOR 2: RESPIRATORY**		**Prev (%)**	**Values**
N02B	Other analgesics and antipyretics	30.15	0.3050	R03A	Adrenergics, inhalants	7.93	0.7548
R03A	Adrenergics, inhalants	6.21	0.8711	R06A	Antihistamines for systemic use	16.74	0.7487
R05C	Expectorants, excl. combinations with cough suppressants	20.41	0.7092	R01A	Decongestants and other nasal preparations for topical use	8.22	0.6301
RES02	Acute lower respiratory tract infection	4.46	0.7032	ASMA	Asthma	6.38	0.5872
R06A	Antihistamines for systemic use	13.51	0.6205	H02A	Corticosteroids for systemic use, pain	6.77	0.4867
ASMA	Asthma	4.45	0.5862	J01F	Macrolides, lincosamides, and streptogramins	10.82	0.4468
R01A	Decongestants and other nasal preparations for topical use	7.03	0.5761	J01M	Quinolone antibacterials	6.61	0.4313
J01F	Macrolides, lincosamides, and streptogramins	9.29	0.5400	ALL03	Allergic rhinitis	10.50	0.4032
J01M	Quinolone antibacterials	6.42	0.5128	J01C	Beta-lactam antibacterials, penicillins	17.97	0.3853
H02A	Corticosteroids for systemic use, plain	5.25	0.5007	N02B	Other analgesics and antipyretics	29.09	0.3269
J01C	Beta-lactam antibacterials, penicillins	17.98	0.4622				
R05D	Cough suppressants, excl. combinations with expectorants	11.74	0.4230				
ALL03	Allergic rhinitis	6.33	0.2741				
FACTOR 3: CARDIOMETABOLIC		**Prev (%)**	**Values**	**FACTOR 3: CARDIOMETABOLIC**		**Prev (%)**	**Values**
DIAB	Diabetes	4.99	0.7288	HTA	Hypertension	20.49	0.9601
HTA	Hypertension	19.06	0.6791	C09A	ACE inhibitors, plain	5.06	0.7041
NUT03	Obesity	9.00	0.6258	DIAB	Diabetes	5.58	0.5854
B01A	Antithrombotic agents	6.49	0.4258	NUT03	Obesity	11.62	0.5014
CAR11	Disorders of lipid metabolism	23.70	0.3817	B01A	Antithrombotic agents	6.51	0.3699
ARTRITIS	Degenerative joint disease	11.66	0.3318	CAR11	Disorders of lipid metabolism	32.89	0.2951
C05C	Capillary stabilizing agents	9.78	0.2882				
EYE08	Glaucoma	2.93	0.2823				
GSU08	Varicose veins of lower extremities	15.78	0.2771				
FACTOR 4: OSTEOMETABOLIC		**Prev (%)**	**Values**	**FACTOR 4: OSTEOMETABOLIC**		**Prev (%)**	**Values**
M05B	Drugs affecting bone structure and mineralization	6.29	0.9690	A12A	Calcium	6.10	0.8032
A12A	Calcium	8.96	0.8944	END02	Osteoporosis	8.98	0.7869
END02	Osteoporosis	9.45	0.8609				

Abbreviations: ATC, anatomical therapeutic chemical classification; COPD, chronic obstructive pulmonary disease; EDC, expanded diagnostic clusters; GERD, gastro-esophageal reflux disease; Prev, prevalenc

Women Aged 15–44 Years

In women in this age group, the epidemiological factors identified in 2015 were already similar in 2011 but appearing less complex (Table 4). Mechanical pain factor was identified in 2011, factor not maintained during 2015, characterized by low back pain as the only condition and drugs such as opioids, muscle relaxants, NSAID. Other factors identified are comparable, such as the respiratory one, which includes asthma, allergic rhinitis, acute lower respiratory tract infection, but more pertaining drugs were recorded during 2015. The mental health factor was also comparable but appeared as a third factor in 2011 and as the first factor in 2015. Depression and anxiety were recorded during the mental health of 2011 with antidepressants, anxiolytics, and antiepileptics, while, during 2015, sleep, neurologic, and peripheral disorders were also recorded. The last factor identified was the endocrinological with iron deficiency in both years and hypothyroidism only in 2015. The KMO sampling adequacy index was 0.77 in 2011 and 0.74 in 2015 and a cumulative variance percentage was 47.0% in 2011 and 35.6% in 2015.

Women Aged 45–65 Years

Scree plot identified the same four factors of 2015, in the same order but, generally, factors identified in 2011 were more complex in terms of clinical conditions number (Table 4). Anxiety, depression, sleep, neurologic, and peripheral disorders were recorded during 2011, while only anxiety, depression, and sleep disorder remained in the 2015 factor. Related drugs were comparable, as opioids remained presents for both years. The second factor identified was respiratory due to the presence of asthma and allergic rhinitis, with the addition of acute lower respiratory tract infection during 2011. This factor was mostly made up of related drugs such as antibiotics, adrenergics, decongestants, and corticosteroids. The third cardiometabolic factor was composed of diabetes, hypertension, obesity, disorders of lipid metabolism equally for both years, but more conditions appeared in 2011, such as glaucoma. The last factor identified for both was the osteometabolic, which was similarly made up of osteoporosis and calcium. The KMO index was 0.86 in 2011 and 0.80 in

2015, while the cumulative variance percentage was 55.0% in 2011 and 31.3% in 2015.

Boys Aged 0–14 Years

This profile was similar to that observed for girls aged 0–14 years, both for 2011 and 2015 factors (Table 5). In fact, likewise, factors identified in 2015 in boys in this age group were generally already detected in 2011, but with the presence of an allergic/derma component. The same differences observed for girls in terms of conditions and factor were observed for boys. The KMO sampling adequacy index was 0.72 in 2011 and 0.74 in 2015, while the cumulative variance percentage was 34.0% in 2011 and 35.6% in 2015.

Table 5. Patterns of chronic diseases (EDC codes) and drugs (ATC codes) and factor loading scores in men. Diseases are highlighted in bold.

Year 2011				Year 2015			
0–14 years							
FACTOR 1: ALLERGIC/DERMA		**Prev (%)**	**Values**	**FACTOR 1: RESPIRATORY/ACUTE INFECTION**		**Prev (%)**	**Values**
J01C	Beta-lactam antibacterials, penicillins	34.08	0.6579	H02A	Corticosteroids for systemic use, pain	11.77	0.6877
M01A	Anti-inflammatory and antirheumatic products, non-steroids	38.23	0.6372	RES02	Acute lower respiratory tract infection	13.69	0.6748
N02B	Other analgesics and antipyretics	17.98	0.6097	R03A	Adrenergics, inhalants	13.79	0.6683
R05C	Expectorants, excl. combinations with cough suppressants	22.80	0.5800	J01C	Beta-lactam antibacterials, penicillins	33.48	0.5854
R05D	Cough suppressants, excl. combinations with expectorants	22.40	0.5611	R03B	Other drugs for obstructive airway diseases, inhalants	4.05	0.5520
J01D	Other beta-lactam antibacterials	4.75	0.4832	N02B	Other analgesics and antipyretics	22.76	0.5332
S01A	Anti-infectives	6.97	0.4410	J01F	Macrolides, lincosamides, and streptogramins	8.83	0.5120
A07C	Electrolytes with carbohydrates	3.12	0.4302	N05B	Anxiolytics	3.49	0.4556
D07A	Corticosteroids, plain	9.50	0.4195	S01A	Anti-infective	9.79	0.4545
J01F	Macrolides, lincosamides, and streptogramins	8.42	0.4027	D07A	Corticosteroids, plain	9.67	0.4018
N05B	Anxiolytics	3.56	0.4009	M01A	Anti-inflammatory and antirheumatic products, non-steroids	34.58	0.3990
A03F	Propulsives	1.91	0.3946	A07C	Electrolytes with carbohydrates	4.48	0.3666
D06A	Antibiotics for topical use	5.00	0.3710	D01A	Antifungals for topical use	3.36	0.3452
H02A	Corticosteroids for systemic use, plain	8.80	0.3262	D06A	Antibiotics for topical use	5.64	0.3344
SKN02	Dermatitis and eczema	16.84	0.2812				
FACTOR 2: RESPIRATORY/ASTHMA/ACUTE INFECTION		**Prev (%)**	**Values**	**FACTOR 2: RESPIRATORY/ASTHMA/ ALLERGIC**		**Prev (%)**	**Values**
R03A	Adrenergics, inhalants	10.09	0.9215	R06A	Antihistamines for systemic use	14.54	0.6159
R03B	Other drugs for obstructive airway diseases, inhalants	3.59	0.8434	ALL03	Allergic rhinitis	5.34	0.7213
RES02	Acute lower respiratory tract infection	10.08	0.7459	S01G	Decongestants and antiallergics	3.86	0.6773
ASMA	Asthma	9.28	0.6818	R01A	Decongestants and other nasal preparations for topical use	4.33	0.6734
				ASMA	Asthma	10.96	0.4222
FACTOR 3: ALLERGIC		**Prev (%)**	**Values**				
R06A	Antihistamines for systemic use	11.26	0.6047				
ALL03	Allergic rhinitis	3.77	0.7499				
R01A	Decongestants and other nasal preparations for topical use	3.40	0.7494				
S01G	Decongestants and antiallergics	2.94	0.6728				
FACTOR 4: MENTAL HEALTH		**Prev (%)**	**Values**	**FACTOR 3: MENTAL HEALTH**		**Prev (%)**	**Values**
N06B	Psychostimulants, agents used for ADHD and nootropics	2.46	0.9564	N06B	Psychostimulants, agents used for ADHD and nootropics	2.18	0.7213
PSY05	Attention deficit disorder	1.97	0.8148	N03A	Antiepileptics	0.39	0.6562
NUR19	Developmental disorder	2.10	0.3823	PSY05	Attention deficit disorder	1.92	0.5889
PSY14	Psychosocial disorders of childhood	5.70	0.3139	PSY14	Psychosocial disorders of childhood	8.59	0.3968
				NUR19	Developmental disorder	3.89	0.3857
				A02B	Drugs for peptic ulcers and GERD	0.60	0.3324

Year 2011				Year 2015			
15–44 years							
FACTOR 1: MENTAL HEALTH/MECHANICAL PAIN		**Prev (%)**	**Values**	**FACTOR 1: MENTAL HEALTH**		**Prev (%)**	**Values**
N03A	Antiepileptics	1.67	0.7159	N06A	Antidepressants	3.74	0.8979
N05C	Hypnotics and sedatives	0.97	0.6100	N05C	Hypnotics and sedatives	1.10	0.7614
N05B	Anxiolytics	4.60	0.6036	N05A	Antipsychotics	2.00	0.7482
N05A	Antipsychotics	1.53	0.5564	N05B	Anxiolytics	6.92	0.6522
A02B	Drugs for peptic ulcer and GERD	7.94	0.5129	N03A	Antiepileptics	2.45	0.6442
N02A	Opioids	1.90	0.5024	PSY09	Depression	3.47	0.6005
M01A	Anti-inflammatory and antirheumatic products, non-steroids	23.05	0.4126	PSY02	Substance use	2.79	0.4973
N02B	Other analgesics and antipyretics	14.24	0.3849	PSY01	Anxiety neuroses	2.55	0.4801
				PSY19	Sleep disorders of nonorganic origin	3.12	0.4604
				FACTOR 2: MECHANICAL PAIN		**Prev (%)**	**Values**
				M01A	Anti-inflammatory and antirheumatic products, non-steroids	25.68	0.7741
				N02B	Other analgesics and antipyretics	17.05	0.6115
				A02B	Drugs for peptic ulcers and GERD	8.49	0.5996
				J01C	Beta-lactam antibacterials, penicillins	18.01	0.5105
				N02A	Opioids	2.92	0.4920
				MUS14	Low back pain	4.18	0.4663
				H02A	Corticosteroids for systemic use, pain	2.58	0.4642
				J01F	Macrolides, lincosamides, and streptogramins	7.10	0.4037
				B01A	Antithrombotic agents	2.01	0.3980
FACTOR 2: RESPIRATORY		**Prev (%)**	**Values**	**FACTOR 3: RESPIRATORY**		**Prev (%)**	**Values**
H02A	Corticosteroids for systemic use, plain	1.65	0.3883	RES02	Acute lower respiratory tract infection	2.05	0.3838
R01A	Decongestants and other nasal preparations for topical use	4.73	0.7461	R03A	Adrenergics, inhalants	4.54	0.7900
R06A	Antihistamines for systemic use	7.83	0.6764	R06A	Antihistamines for systemic use	11.97	0.7005
R05C	Expectorants, excl. combinations with cough suppressants	10.13	0.5909	ASMA	Asthma	6.89	0.6227
ALL03	Allergic rhinitis	6.06	0.5124	R01A	Decongestants and other nasal preparations for topical use	6.99	0.5562
J01F	Macrolides, lincosamides, and streptogramins	5.22	0.4957	ALL03	Allergic rhinitis	12.12	0.4093
ASMA	Asthma	3.53	0.4573				
R05D	Cough suppressants, excl. combinations with expectorants	5.99	0.4383				
J01C	Beta-lactam antibacterials, penicillins	15.47	0.3796				
FACTOR 3: CARDIOMETABOLIC		**Prev (%)**	**Values**				
HTA	Hypertension	2.05	0.7494				
NUT03	Obesity	2.62	0.5822				
CAR11	Disorders of lipid metabolism	6.10	0.5101				
B01A	Antithrombotic agents	1.61	0.5063				
FACTOR 4: DERMA		**Prev (%)**	**Values**				
SKN02	Dermatitis and eczema	4.94	0.8586				
D07A	Corticosteroids, plain	3.62	0.6772				
D01A	Antifungals for topical use	3.15	0.4985				

Year 2011				Year 2015			
45–65 years							
FACTOR 1: RESPIRATORY		**Prev (%)**	**Values**	**FACTOR 3: RESPIRATORY**		**Prev (%)**	**Values**
R05C	Expectorants, excl. combinations with cough suppressants	14.43	0.7394	N02B	Other analgesics and antipyretics	22.35	0.3056
R06A	Antihistamines for systemic use	8.06	0.6970	RES04	Emphysema, chronic bronchitis, COPD	3.64	0.3491
R01A	Decongestants and other nasal preparations for topical use	5.05	0.6485	R03A	Adrenergics, inhalants	5.88	0.8130
RES02	Acute lower respiratory tract infection	3.15	0.5805	R06A	Antihistamines for systemic use	11.10	0.7063
J01F	Macrolides, lincosamides, and streptogramins	5.57	0.5787	RES02	Acute lower respiratory tract infection	3.45	0.5897
R05D	Cough suppressants, excl. combinations with expectorants	7.00	0.5409	R01A	Decongestants and other nasal preparations for topical use	6.26	0.5803
J01C	Beta-lactam antibacterials, penicillins	14.33	0.5140	ASMA	Asthma	3.43	0.5666
N02B	Other analgesics and antipyretics	21.11	0.5065	J01M	Quinolone antibacterials	5.53	0.4548
M01A	Anti-inflammatory and antirheumatic products, non-steroids	32.37	0.4865	J01F	Macrolides, lincosamides, and streptogramins	6.91	0.4383
J01M	Quinolone antibacterials		0.4676	J01C	Beta-lactam antibacterials, penicillins	15.46	0.3981
ALL03	Allergic rhinitis	4.03	0.4222	ALL03	Allergic rhinitis	7.53	0.3589
ASMA	Asthma	2.05	0.4190				
D07A	Corticosteroids, plain	32.37	0.3434				
M02A	Topical products for joint and muscular pain	6.25	0.3159				
RES04	Emphysema, chronic bronchitis. COPD	2.69	0.2818				
FACTOR 2: CARDIOMETABOLIC		**Prev (%)**	**Values**	**FACTOR 2: CARDIOMETABOLIC**		**Prev (%)**	**Values**
A02B	Drugs for peptic ulcer and GERD	24.46	0.3434	A02B	Drugs for peptic ulcer and gastro-esophageal reflux disease (gord)	25.26	0.3952
HTA	Hypertension	22.12	0.8007	B01A	Antithrombotic agents	11.01	0.7832
B01A	Antithrombotic agents	9.93	0.6619	HTA	Hypertension	27.96	0.6610
DIAB	Diabetes	8.73	0.6547	IHD	Ischemic heart disease	4.07	0.6085
C09C	Angiotensin II receptor blockers (ARBs), plain	6.49	0.6080	DIAB	Diabetes	11.00	0.5750
IHD	Ischemic heart disease	3.23	0.5763	C09C	Angiotensin II receptor blockers (ARBs), plain	6.85	0.5396
NUT03	Obesity	6.73	0.5377	CAR16	Cardiovascular disorders, other	2.14	0.4854
CAR11	Disorders of lipid metabolism	26.32	0.4817	CAR09	Cardiac arrhythmia	2.50	0.4723
RHU02	Gout	2.88	0.3703	NUT03	Obesity	10.24	0.4283
				CAR11	Disorders of lipid metabolism	39.37	0.3296
				RHU02	Gout	4.17	0.3014
FACTOR 3: MENTAL HEALTH		**Prev (%)**	**Values**	**FACTOR 1: MENTAL HEALTH**		**Prev (%)**	**Values**
N06A	Antidepressants	6.04	0.9434	N06A	Antidepressants	7.22	0.7887
PSY09	Depression	4.42	0.7844	N05B	Anxiolytics	12.79	0.7326
N05B	Anxiolytics	10.25	0.7607	N03A	Antiepileptics	5.10	0.6613
PSY19	Sleep disorders of nonorganic origin	3.60	0.3751	PSY09	Depression	6.86	0.5530
PSY02	Substance use	2.61	0.3104	N02A	Opioids	6.60	0.4891
				PSY01	Anxiety, neuroses	3.04	0.4447
				M01A	Anti-inflammatory and antirheumatic products, non-steroids	31.42	0.4166
				PSY19	Sleep disorders of nonorganic origin	6.66	0.3594
				MUS14	Low back pain	6.13	0.3367
				MUS13	Cervical pain syndromes	2.48	0.3161
				NUR21	Neurologic disorders, other	3.69	0.2959

Abbreviations: ATC, anatomical therapeutic chemical classification; COPD, chronic obstructive pulmonary disease; EDC, expanded diagnostic clusters; GERD, gastro-esophageal reflux disease; Prev, Prevalence.

Men Aged 15–44 Years

Among men of this age group, the order and the composition of epidemiological patterns identified in 2015 were not maintained in 2011 (Table 5). In fact, during 2011, four factors were identified. The first one, recognized as mental health/mechanical pain, was comparable with the first two identified during 2015. Moreover, this factor appeared without condition but was only made up of drugs such as opioids, antiepileptics, anxiolytics, and NSAID. During 2015, mental health and mechanical pain were split into two factors containing, in the first case, depression, substance use, anxiety, and sleep disorders with related drugs, and, in the second case, low back pain. Respiratory factor observed during 2015 was already present in 2011 both for disease and drugs. The last two 2011 factors identified as cardiometabolic and derma were not present in 2015. The KMO sampling adequacy index was 0.85 in 2011 and 0.75 in 2015, while the cumulative variance percentage of 26.0% in 2011 and 37.0% in 2015.

Men Aged 45–65 Years

All three factors identified in 2015 were already present in 2011 but in a different order (Table 5). In this age group, respiratory factor was enriched with emphysema, chronic bronchitis, COPD for rather than other age groups, equally during 2015 and 2011. This factor appeared first during 2011 and last in 2015. The cardiometabolic factor seemed more complex in this age group for both years, due to the number of conditions that emerged such as hypertension, obesity, diabetes, ischemic heart disease, and gout. Mental health factor appeared firstly during 2015 and has become more complex than in 2011. The KMO sampling adequacy index was 0.82 in 2011 and 0.63 in 2015, while the cumulative variance percentage was 40.0% in 2011 and 30.4% in 2015.

Discussion

This study found that baseline epidemiologic patterns of multimorbidity and polypharmacy identified in the young and adult Spanish population during 2015 were already present in 2011 but with the addition of an allergic/derma pattern, which is not maintained in 2015. Globally, our findings also revealed that patterns identified in 2011 were more complex

in terms of both disease and drugs; this could be a sign of an improvement and greater accuracy over the years in the computerized medical records systems. Other reason for the decreasing in the number of drugs taken by all age groups between 2011 and 2015 can be explained by the fact that after 2011, some medication was no longer reimbursed by the Spanish NHS, so this cannot be translated into a decrease in their use. We found that the complexity of patterns in terms of diseases and drugs, identified in both sexes, increases with age, and this trend remains unchanged in 2015. The first difference identified can be represented by the presence of dermatitis and eczema as a condition more often diagnosed during 2011. In young subjects, the respiratory pattern was the most prevalent, even after four years. During 2015, the respiratory allergic component was predominant in children. This aspect was recorded during 2011, but it seems that respiratory conditions were better registered during 2015, as shown from the more accurate patterns resulted. Corroborating with our results, the high frequency of allergic and asthmatic components in childhood was widely discussed in the literature [15–18]. Similar was the case of childhood mental disorders and illnesses, conditions also found in 2011, with the addition in 2015 of the drugs for peptic ulcers and GERD, highlighting an increase in their use over the years attributable to prescriptive inappropriateness [19,20]. Additionally, a register of developmental and psychosocial disorders in children associated with antiepileptic treatments and attention deficit hyperactivity disorder (ADHD) treatments were established in both 2011 and 2015. The same pattern of drugs appeared in both sexes, but the diagnosis in girls seemed less accurate than in boys [21]. This could be explained as, in general, the clinic is more evident in boys, and among girls the symptoms are less intense, and therefore, a more general descriptor is used. For these reasons, since 2011, pediatricians started to collaborate with psychiatrists in the follow-up and treatment of affected children [22].

Various changes have been highlighted over the years among the age group 15–44 years in both sexes. Drugs such as cough suppressants and propulsives were dispensed to both men and women in 2011, also in younger and older age groups, but not in 2015, but this can be explained by the fact that after 2011, they were no longer reimbursed by the Spanish NHS. Another considerable difference is related to the mental factor that

has become more complex in 2015, differently for men and women. Hence, during 2015, the mental factor was more prevalent among women. The prevalence of depression increased from 4.5% in 2011 to 6.7% in 2015, and more neurological disorders were diagnosed. This could be partly explained by an increase in psychophysical stress caused by more accelerated life rhythms over the years [23]. Similarly, in 2015, men were diagnosed with more disorders not present in 2011, and there was also evidence of substance use disorder, not present in women [24]. Substance use in men, in this age group, could be the cause of the worsening of the diagnosis picture in 2015; in fact, it appears to be a mechanical pain factor that was not present at all in 2011.

It is likely that as polypharmacy increases, drug dependence also increases, which leads to the development of a phenomenon of drug tolerance that complicates the overall clinical framework [25]. In women, it is noteworthy that the mental factor appeared in some psychosocial disorders, such as psychosocial disorders of childhood, combined with a drug cluster in which opioids appeared only in 2015. Perhaps this could be related to the higher prescription of tramadol in 2011, as this molecule was associated with the mechanical pattern. To date, several observational studies are alerting health authorities due to the adverse effects of opioid drugs associated with gabapentin. In fact, in Canada and France, there has been a warning about the risk of combining gabapentin and opioids, both in clinical practice and for recreational use [26,27]. In Ireland, the Medical Council has urged doctors to reduce the prescription of sedative drugs, including gabapentin [28]. Additionally, a recently published study linked the use of these drugs, especially pregabalin, to an increased risk of suicidal behavior, involuntary overdoses, injuries, traffic accidents, and crime [29]. Furthermore, among women, mechanical pain was detected in 2011 but not in 2015; in this year, the neurologic disorders that produce pain as neurologic disorders and peripheral neuropathy are included in the mental health patterns. A significant difference is, in fact, evident with men in the same age group, for whom, as in 2011, the mechanical pain factor remained in 2015.

Our results showed that in 2011 a cardiometabolic factor appeared in men in the 15–44 age group, while during 2015, in the older age group. It could be that until 2011, the occurrence of an episode of hypertension was

sufficient to be diagnosed; however, with the subsequent establishment of new guidelines, the diagnosis has to be more accurate and well confirmed [30]. Furthermore, our findings also revealed that in 2011, as for 2015, the association between age and epidemiological pattern complexity is confirmed, as already discussed in literature [31,32]. Therefore, both for 2011 and 2015, among adults until 65 years, all the patterns appeared more complex than other age groups. In fact, the most predominant factors maintained over time were respiratory, cardiometabolic, and mental factors. Respiratory factor generally appeared more complex in 2011 than 2015, because it has been widely studied and identified the systematic association between asthma and allergic rhinitis; this has allowed for making a more accurate diagnosis [33–35]. Cardiometabolic factor appears similar for men and women with the addition of gout in men. This is in line with other studies, reporting that a prevalence rate of 1–2% for adults, underlining that it represents the most common inflammatory arthritis in men [36,37]. Another difference between sex was that this pattern in men included consequences of metabolic syndrome such as cardiovascular disease, ischemic heart disease, and cardiac arrhythmia, which is possibly due to increased cardiovascular risk in men, together with an increased incidence of ischemic heart and cerebrovascular diseases [38].The mechanical pain in men aged 15–44 group in 2011 is included in the mental health pattern, while is separated in 2015. Contrarily, for women of the same age group, mechanical pain appeared only in 2011. The association of anxiety, depression, and somatic symptoms displayed in this pattern is well described, and somatic symptoms are mainly associated with emotional and brain functions, and they may reflect potential emotional conflicts that patients cannot face [39].

Finally, for the 45–56 age group, another gender difference can be highlighted, such as the presence of osteometabolic factor among women. This factor made up of osteoporosis and calcium, during 2011 also contained drugs affecting bone structure and mineralization that disappeared during 2015. The absence of these drugs in 2015 could be partly explained by the restrictions in use of bisphosphonates, recommended by the Spanish Agency of Medicines and Medical Devices in 2011, due to their association with a higher risk of atypical fractures [40].

In various patterns, we revealed potential DDIs, which could increase the risk of adverse health outcomes. Among them, we could highlight the use of inhaled beta-adrenergic agonists and corticosteroids, which decreased potassium levels, thus increasing the risk of arrhythmia [41]; the use of macrolides with inhaled beta-adrenergic and antihistamines, producing a QT prolongation and thus increasing the risk of arrhythmia [42]; the combined use of benzodiazepines and opioids, which increases sedation and respiratory depression [41].

Comparison with Other Studies

Multiple studies have been published in the recent years describing the different multimorbidity patterns, such as a study conducted in patients over 14 years old that described the existence of mechanical obesity, metabolic, neurovascular, liver disease, psychiatric substance abuse, anxiety, and depression-related patterns [8]. In addition, others studies only described the polypharmacy patterns [35]. However, in 2019, a study on multimorbidity and polypharmacy patterns showed the existence of some unexpected systematic associations among chronic diseases and drugs, as well as potential DDIs and prescribing cascades described in multimorbid patients [11]. Other authors had identified patterns between drugs and chronic disease in populations with a specific disease. For example, Hanlon et al. in 2018 describe the pattern and extent of multimorbidity and polypharmacy in patients with chronic obstructive pulmonary disease [43]. Nevertheless, our study described the patterns that influence to all the population. Aoki et al. in 2018 developed a study similar to ours identifying the multimorbidity patterns in a Japanese population, determining the effects on polypharmacy and dosage frequency [44].

The present study could be considered more exhaustive, because it compared the evolution of multimorbidity and polypharmacy patterns between 4 years in the same population, although this time span is not enough to detect long-term changes.

Strengths and Limitations

To our knowledge, this is the first large-scale population study comparing the differences observed in 4 years in the systematic associations among

chronic diseases and dispensed drugs. The large population size of the EpiChron Cohort, together with the quality of data, resulting in reliable and representative results compared to those based only on medical records or drug use surveys [11]. In order to compare the same population at two different times, in this study, we have considered the population as an open cohort and, thus, not a cohort composed of a fixed number of members, but a dynamic cohort in which over time some subjects became lost and others are involved in the study. A population residing in a geographical area is, by definition, an open (or dynamic) cohort made up of individuals who contribute their personal time to the cohort, as long as they meet the membership criteria, i.e., place of residence, age, and health status. Therefore, having analyzed the variations in terms of multimorbidity and polypharmacy patterns in the population of Aragon, the cohort observed in 2011 and 2015 was considered as dynamic.

During the last five years, valuable information has been published regarding the security profile of numerous drugs, as was the case of benzodiazepines and opioids, allowing us to discuss our findings from both 2011 and 2015 in a more comprehensive manner. One of the essential methodological limitations of this study concerns the impossibility of including some drugs in the analyses due to multicollinearity with specific diseases, thus leading to the absence of specific drugs that would be, a priori, expected in some patterns. The issue of multicollinearity was also responsible for excluding the population aged >65 years from the analysis, which limited the comprehensiveness of the study. Nevertheless, in the present study, we used the same methodological criteria as the reference study to compare two populations that are as homogeneous as possible [11]. Furthermore, we conducted this study in order to assess the variations in most common clinical profiles among real-world population over the years. The 4 years evaluated were from 2011 to 2015 due to the availability of such data; in the future, a further survey may be carried out over more recent years. Providing information based on real-world data [45–51] may be a useful way to explore the dynamics in real clinical practice and to improve single-patient care model.

Conclusions

This study investigated the nature and complexity of a population, investigating the presence of systematic associations between diseases and drugs at two different times. We found that most clinical profiles were maintained over time as in the case of mental, cardiometabolic, mechanical, endocrinological, and osteometabolic patterns. Our findings revealed that baseline multimorbidity and polypharmacy patterns are maintained over time, as the nature of patterns identified in 2011 was also confirmed in 2015. Furthermore, our results also confirmed the existing association between age and clinical complexity, confirming a correlation between multimorbidity and ageing. The present study, therefore, confirmed systematic associations between diseases and drugs in the patterns over time. This could help in the early identification of potential interactions in multimorbid patients with a high risk of adverse health outcomes due to polypharmacy.

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Conflicts of Interest: The authors declare no conflict of interest.

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4.2 STAGE 2 Implementation of a new paradigm to define and measure medication adherence

To date, adherence-related quality and performance indicators have been rarely explicitly included in national health policy agendas. According to the OECD report, very few countries routinely measure and report adherence as a quality improvement indicator or performance measures at the system level [11]. One of the possible reasons for this is the lack of standardized adherence terminology and use of routine measures of adherence in clinical practice [12]. This has also limited the use of Big Data in developing monitoring systems capable of reporting timely, reproducible and accurate information on medication-taking behavior [12]. For the first time in 2012, a *consensus-based taxonomy* (**Ascertaining Barriers to Compliance; ABC**) defined adherence as a temporal sequence of three elements: *Initiation* (taking the first dose), *Implementation* (the extent to which actual use matches prescribed use), and *Discontinuation* (omission of a dose followed by no other dose taken, ending a period of drug persistence) [13]. Briefly, this conceptualization describes adherence as a multifaceted process developing through phases over time, which may totally or partially fail because of late initiation or non-initiation (initiation), suboptimal pursuance and perdurance (implementation and persistence, respectively) or early interruption (discontinuation) of a certain drug treatment. Thanks to its growing interest in scientific research and to its implications for improving medication adherence in the daily practice, the ABC Taxonomy may be considered a promising and useful model to conceptualize and study medication adherence [13]. The ABC taxonomy represented a breakthrough in the field by providing a general framework for adherence research, regardless of the type of data source (e.g., electronic healthcare databases, electronic monitoring, self-report). The new taxonomy requires international standardization and thus adaptation to the specific needs of accessible big-data limitations [13].

On these basis, main goals of the scientific production carried out across the **Stage 2** was:

i) To implement the new medication adherence taxonomy in the Italian setting.

4.2.1 Italian translation and validation of the original ABC Taxonomy for Medication Adherence.

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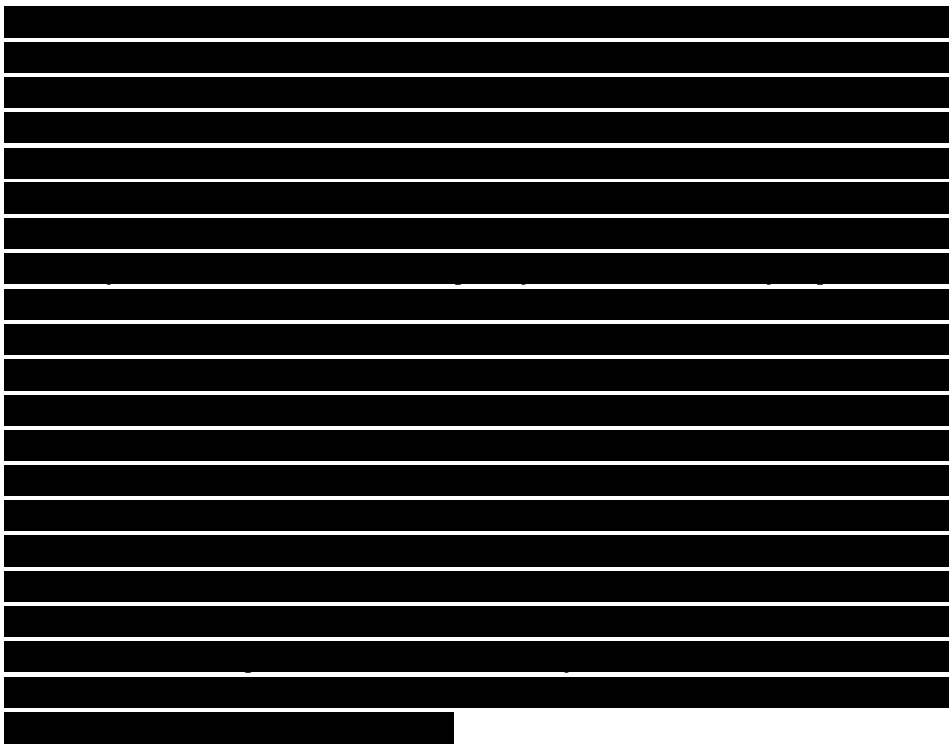

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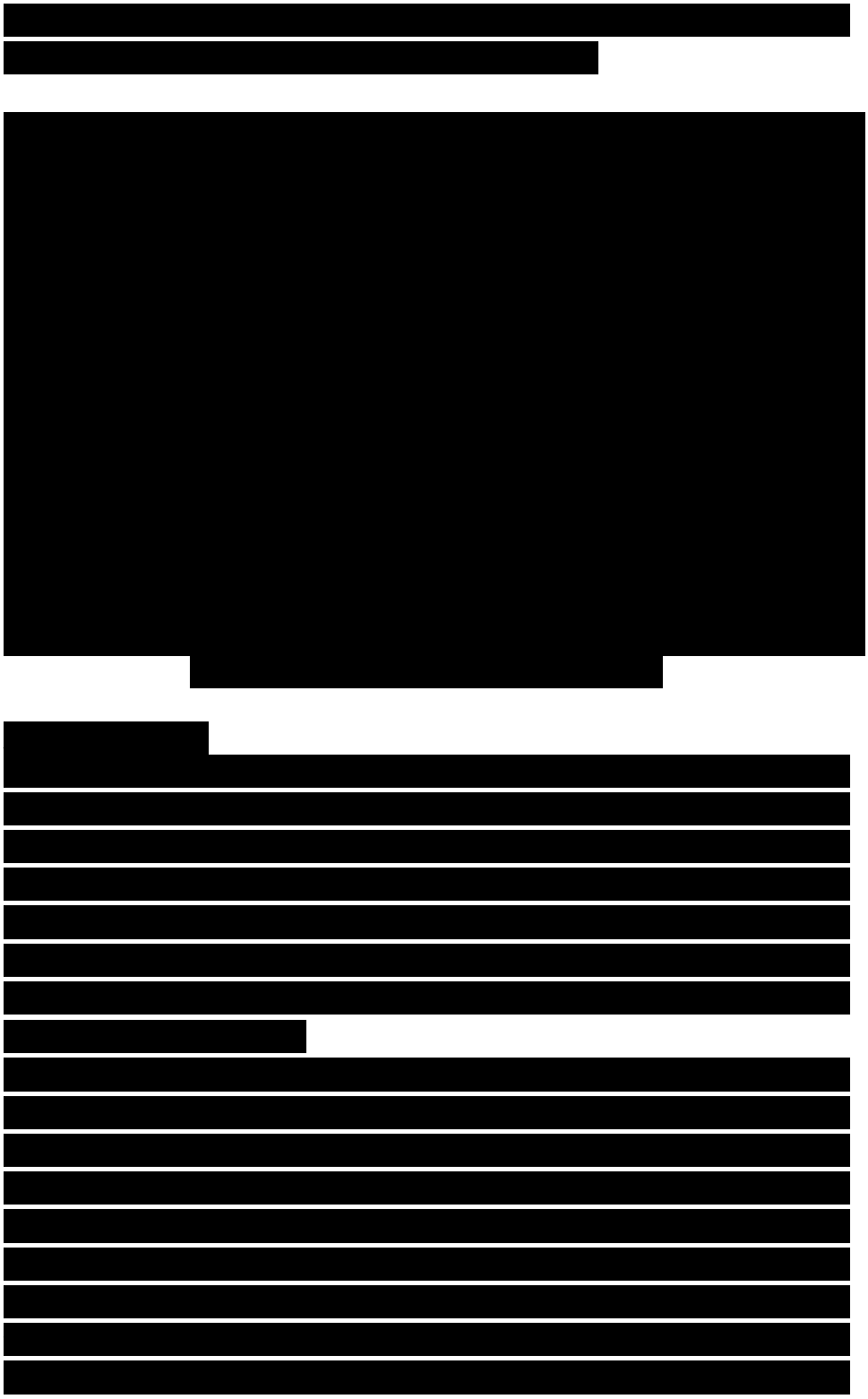

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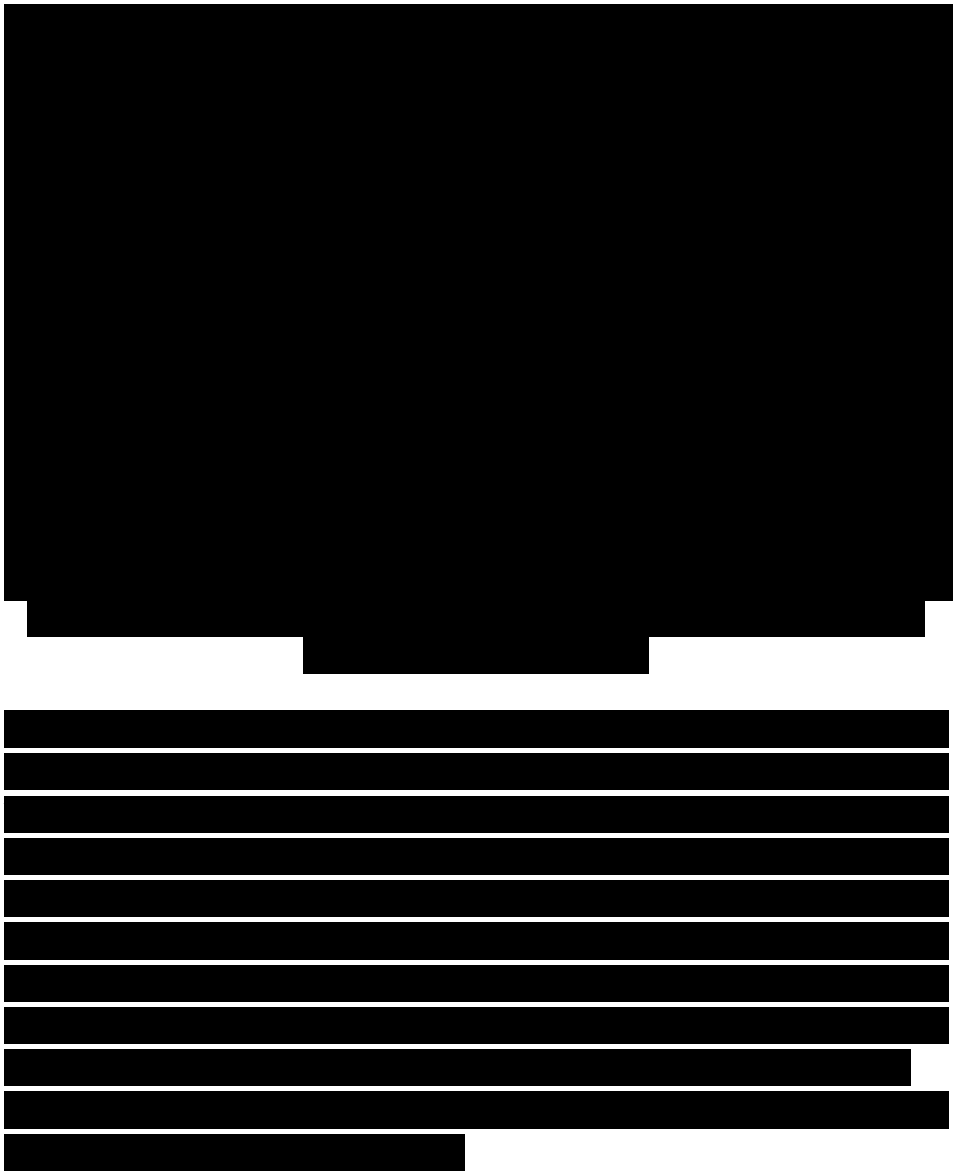

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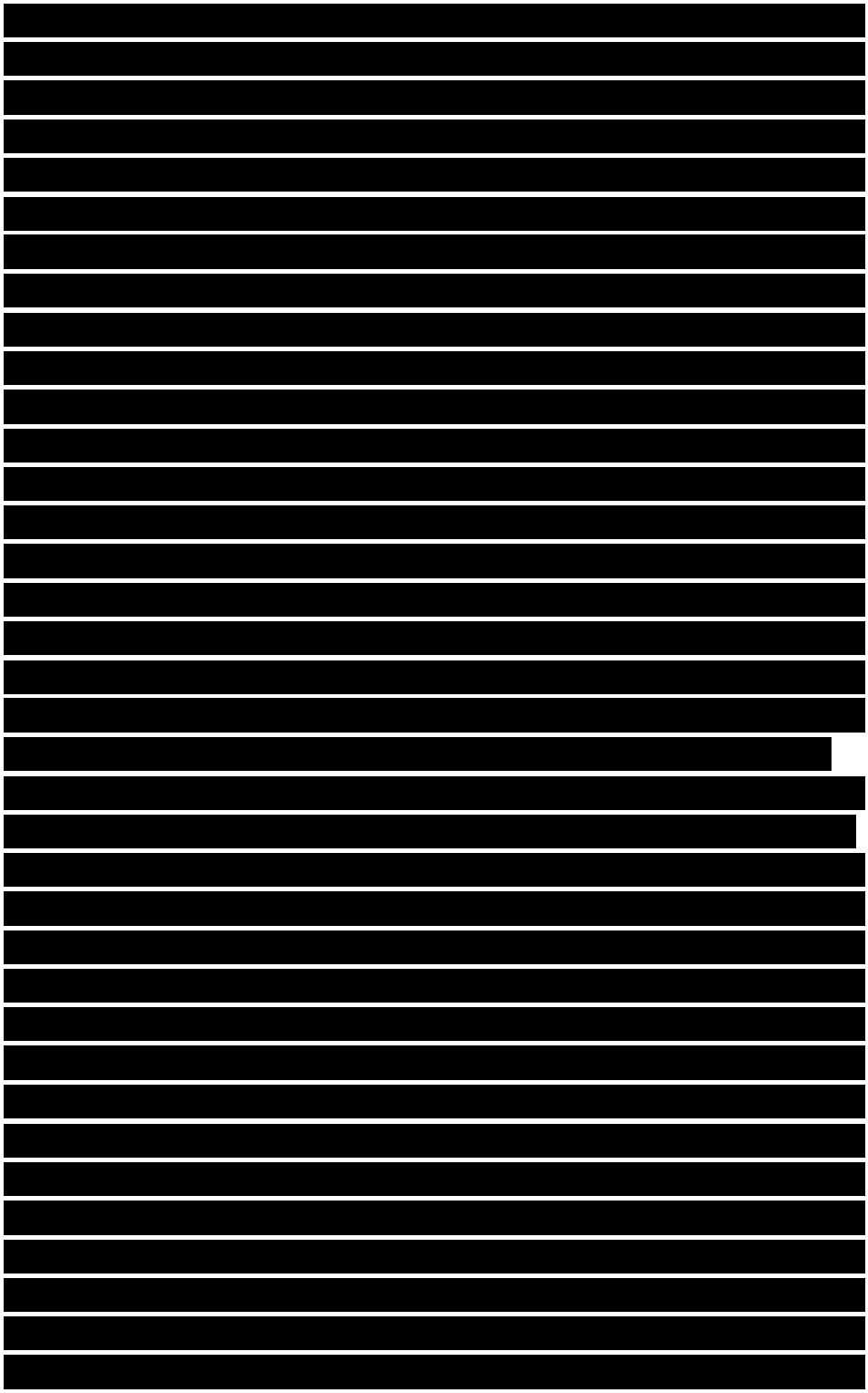

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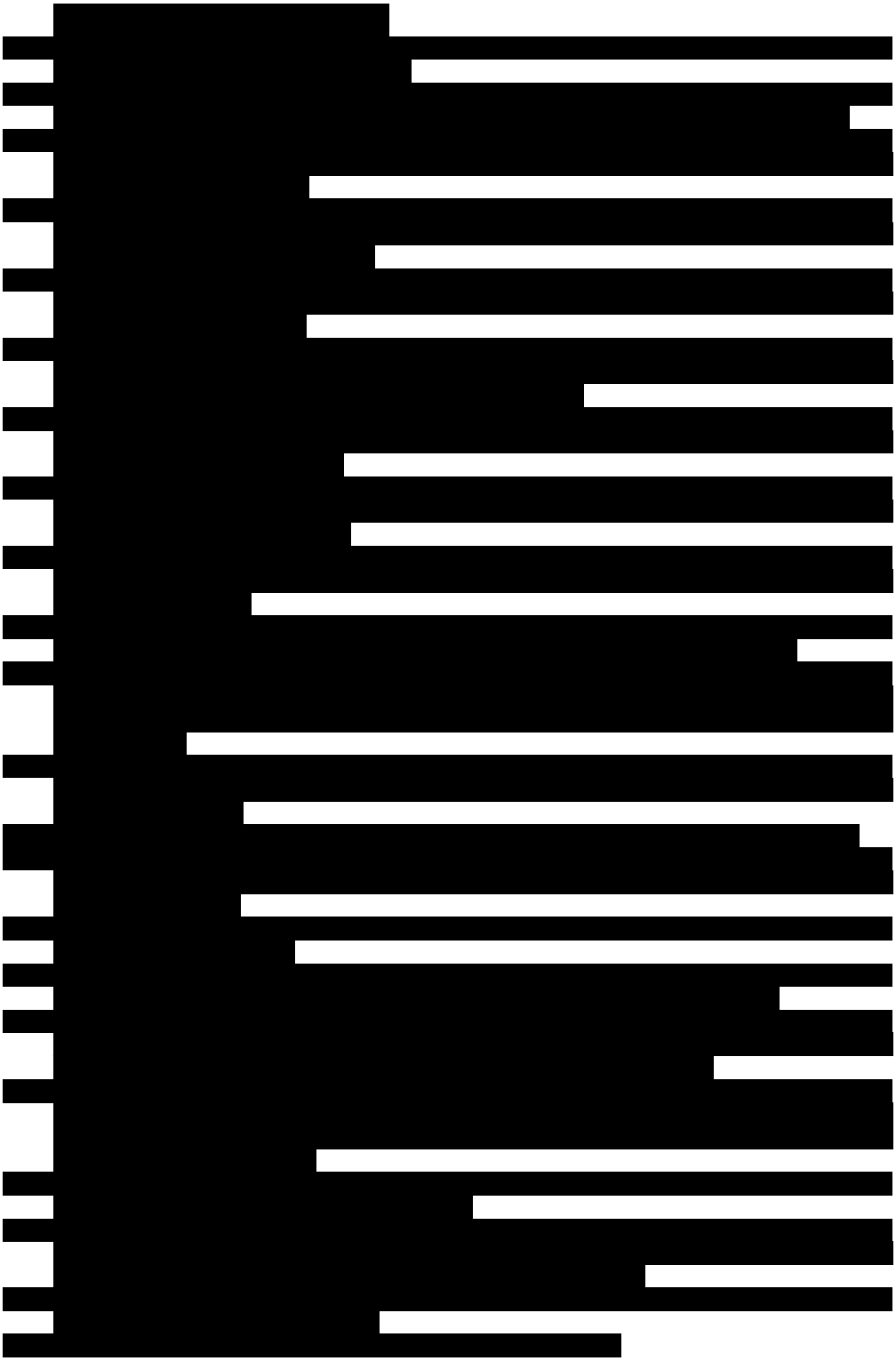

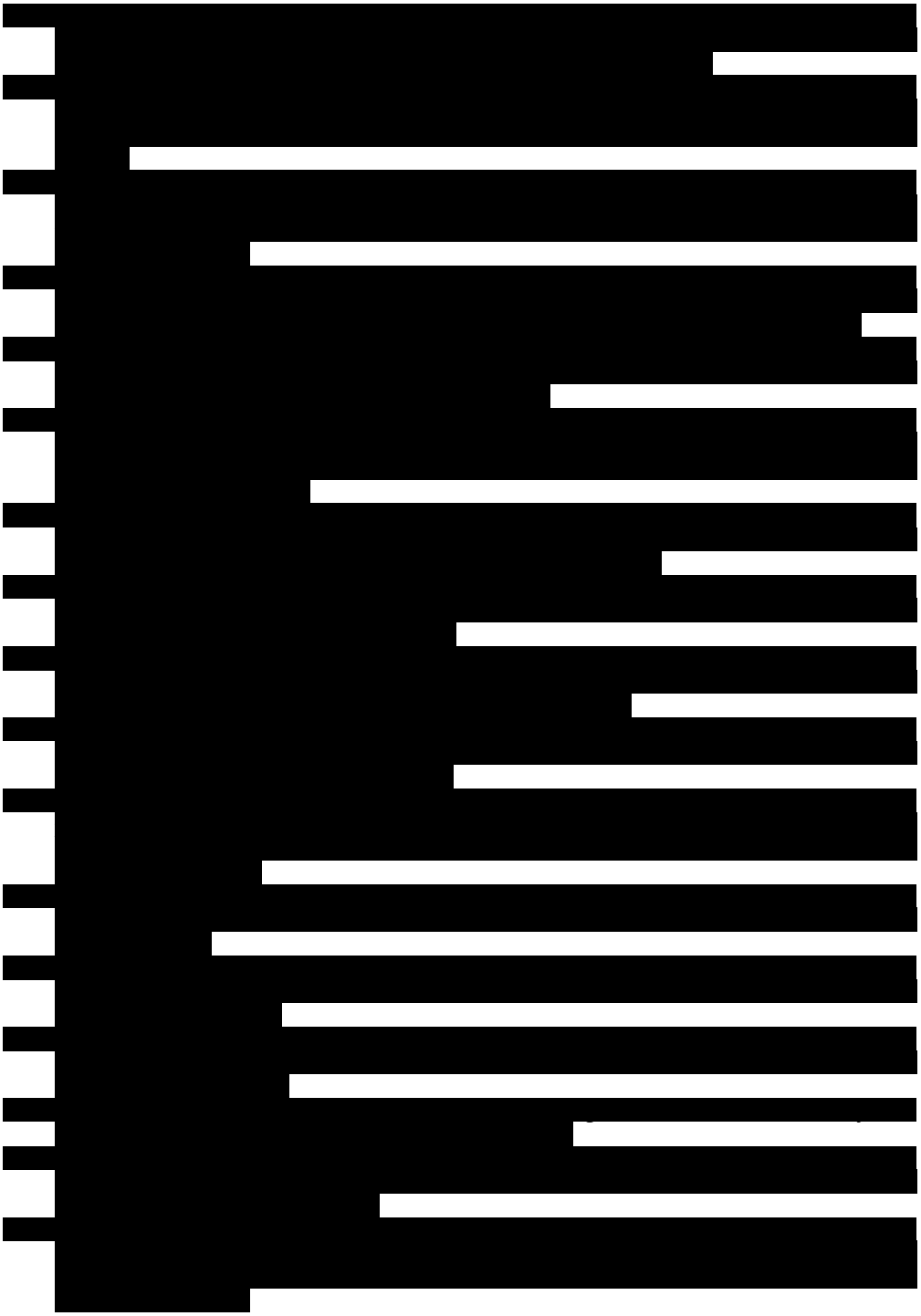

4.2.2 Treatment patterns and medication adherence among newly diagnosed patients with migraine: a drug utilization study.

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Abstract: ***Objectives***: Prophylactic drugs currently used for migraine treatment are not specific. Furthermore, few studies in existing literature describe drugs utilization patterns and adherence to migraine prophylactic treatment. This study is aimed to describe utilization patterns of migraine drugs, evaluate adherence to prophylactic medications, and investigate drug-related costs. ***Design***: Retrospective population-based study using an administrative health-related database. ***Setting***: Primary care setting in the Campania region, Southern Italy. ***Participants***: This study was carried out between 1st January 2016 and 31st December 2018, involving 12,894 subjects with any primary or secondary hospital discharge with migraine diagnosis, or at least two medical dispensations of migraine-specific acute or prophylactic medications (triptans or pizotifen). Subjects were classified into four treatment cohorts: no treatment, acute, prophylactic, and both acute and prophylactic. Subjects were followed-up for one year. ***Outcome measures***: Utilization patterns of migraine drugs at treatment initiation; adherence to prophylactic treatment; discontinuation, restart, and switching rates; annual migraine drug costs per patient. ***Results***: Overall, 81.1% of subjects received acute treatment as their initial migraine treatment regimen, 10.7% prophylactic treatment, 8.2% both acute and prophylactic treatment. 599 patients were treated prophylactically; of these, 26.2% adhered to their initial treatment while 73.8% reported interruptions in treatment. Among the latter, 46.4% of patients discontinued the treatment completely within 103 days (interquartile range [IQR]: 89.0), 31% restarted treatment 46 days after interruption (IQR: 60.0), and 22.6% switched to another treatment within 98 days (IQR: 57.5) ($p<0.001$). The median annual cost of drugs per patient was €103 for those treated acutely, €75 for those treated prophylactically, €163 for those treated both. ***Conclusions***: Migraine treatment with acute medications is still prevalent in Italy; only few patients received prophylactic treatment with poor adherence to treatment. These findings reflect an unmet need for improved prophylactic therapies in order to provide a better disease management.

Introduction

Migraine is a common disabling primary headache disorder. Numerous studies have documented the high prevalence and socio-economic and personal impacts of migraine, resulting in an estimated economic impact of €27 billion per year in the European Union alone [1–5]. According to the World Health Organization's ranking of the main causes of disability, headache disorders are among the 10 most disabling conditions [6]. According to the Italian Guidelines for Primary Headaches [7], a range of treatments are available for migraine. Furthermore, the guidelines for the pharmacological treatment of migraine describe both acute and prophylactic approaches [7]. Although prophylactic therapy is primarily used to reduce the frequency, duration, or severity of attacks, it also enhances a patient's response to acute treatments while improving socioeconomic function [8]. However, prophylactic drugs are not migraine-specific, because they are mainly indicated for other conditions such as depression, epilepsy, and hypertension. There is evidence that these medications are frequently associated with side effects and low adherence to therapy, thus leading to poor efficacy [9]. In recent years, a range of novel therapies have emerged for the specific treatment of migraine by both acute and prophylactic regimens [10]. For example, the injection of botulinum toxin A was approved in 2013 as a preventive therapy for migraine [11]. More recently, monoclonal anti-bodies directed against the calcitonin gene-related peptide (CGRP) have been introduced as a novel therapeutic strategy for migraine, thus indicating potential new strategies for the treatment of this disease [12].

In the context of development of these novel therapies, it is therefore critical to understand the current use of prophylactic therapies in real-world clinical practice and evaluate how these drugs are used over time. This can be achieved by using health-related administrative databases as tools for tracking and monitoring drug use. The aims of this drug utilization study were to (i) describe the utilization patterns of migraine drugs, ii) evaluate adherence to prophylactic medications, and (iii) investigate drug-related costs.

Methods

Study design

A retrospective population-based study was performed using administrative health-related database in the primary care setting of Campania region, one of the largest Italian regions situated in the South of the country and representing approximately 10% of the Italian population (i.e. 5.9 million inhabitants). We used the STROBE cross sectional checklist when writing our report [13].

Data Sources

The data required for this study were retrieved from the Campania Regional Database for Medication Consumption and the discharge record database held by the regional hospital. The first database contains the records of drugs dispensed by community pharmacies and reimbursed by Local Health Authorities (LHUs). Further details relating to data sources have been published previously [14, 15]. Data were collected between 1st January 2016 and 31st December 2018. All data sources were matched by record-linkage analysis via the use of a unique encrypted personal identification code and linked to the civil registry in order to collect important demographic information, including age, gender, and date of death or migration. The World Health Organization's International Classification of Diseases, Ninth Revision (ICD-9), was used to classify cases of migraine, and the Anatomical Therapeutic Chemical (ATC) code to classify active substances.

Study population

The study population included all subjects who were alive and residing in the Campania region during the study period. Figure 1 shows a flowchart depicting how patients were selected.

The presence of migraine was defined by any diagnosis of migraine as primary or secondary hospital discharge or at least two medical dispensations of migraine-specific acute or prophylactic medication (triptans, ATC IV: N02CC or pizotifen, ATC V: N02CX01) between 1st January 2016 and 31st October 2017 (the recruitment period). The date of identification (entry into the migraine cohort) was defined as either the

date of hospital discharge or the second drug dispensation, depending on which occurred first.

In order to identify incident users, it was applied a washout period prior to the date of identification in order to exclude all individuals with a previous diagnosis of migraine or those with a relevant history of medication. Furthermore, patients with a diagnosis of epilepsy or seizure (ICD-9 345.X) or with a dispensation of topiramate (ATC V: N03AX11), valproic acid (ATC V: N03AG01), or lamotrigine (ATC V: N03AX09), between 1st January 2012 until the date of entry into the migraine cohort, were also excluded in order to avoid misclassification. This procedure was followed because these drugs are specifically indicated for epilepsy and seizure.

Following the protocol adopted by Thomsen et al [16], patients were followed-up for 60 days after the day of identification. Within this timeframe, four incident treatment cohorts were identified based on the initial migraine treatment: (i) 'No treatment', defined as patients who received no migraine treatment; (ii) 'Acute treatment', defined as patients who received at least one specific or non-specific acute treatment for migraine; (iii) 'Prophylactic treatment', defined as patients who received at least one specific or non-specific prophylactic treatment for migraine; and (iv) 'Both acute and prophylactic treatment', defined as patients who received both acute and prophylactic treatments for migraine that were either specific or non-specific. The drugs encountered in this study are listed in Supplementary Table 1. After this initial timeframe, patients were followed-up until the end of the study period (365 days). Figure 2 shows a schematic representation of the study.

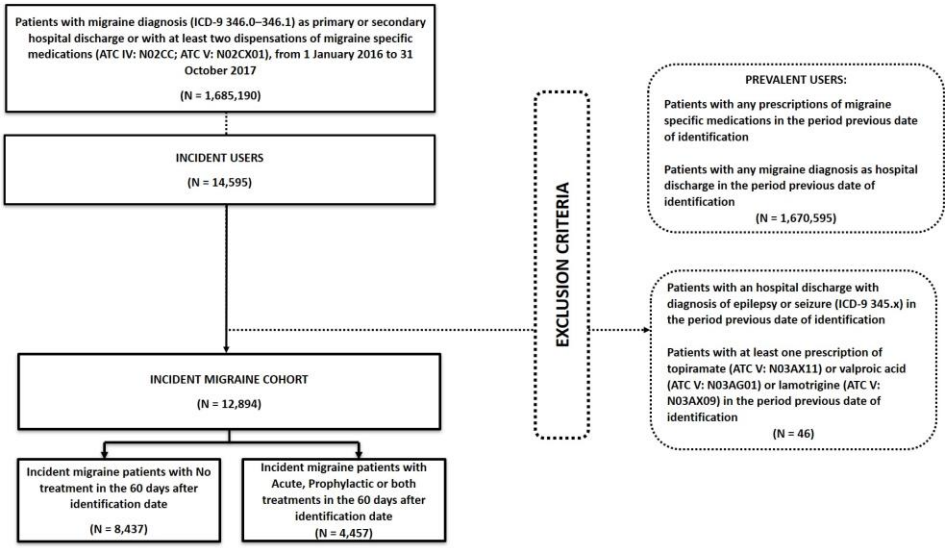

Figure 1. Study flow chart.

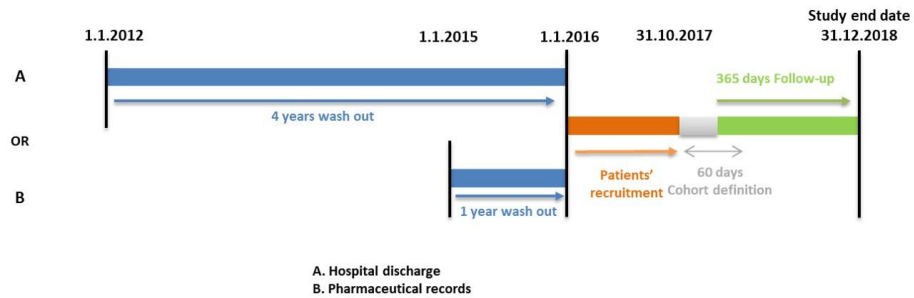

Figure 2. Schematic presentation of study design and patients' selection.

Adherence to therapy

The main outcome of the present study was the adherence of patients to prophylactic migraine therapy. Adherence to therapy was evaluated in accordance with the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE), which recommends standard reporting approaches that are based on accepted taxonomy. This guideline divides adherence to medication into 3 interrelated yet distinct phases: initiation, implementation, and persistence [17]. The present study is focused on the persistence phase.

One year after the initiation of therapy, the persistence of all patients receiving prophylactic medications was measured. Persistence was defined as the continuation of treatment for one year after the index date and was estimated by measuring the time gap between a drug dispensation and the following one. The number of days of medication supplied in each package was calculated from the number of Defined Daily Doses (DDDs) contained in the package. Persistence was identified as refilling a prescription for a prophylactic drug during the time period corresponding to all DDDs in the package prescribed previously, plus the following 60 days (the grace period). Subjects were considered to be non-persistent if the gap between two refills exceeded the grace period. Sensitivity analyses were performed with a 30-day and 90-day gap. Persistence to medication was measured at the drug class level (ATC V level).

Non-persistent subjects were categorized as: restarting (re-initiation of the same pharmacological treatment received at the index date); switching (re-initiation of a pharmacological treatment that was different from that dispensed at the index date); and full discontinuers (definitive interruption of a prophylactic migraine treatment).

Covariates

The following variables were assessed at baseline: sex, age, type of patient recruitment, comorbidities, comedications, and the number of concomitant drugs (polypharmacy). Polypharmacy was defined according to three classes: “excessive polypharmacy” was defined as the use of ten or more drugs; “polypharmacy” as the use of five to nine drugs; and “no-polypharmacy” as the concomitant use of four drugs or fewer.

The time to treatment switching, restarting, or full discontinuation was calculated as the median number of days and interquartile range (IQR). Comorbidities and comedications are summarized in Supplementary Material Tables 2 and 3, respectively.

Statistical analyses

Descriptive analysis was performed for all patient characteristics and the initial patterns of prophylactic migraine treatment. Differences between patient characteristics were compared using the chi-squared test for categorical variables or the unpaired t-test for numerical variables, as appropriate. A P value <0.05 was considered to indicate statistical significance. Persistence rates were estimated using the Kaplan–Meier

method and statistical differences were assessed between curves using the log-rank test.
Data management was performed with Microsoft SQL server (version 2018), and all analyses were performed with SPSS software for Windows (version 17.1, SPSS Inc., Chicago, IL, USA) and platform R (version 3.6, The R Formulation for Statistical Computing, Vienna, Austria).

Cost analysis

Finally, the drug costs of specific and non-specific migraine treatments were evaluated. Costs were expressed in Euro (€) currency and are presented as the annual median cost per patient. Cost analysis was conducted from the perspective of the third-party payer, the NHS. In Italy, the NHS is responsible for financing and providing healthcare services. The total treatment cost was computed by multiplying the number of drugs prescribed during the entire follow-up period by the unit cost of the drug. This was made for each treatment cohort: acute, prophylactic, both acute and prophylactic. Drugs were costed according to the purchase price incurred by the NHS. The cost of each drug was calculated with reference to the time at which it was dispensed.

Ethical considerations

All procedures performed in this study were in accordance with the current national law from the Italian Medicines Agency. The article does not contain clinical studies, and all patients' data were fully anonymized. For this type of study, formal consent was not required. Permission to use anonymized data for the present study was granted by the responsible authority, "Unità del Farmaco, Regione Campania".

Results

Study population characteristics

Our analyses identified 1,685,190 patients who were prescribed at least one drug for the treatment of migraine between 1st January 2016 and 31st December 2017. Of these, 14,595 were incident migraine patients; after applying the exclusion criteria, the final cohort of incident patients with migraine included 12,894 subjects (Figure 1). Characterization of the incident migraine cohort over the first 60 days after the date of

identification revealed 8,437 patients who did not receive treatment. Consequently, the remaining 4,457 patients received treatment and were included in the final analysis cohort. The characteristics of the study cohort at baseline are shown in Table 1. Most patients (81.1%) received acute treatment only as their index migraine treatment regimen, 10.7% of patients received prophylactic treatment, and 8.2% of patient received both acute and prophylactic treatment. Median patient age was 49.8 years, and approximately two-thirds of the study cohort were females. A higher proportion of patients (88.4%) were recruited via the prescription of migraine-specific treatments; only a minor percentage (11.6%) were recruited via hospital discharge records with a diagnosis of migraine. The most common comedications were cardiovascular drugs (35.7%); the next most common drugs were those taken for the respiratory system (16.1%). It was observed that 50.7% of the total incident migraine cohort were prescribed up to 4 comedications, 29.8% of patients were prescribed with 5 – 9 comedications, and 19.5% of patients were prescribed with over 10 comedications.

Table 2 lists the types of initial specific or non-specific treatments that were taken acutely or prophylactically, stratified by sex. Of the subjects receiving only acute treatment, most (53%) received triptan; the next most common treatment in this cohort was Nonsteroidal anti-inflammatory drugs (NSAIDs) (31.4%). Approximately 13% of patients received more than one specific or non-specific acute medication simultaneously. Of the subjects receiving only prophylactic treatment, 31.7% received anticonvulsants (such as valproic acid or lamotrigine), 20% received a specific treatment (such as pizotifen), while 18.7% received antidepressants (such as amitriptyline or mirtazapine).

Table 1. Characteristics of the sample at time of index date

	Total N = 4,457 (100%)	Acute Treatment** N = 3,613 (81.1%)	Prophylactic Treatment** N = 477 (10.7%)	Both** N = 367 (8.2%)	*P value*
Sex					
Males	1,393 (31.3)	1,121 (31.0)	159 (33.3)	113 (30.8)	
Females	3,064 (68.7)	2,492 (69.0)	318 (66.7)	254 (69.2)	
Mean age ± SD	49.8 ± 17.0	50.1 ± 16.3	49.2 ± 22.0	47.6 ± 16.1	
Age groups					<0.001
≤ 29 years	509 (11.4)	366 (10.1)	92 (19.3)	51 (13.9)	
30 - 55 years	2,413 (54.1)	2,000 (55.4)	195 (40.9)	218 (59.4)	
≥ 56 years	1,535 (34.4)	1,247 (34.5)	190 (39.8)	98 (26.7)	
Type of patients' recruitment					<0.001
Migraine specific treatment	3,939 (88.4)	3,338 (92.4)	274 (57.4)	327 (89.1)	
Hospital diagnosis of migraine	518 (11.6)	275 (7.6)	203 (42.6)	40 (10.9)	
Comorbidities					<0.001
Autoimmune disease	52 (1.2)	37 (1.0)	6 (1.3)	9 (2.5)	
Chronic kidney disease	48 (1.1)	35 (1.0)	10 (2.1)	3 (0.8)	
COPD	797 (17.9)	651 (18.0)	79 (16.6)	67 (18.3)	
Diabetes	361 (8.1)	288 (8.0)	49 (10.3)	24 (6.5)	
Hypertension	1,485 (33.3)	1,178 (32.6)	187 (39.2)	120 (32.7)	
Comedications					<0.001
Drugs for respiratory system	717 (16.1)	596 (16.5)	63 (13.2)	58 (15.8)	
Anticonvulsants	323 (7.2)	243 (6.7)	51 (10.7)	29 (7.9)	
Antidepressants	435 (9.8)	322 (8.9)	64 (13.4)	49 (13.4)	
Cardiovascular	1,592 (35.7)	1,276 (35.3)	182 (38.2)	134 (36.5)	
Polypharmacy					*<0.001*
0 – 4 drugs (no-polypharmacy)	2,258 (50.7)	1,838 (50.9)	241 (50.5)	179 (48.8)	
5 – 9 drugs (polypharmacy)	1,330 (29.8)	1,070 (29.6)	150 (31.4)	110 (30.0)	
≥ 10 drugs (Excessive olypharmacy)	869 (19.5)	705 (19.5)	86 (18.0)	78 (21.3)	

****Acute cohort** includes incident patients who have received a prescription of acute medication for migraine treatment 60 days after their index date. **Prophylactic cohort** includes incident patients who have received a prescription of prophylactic medication for migraine treatment 60 days after their index date. **Both** includes incident patients who have received a prescription of both acute and prophylactic medications for migraine treatment 60 days after their index date. Abbreviations: COPD, Chronic obstructive pulmonary disease; sd, standard deviation.

Table 2. Type of migraine treatment dispensed within 60 days following the entry in the incident migraine cohort

Migraine treatment	INCIDENT MIGRAINE COHORT			
	Total	Males	Females	*P value*
	N = 4,457 (%)	N = 1,393 (%)	N = 3,064 (%)	
TREATMENT TYPOLOGY				*<0.001*
Acute°	**3,613 (81.1)**	**1,121 (80.5)**	**2,492 (81.3)**	
Specific Acute Treatment §				
Triptans (Sumatriptan, Zolmitriptan, Rizatriptan, Almotriptan, Eletriptan, Frovatriptan)	1,915 (53.0)	567 (50.6)	1,348 (54.1)	
Non-specific Acute Treatment §				
Antiemetics (Ondansetron)	9 (0.2)	5 (0.4)	4 (0.2)	
Aspirin	5 (0.1)	1 (0.1)	4 (0.2)	
Drugs for functional gastrointestinal disorders (Metoclopramide)	12 (0.3)	4 (0.4)	8 (0.3)	
NSAIDs (Diclofenac, Flurbiprofen, Ibuprofen, Indometacin, Ketoprofen, Ketorolac, Naproxen, Nimesulide, Piroxicam)	1,136 (31.4)	380 (33.9)	756 (30.3)	
Opioids (Tramadol, Codeine/Paracetamol)	61 (1.7)	17 (1.5)	44 (1.8)	
More than one specific/non-specific acute medication §	*475 (13.1)*	*147 (13.1)*	*328 (13.2)*	
Prophylactic °	**477 (10.7)**	**159 (11.4)**	**318 (10.4)**	
Specific Prophylactic Treatment #				
Antiserotonin agents (Pizotifen)	95 (19.9)	28 (17.6)	67 (21.1)	
Non-specific Prophylactic Treatment #				
Antidepressants (Amitriptyline, Mirtazapine)	89 (18.7)	17 (10.7)	72 (22.6)	
Beta-blockers (Metoprolol, Propranolol)	40 (8.4)	19 (11.9)	21 (6.6)	
Other anticonvulsants (Valproic acid, Lamotrigine)	151 (31.7)	76 (47.8)	75 (23.6)	
Antiepileptics (Topiramate)	83 (17.4)	16 (10.1)	67 (21.1)	
More than one specific/non-specific prophylactic medication #	19 (4.0)	3 (1.9)	16 (5.0)	
Both acute and prophylactic medication °	**367 (8.2)**	**113 (8.1)**	**254 (8.3)**	

° The percentage was calculated on the total of treated patients
§ The percentage was calculated on the total of patients received acute treatment
# The percentage was calculated on the total of patients received prophylactic treatment

Adherence to therapy

Analysis of persistence in the cohort of patients receiving only prophylactic treatment was analysed one year after the initiation of therapy (Table 3); this analysis involved 599 patients. During the one-year follow-up period, 26.2% of these patients were persistent to their initial prophylactic treatment, while 73.8% had discontinued their initial treatment. Among the latter patients, 46.4% had fully discontinued the treatment within 103 days (IQR: 89.0), 31% had restarted treatment with the same prophylactic medication 46 days after the interruption (IQR

60.0), and 22.6% of patients had switched to another prophylactic medication within 98 days (IQR 57.5) (Table 3). Figure 3 shows the results obtained from Kaplan-Meyer analysis. Compared with males, females were significantly less likely to be persistent to prophylactic treatment (log-rank, p<0.001). In addition, Kaplan-Meier analysis was used to identify the proportion of persistent patients, as grouped by the class of prophylactic medication taken. At 365 days, the number of patients who remained on specific treatments were as follows: anticonvulsants (38.3%), beta-blockers (31.4%), antiepileptics (22.7%), antidepressants (21.8%), and antiserotonin agents (13.8%).

Table 3. One-year persistence with prophylactic migraine treatment

	Total	Antiserotonin agents	Antidepressants	Beta-blockers	Antiepileptics	Other Anticonvulsants	*p-value*
	N = 599[¥] (100%)	**N = 123 (20.5%)**	**N = 110 (18.4%)**	**N = 51 (8.5%)**	**N = 132 (22.0%)**	**N = 183 (30.6%)**	
Persistent patients °	157 (26.2)	17 (13.8)	24 (21.8)	16 (31.4)	30 (22.7)	70 (38.3)	*<0.001*
Nonperistent patients °	442 (73.8)	106 (86.2)	86 (78.2)	35 (68.6)	102 (77.3)	113 (61.7)	*<0.001*
Full Discontinuer [§]	205 (46.4)	42 (39.6)	43 (50.0)	12 (34.3)	46 (45.1)	62 (54.9)	
Restarting [§]	137 (31.0)	19 (17.9)	24 (27.9)	18 (51.4)	36 (35.3)	40 (35.4)	
Switch [§]	100 (22.6)	45 (42.5)	19 (22.1)	5 (14.3)	20 (19.6)	11 (9.7)	
Days on treatment before stopping (discontinuation), median (IQR)	103.0 (89.0)	110.0 (79.0)	97.0 (120.0)	93.0 (78.5)	90.5 (71.0)	108.5 (87.0)	
Days after treatment interruption before restarting, median (IQR)	46.0 (60.0)	39.0 (109.0)	59.5 (83.0)	65.0 (64.0)	26.5 (32.0)	50.0 (66.0)	
Days on treatment before stopping (switching), median (IQR)	98.0 (57.5)	91.0 (42.0)	102.0 (44.0)	87.0 (57.0)	134.0 (76.0)	87.0 (60.0)	

[¥] Number of patients with prophylactic treatment is higher than that reported in Table 2 as some patients who started treatment with both acute and prophylactic medications, later continued their treatment only with prophylactic medication.
° The percentage was calculated on the total of treated patients.
[§] The percentage was calculated on the total of nonpersistent patients.

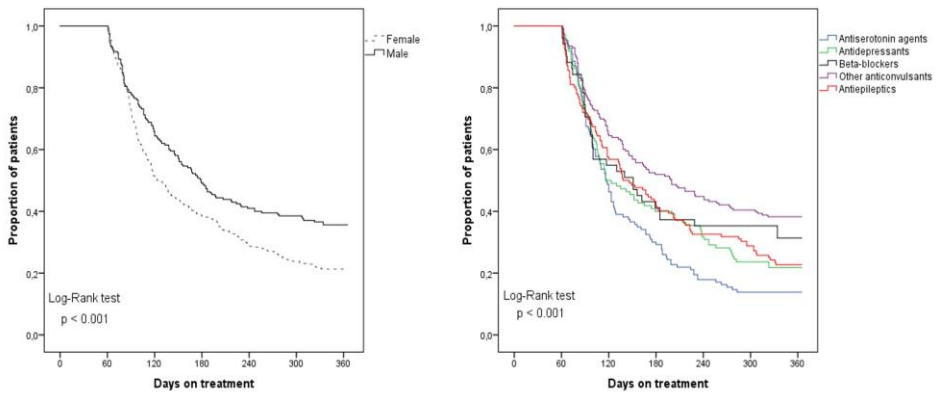

Figure 3. Time to discontinuation up to 365 days' follow-up from the initial prophylactic treatments, stratified by sex and drug category at index date.

Cost analysis

Figure 4 shows the median annual pharmaceutical costs stratified by the treatment typology of incident migraine patients. The annual median drug cost per patient treated with acute medications was €103; the cost per patient for those taking prophylactic medications was €75. The annual cost per patient for those taking both acute and prophylactic treatments was €163.

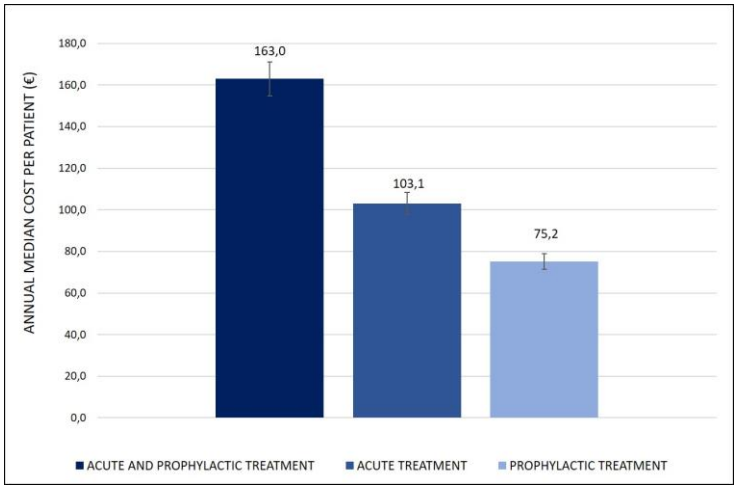

Figure 4. Annual median cost per patient (€) stratified by treatment typology.

Discussion

In this retrospective population-based study, the clinical characteristics and initial treatment pattern of incident migraine patients living in the Campania region of Southern Italy were analysed. Our analysis showed that fewer than 20% of newly treated subjects began prophylactic migraine therapy. Furthermore, remarkably, 73.8% of these subjects discontinued their initial prophylactic treatment after approximately three and a half months; it was founded that only half of these patients resumed therapy (either by switching to another drug or restarting the same medication).

To the best of our knowledge, this is the first Italian study to investigate the patterns of persistence in incident migraine patients treated with prophylactic medications. The present study also involved a database of drug prescriptions within a stable and specific geographic population. By characterising the use of migraine treatment in this context, it is possible

to obtain useful data regarding the dynamics of therapy in the real-world setting.

The subjects analysed in this study mainly received acute medications; this is in line with other studies. Indeed, this pattern of usage has been described in publications from many different countries, including Denmark, Japan, and the US [16,18–20]. A recent retrospective study stated that prophylactic medications are used less frequently than acute medications; furthermore, and in line with our present results, patients treated with prophylactic medications showed a high rate of discontinuation following a brief treatment period [18]. The authors of this earlier study also reported rates of re-initiation and switching that were comparable to our present results [18].

A recent Italian drug utilization study suggested that there was an unmet need in the management of migraine, and that only 9.9% of patients with migraine are treated with prophylactic drugs [21].

In the US, Wolley et al. reported low rates of persistence to migraine prophylactics, thus confirming the trend for early therapeutic discontinuation in these patients [22]. Wolley et al. further observed that opioids were the most commonly prescribed non-specific acute medication. In this regard, our current data are slightly different: the most common treatment regimen prescribed was NSAIDs (31.4%) and rarely, opioids (1.7%). This difference can be explained by the fact that the use of opioids for pain treatment is common in the US; in contrast, NSAIDs are preferred in Italy. However, it is evident that trends are beginning to change in the US. This follows a Food and Drug Administration (FDA) warning in March 2016 relating to the co-prescription of opioid, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) or opioid–triptan and the risk of serotonin syndrome [23]. It is also interesting to note that our analysis showed a remarkable proportion of switchers among patients using pizotifen (42.5%). This can be related to the fact that this drug ceased to be available on the Italian market in February 2018 [24].

In addition, the cost aspect of migraine treatment is not negligible. Our results showed that the median annual cost per patient taking both acute and prophylactic migraine treatment was €163, this is slightly lower than other evidences, such as the case of Latvia recording €801 annually per

patient, and €721 in Lithuania, and in these latters countries two thirds of total cost were related to lost workdays due to absenteeism and presenteeism [25]. Therefore, improving and implementing the care of migraine patients, such as through a wider availability of prophylactic drugs, would lead to higher direct costs, but this cost increase could be balanced by a lower loss of productivity related to migraine.

This study was limited by the very nature of the Italian administrative databases used to obtain data. For example, our data source does not track diagnostic information. Therefore, patient identification had to be performed ex-post by using proxy drugs that are reimbursed by the NHS. To mitigate the impact of this limitation the authors adopted the same methodology as that used previously by Thomsen et al 16. It is also possible that some patients with migraine may not have been identified because they used drugs that are not reimbursable by the NHS (e.g., ergots ATC IV: N02CA; flunarizine ATC V: N07CA03). For this reason, the no-treatment cohort (n=8,437) may have included some subjects that were actually taking these drugs. Therefore, in this study there could be an underestimation of the prevalence and incidence of migraine. Another limitation, also related to the administrative database, was the lack of information relating to the specific reasons for treatment discontinuation.

In general, the results of this study highlight the unmet need for an effective and sustainable therapy for migraine. Indeed, current prophylactic therapies can suffer from a lack of specificity, poor tolerability, potential side effects, and limited efficacy. Collectively, these factors lead to dissatisfaction in a large proportion of patients, thus resulting in low adherence to treatment [26]. Furthermore, non-adherence to medication could reduce the efficacy of pharmacological therapies; this may simultaneously increase the direct and indirect costs related to such treatment [27–32]. These factors are driving research and significant advances in the prophylactic treatment of migraine, including the generation of anti-CGRP (calcitonin gene-related peptide) monoclonal antibodies. These drugs are useful for migraine-specific prophylactic treatment and appear to perform better than current therapies [33,34]. However, the high costs related to these emerging drugs could represent a significant issue when selecting the migraine patients who would benefit. In this promising scenario, the provision of information based on real-

world data represents a highly useful way to support stakeholders towards creating better management strategies for this disease [35–38].

Conclusion

The present analysis showed that the treatment of migraine with acute medications is still prevalent in the Italian clinical practice. Only a small number of patients began prophylactic treatment and persistence was poor; these observations were not consistent with the clinical guidelines for primary headaches. In addition, most of the non-persistent patients tended to quit prophylactic therapy within three months of starting treatment. These findings reflect an unmet need for improved prophylactic therapies in order to improve the management strategies used for migraine. This unmet need must be addressed in future treatment guidelines. New monoclonal antibodies for the specific prophylactic treatment of migraine could represent a significant opportunity for improving long-term persistence and ensuring therapeutic efficacy in order to reduce the number of acute migraine episodes. Analysis of patient characteristics could help to identify patients who would specifically benefit from these emerging therapies or design a more effective clinical management plan for existing prophylactic migraine medications. These scenarios may require further research to be based on real-world data in order to enable investigation of the dynamics underlying the prophylactic treatment of migraine, and to optimize resources, so that disease management can be improved.

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4.2.3 Mapping the use of Group-Based Trajectory Modelling in medication adherence research: A scoping review protocol.

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Abstract: The use of group-based trajectory modelling (GBTM) within the medication adherence literature is rapidly growing. Researchers are adopting enhanced methods to analyse and visualise dynamic behaviours, such as medication adherence, within 'real-world' populations. Application of GBTM based on longitudinal adherence behaviour allows for the identification of adherence trajectories or groups. A group is conceptually thought of a collection of individuals who follow a similar pattern of adherence behaviour over a period of time. A common obstacle faced by researchers when implementing GBTM is deciding on the number of trajectory groups that may exist within a population. Decision-making can introduce subjectivity, as there is no 'gold standard' for model selection criteria. This study aims to examine the extent and nature of existing evidence on the application of GBTM for medication adherence assessment, providing an overview of the different GBTM techniques used in the literature. The methodological framework will consist of five stages: i) identify the research question(s); ii) identify relevant studies; iii) select studies; iv) chart the data and finally, v) collate, summarise and report the results. Original peer-reviewed articles, published in English, describing observational and interventional studies including both concepts and/or sub-concepts of GBTM and medication adherence or any other similar terms, will be included. The following databases will be queried: PubMed/MEDLINE; Embase (Ovid); SCOPUS; ISI Web of Science and PsychInfo. This scoping review will utilise the PRISMA extension for Scoping Reviews (PRISMA-ScR) tool to report results. This scoping review will collect and schematise different techniques in the application of GBTM for medication adherence assessment available in the literature to date, identifying research and knowledge gaps in this area. This review can represent an important tool for future research, providing methodological support to researchers carrying out a group-based trajectory analysis to assess medication adherence in a real-world context.

Introduction

Medication adherence is generally described as the process by which people take their medication as prescribed or as agreed with their prescriber. A taxonomy has been developed to describe the three distinct, yet, inter-related processes involved in medication adherence; initiation, implementation and discontinuation [1]. Initiation adherence refers to the first prescription for the medication being dispensed in the pharmacy. The implementation phase refers to the execution of the recommended dosing regimen; skipping doses, delaying refills or taking drug holidays are examples of implementation non-adherence. Discontinuation occurs when the patient stops taking the medication, thus beginning a period of non-persistence. Persistence is another term that is commonly used and refers to the duration the patient takes the medication for, encompassing the initiation and implementation phases [1]. Initiation, discontinuation and persistence are usually modelled as time-to-event phenomena, whereas implementation adherence can be reported in a variety of ways, usually involving summary statistical estimates [2]. Summary adherence estimates include measures such as the proportion of days covered (PDC) and medication possession ratio (MPR), which are commonly used to describe adherence using administrative claims data [2].

However, adherence is a dynamic behavior, potentially varying over time due to a number of factors. It has been suggested that longitudinal methods should be used to analyse implementation adherence, as aggregating behaviors over time into a single summary estimate of adherence which is then dichotomized can result in a loss of information about the detailed patterns of adherence [1,3]. This is of particular concern for the estimation of adherence to medications used to treat long-term, chronic conditions. Using summary measures can often lead to difficulty in estimation of the time point or phase at which non-adherence is likely to occur in a population. Indeed, two individuals may have the same average adherence value over a period of time (i.e. 50%) but one may skip doses regularly, whereas the other may have had high initial adherence followed by a long gap in dispensing3. Over the past number of years, group-based trajectory

GBTM is a type of finite mixture modelling which uses trajectory groups to estimate an unknown distribution of trajectories that exist within a

population [9]. The groups identified by the models should not be thought of as literal entities, but rather as discrete groups that may exist within a population [9]. Considering the application of GBTM within adherence research, a group is conceptually thought of as a collection of individuals who follow approximately the same pattern of adherence behaviour, equivalent to a contour line on a contour map [9]. GBTM is operationalised by repeatedly measuring adherence at frequent time intervals (i.e. monthly) and grouping individuals with similar longitudinal adherence patterns [10]. GBTM may aid the precise identification of the timing of transition from one adherence phase to another, namely movement from the implementation phase into the discontinuation phase. The model assumes that within-person correlation is explained completely by the adherence trajectory curve estimated for each person's group [10]. Model parameters are estimated using maximum likelihood [4], meaning unbiased estimates can be produced in the presence of missing data, provided such data are missing at random [9].

A common obstacle faced by researchers when implementing GBTM is deciding on the number of trajectory groups that may exist within a population. Prior to conducting any statistical analysis, the maximum number of groups likely to exist based on the size of the population and existing evidence is estimated. However, adherence is often reported as a dichotomous variable in the literature, resulting in participants being classified into two adherence groups; adherent and non-adherent. The threshold most commonly used to determine this classification has been arbitrarily set at 80% [3,11], originating from anti-hypertensive medication studies [12,13], with little validation across other conditions. Therefore, a priori theories on the number, shape and size of adherence trajectory groups are often absent [9].

Determining the number of optimum number of adherence groups that hypothetically exist within a population is based on statistical fit indices, most commonly the Bayesian Information Criteria (BIC) [14], Akaike Information Criteria (AIC) [15], Lo-Mendall- Rubin likelihood ratio test (LMR-LRT) [16] and entropy [9]. BIC and AIC aim to identify the most parsimonious model by balancing model complexity versus goodness to fit to the study data [9]. Lower index values indicate improved model fit. The LMR-LRT utilises a likelihood-ratio-based approach, helping to

determine the optimum model between 'k-1' and k class models; a p value >0.05 is used to reject a new model class containing an additional group (k) [9,17]. Entropy is used to measure how accurately the model classifies participants into different trajectories or groups. The average posterior probabilities of group membership are calculated with values closer to 1 indicating greater precision. Previous adherence GBTM studies have used thresholds of probability ≥0.70 to indicate presence of sufficient entropy in a model [7,17], whereas others did not use explicit cut-offs [5,6,10].

Rationale

To date, and to the best of our knowledge, there is no existing peer-reviewed or published synthesis of the use of GBTM in medication adherence research. As the popularity of GBTM is growing in the adherence literature, it is necessary to map the evidence within this area, to help summarise existing evidence and guide future research. A scoping review methodology is used for such a mapping exercise as it is suited to broad research questions and is useful in fields such as adherence measurement, where there is a lot of measurement heterogeneity [18]. Scoping reviews not only highlight the extent of research available on a topic, but also allow for a description of the conduct of such research18. A synthesis of the literature of the use of GBTM in medication adherence measurement will help to identify research deficits and knowledge gaps in this area, informing future research [18–20].

Objective and aims

The objective of this scoping review is to describe the nature, number, scope and methodology of published research articles using group-based trajectory modelling to measure medication adherence and to identify what further research is required.

Specifically, we will aim to:

- Systematically explore the extent of relevant empirical literature on the use of group-based trajectory analysis applied to medication adherence in longitudinal studies.
- Map and categorise publications obtained according to the following taxonomy: purpose of study (identify adherence behaviours, groups for intervention targeting), model selection criteria used to determine

adherence groups, and outcomes typology (validation against clinical/other health outcomes or absent).
- Provide an overview of the different GBTM techniques used for medication adherence measurement in the literature and guidance for future adherence research.

Methods

The methodological framework for conducting this scoping review was informed by published guidance [18–20]. This process consists of five different stages [19]: (1) identify the research question(s); (2) identify relevant studies; (3) select studies; (4) chart the data and (5) collate, summarise and report the results. There is an optional sixth stage, 'consultation with relevant stakeholders' that may be prioritised in social science research [20]. However, the relevance of this stage in the current scoping review is not apparent, and as such we will not be formally engaging with external stakeholders prior to completion of the scoping review. In order to provide a descriptive account of the status of GBTM in adherence research and identify knowledge gaps, a scoping review of the literature is most appropriate. Findings from the review may help to promote standardisation of GBTM methodology in future adherence studies. As in the case of systematic reviews, scoping reviews also use a systematic approach to research, screening and reporting.

Identifying the research question

There has been an increasing use of GBTM as a tool for longitudinal adherence measurement and visualisation; however, there appears to be a lack of standardisation in the methodological approach similar to the existing heterogeneity in medication adherence measurement [21,22]. The lack of standardisation can introduce varying degrees of subjectivity into the decision- making process required with application of GBTM, limiting comparison across studies. While some degree of subjectivity may be necessary [23], it would be advantageous to summarise the various approaches used to help inform future research. The following research questions were identified for the review based on the aims of the review:

1. What is main purpose of application of GBTM in medication adherence research?

2. What is the range of statistical techniques employed to apply GBTM for the measurement of medication adherence in the literature?
3. Which clinical or other outcomes been used to validate the use of GBTM in medication adherence research?
4. Is the use of GBTM for measurement of medication adherence prominent in specific populations or cohorts? Are there differences in methodological approaches consequentially?
5. Are there recommendations for the standardisation of GBTM techniques within adherence research?
6. What are the current knowledge gaps relating to the application of GBTM in medication adherence research that require further research?

Identification of additional research questions may be an iterative process, informed by emerging themes that appear while conducting the scoping review.

Identifying relevant studies

Inclusion criteria. Peer-reviewed publications of empirical research which apply GBTM to the measurement of medication adherence will be considered for inclusion. Furthermore, publications will have to include in their abstract both concepts and/or sub-concepts of group-based trajectory modelling or any other similar term (e.g., group-based analysis, trajectory model) and medication adherence.

Original articles, published in English, describing observational studies will be included. No restrictions will be placed on study design (case-control, cohort, prospective, retrospective etc), although it is unlikely cross-sectional studies will be suitable, given the need for longitudinal data to perform GBTM. Randomised controlled trials will be included if it is specified in the study abstract that longitudinal analysis was performed as part of the study.

In the first instance, no limitations will be applied in the year of publication, therefore, all studies in the literature to date will be identified. However, if excessive search results are identified after de-duplication (>4000), search results will be narrowed to articles published after January 2005, as it is after this time that GBTM mainly emerged in the medication adherence field.

Exclusion criteria

Only articles available in English will be included. Furthermore, grey literature including guidelines, booklets, reports, and clinical guidelines will not be included. Unpublished academic documents such as theses and dissertations will be not included in the scoping review. In addition, conference abstracts will not be considered as the purpose of this scoping review is to extract data relating to the methodological approach used in GBTM studies, of which abstracts provide limited detail. Similarly, study protocols will be excluded as hypothetical analytic approaches may differ from actual methodological approaches applied. However, we will attempt to contact authors of relevant protocols and abstracts to ascertain the availability of full research reports, if not identified by the existing search. Systematic and literature reviews will not be included in the review, but instead, will be used to identify potentially relevant observational studies.

Information sources and search strategy

For the present scoping review, the identification of relevant studies will be achieved by searching electronic databases of the published literature, which will include the following: Medical Literature Analysis and Retrieval System Online (PubMed/MEDLINE); Embase (Ovid); SCOPUS; ISI Web of Science and PsychInfo. A comprehensive search strategy has been developed with the assistance of a medical librarian, to identify relevant studies. Search terms were determined by team members and further developed after consultation with the medical librarian. Search strings combined keywords, phrases and Medical Subject Headings (or equivalent) across two concepts using the AND Boolean operator: (1) medication adherence; (2) group-based trajectory modelling. Terms for medication adherence were informed by a previous systematic review involving some of the authors [22], and expanded upon. Search terms relating to ‘medication adherence’ include patient compliance, treatment adherence, medication (non-) compliance, medication persistence as well as the phases of medication adherence as per the ABC taxonomy (initiation, implementation, discontinuation) [1]. For ‘group-based trajectory modelling’, related terms include ‘gbtm’, ‘trajectory analysis’, ‘longitudinal trajectory’ and ‘adherence pattern’. Within each concept,

relevant terms were combined using the 'OR' Boolean operator. The search strategy was developed for use in PubMed/Medline and will be further adapted for use across the four other electronic databases. The full search strategy will be included in the final manuscript. Electronic databases will be searched from inception, with no limitations or filters placed on records obtained, until acceptance for publication.
Further, a citation search of included full-texts will be undertaken in Google Scholar to identify relevant published studies that were not retrieved through database searching.

Selecting relevant studies

The search results will be downloaded to an electronic referencing system and duplicates removed. As stated previously, should an excessive number of independent records be retrieved, records will be limited to those published during or after 2005. One author (CW) will independently screen the title and abstracts of all retrieved articles for studies that use GBTM to measure medication adherence. A second reviewer (SM) will independently screen a 50% random sample of abstracts. Abstracts that are deemed unsuitable for progression to full-text review will be allocated to folders citing the reason for exclusion. Once each reviewer has selected relevant records for full-text review independently, results will be compared between reviewers and discussions held until consensus is reached. The second reviewer will review the abstracts, excluded from their random sample, that were selected for full text review by the main reviewer. If a conflict remains following discussions, a third reviewer (CC or EM) will be consulted until consensus is reached. Two reviewers (SM and CW) will review each full text independently, citing reasons for exclusion if not deemed suitable for inclusion in the scoping review. Discussions will be held until consensus is reached, adhering to the inclusion and exclusion criteria specified a priori. Similar to the abstract screening process, a third reviewer will be consulted (CC or EM) to resolve any conflict. Reasons for exclusion of texts after full-text review will be documented and reported in the PRISMA study flow diagram.

Charting the data

A standardised data charting form was created in Excel a priori, based on guidance pertaining to data charting in scoping reviews from the Joanna Brigg's Institute Reviewer's Manual [24]. We have updated the form based on useful suggestions provided by protocol reviewers. Initial categories included general study characteristics such as authors, title, DOI, year of publication and country. Next, information on the study design will be collected including the aims/purpose of the study, whether adherence was modelled as an exposure, covariate or outcome, descriptive of the study population and sample size (e.g. age, gender, and ethnicity) and the medication or disease group studied. Further, information specific to medication adherence measurement will be collected including the data source, duration of adherence measurement (length of observation), the time intervals used, the GBTM method applied (statistical package used), the maximum number of adherence trajectories selected, along with the evidence base used to inform this number, if applicable, and finally, the model selection criteria used to select the optimum number of adherence trajectories. Information on the order used (cubic, quadratic etc) to model groups will be extracted, if available. Lastly, information pertaining to results and findings from the study will be extracted, including the number of adherence trajectories identified, details relating to validation against clinical outcomes, if applicable, and any adjustment for covariates and limitations of the study. Initially, the data charting form will be piloted using two or three relevant studies identified from database searches. This will be done independently by two reviewers (SM and CW) and discussions will be held between the two reviewers following this to identify additional data that needs to be charted, along with amendments of existing headings if required [19,20]. Study authors will be contacted if further clarification is required in relation to data extracted.

Collating, summarising and reporting the results

This scoping review will utilise the PRISMA extension for Scoping Reviews (PRISMA-ScR) tool [25]. A flow diagram will be used to outline the selection of data sources, including descriptive reasons for exclusion at the full-text review stage. Characteristics of the included studies will be described based on the descriptive headings in the data extraction form. Specifically, the evidence will be summarised and reported using the

taxonomy described in the aims; purpose of the study, model selection criteria use and outcomes typology (if applicable). Guided by the research questions, additional headings will be used to summarize the studies if findings are not sufficiently communicated using the aforementioned taxonomy. For instance, it may be possible to categorise studies based on their study population (paediatric vs older people) or disease area (cardiovascular, musculoskeletal etc). Formal quality appraisal of included studies will not be undertaken, as the aim of scoping reviews is to provide an overview of the existing evidence base regardless of quality [18]. A general interpretation of the evidence will be provided, as well as identification of potential knowledge gaps. The strengths and limitations of the scoping review will be outlined, as well as potential guidance for future research in the final report. Any deviations from this protocol, including reasons, will also be detailed.

Conclusion

The over-arching purpose of GBTM is to identify discrete groups that have meaningful differences in terms of pre-existing characteristics or subsequent outcomes or treatment response. If the groups or trajectories cannot be distinguished on the basis of such dimensions, identification of different trajectories serves little purpose [9]. This scoping review will collect and schematize different techniques in the application of group-based trajectory modelling for medication adherence assessment available in literature to date. The main expectation of the exploration of the literature will be to summarise evidence and identify research and knowledge gaps in this area to inform future research. Indeed, recent studies have called for greater transparency over the subjective decisions involved in applying GBTM for medication adherence assessment [23]. This review may represent an important tool for future research, in order to methodologically support researchers who will carrying out group-based trajectory analysis to assess medication adherence in real-world contexts.

Data availability: No data are associated with this article.
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4.3 STAGE 3 Development and validation of a tool to assess medication adherence in real practice

The barriers to patients' successful medication adherence behavior could be reduced through tailored pharmacy-based interventions by examining the factors affecting medication-taking-behaviors [14-16]. These barriers may be complex and include factors related to socioeconomics, health care system structures and processes, severity of co-occurring medical conditions, complexity of medication and nonmedication therapies, and patient concerns [16]. Corroborating with this, part of medication adherence research should be aimed to explore various aspects of health care delivery, the relationship between pharmacy and patients, practitioner and patient perspectives, and is closely related to the health services research. Many studies to date have shown that communication is a powerful tool for promoting successful medication adherence behavior, confirming that patients who communicate well with their HCPs have 19% higher medication adherence than patients who do not have effective communication with providers [16, 17]. Although these studies provided valuable information on medical communication, they did not relate communication strategies to specific barriers to medication adherence. These barriers vary between patients and patient groups and require the development of effective communication strategies designed to meet patients' needs [16-19]. Since medication misbehavior is considered to be a widespread problem, it is noteworthy that no study has adequately described which different communication strategies, designed to meet specific patient needs, can be used to address specific barriers to medication misbehaviour. The final goal in real clinical practice is to support and encourage the pharmacist-patient relationship as a driver of improved medication adherence and clinical and economic outcomes [16]. Therefore, main goals of the scientific production carried out across the **Stage 3** were:

i) To provide a specific tool for pharmacist use in order to benefit from patient's assessment and to develop and deliver tailored guidance and services reducing identified barriers.

ii) To assess medication adherence in real practice by new developed and adapted assessment to identify adherence barriers.

4.3.1 Developing and piloting a communication assessment tool assessing patient perspectives on communication with pharmacists (CAT-Pharm).

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Abstract: ***Background*** Effective communication strategies in health care help to enhance patient empowerment and improve clinical outcomes. ***Objective*** Adapt the original Communication Assessment (CAT) instrument for the pharmacist profession (CAT-Pharm) and to test its validity and reliability in two different settings. ***Setting*** Five hospital pharmacies in Italy and five community pharmacies in Malta. ***Method*** Pilot study involving a standardized multi-step process adhering to internationally accepted and recommended guidelines. Corrections and adjustments to the translation addressed linguistic factors and cultural components. CAT-Pharm, compared to the original CAT, maintained 10 out of the 14 items: one was slightly modified; three were changed to better fit the pharmacist role; one was added. ***Main outcome measures*** CAT-Pharm development and testing its practicality to assess patient perceptions of pharmacists' interpersonal and communication skills. ***Results*** CAT-Pharm was tested on 97 patients in the Italian setting and 150 patients in the Maltese setting to assess the practicality of the tool and its usefulness in investigating gaps and priorities for improving pharmacist-patient communication. Results Show reliability and internal validity of the CAT-Pharm tool. The analysis of patient perceptions of communication with the pharmacist in Italy indicated differences from that in Malta. The different settings provided insight into the utility of CAT-Pharm. ***Conclusion*** This study provided a valid and reliable tool that could be applied to assess patient perception of the pharmacist's communication abilities.
Keywords Communication · Communication assessment tool · Community pharmacy · Hospital pharmacy · Patient- pharmacist relationship · Patient empowerment

Introduction

Communication between health professionals and patients is a key element contributing to patient safety and quality care. Patient evaluation of the communication skills of health professionals can have a profound effect on perceptions of quality of treatment received and may influence patient satisfaction and behavioral intentions [1, 2].

There is evidence that effective communication can generate a degree of trust and improve patient empowerment, resulting in better clinical outcomes of chronic medical issues, such as diabetes, hypertension, obesity, HIV/AIDS, cancer, cardiovascular disease, and rheumatoid arthritis [3–6]. Promoting strategies of communication in the health system is an essential element for preventing errors and failures in health care [7]. Within this context, the role of "communicator" is one of the essential functions attributed to pharmacists by the World Health Organization (WHO) [8]. The WHO proposed the concept of the "Seven-star pharmacist" in 1997, which evolved and was taken up by the International Pharmaceutical Federation and covered the following roles: Caregiver, decision-maker, communicator, manager, life-long learner, teacher, and leader [9, 10].

Pharmacists are in an ideal position to facilitate communication between physicians and patients since they have frequent contact with patients, have extensive knowledge about drug therapy, and are equipped to provide information, monitor patients' experiences and adherence, and co-ordinate care between different healthcare professionals [2, 11, 12]. Pharmacists' contribution is related to supporting patients in safe and effective medicines use, whether the pharmacist is practicing in a community or hospital setting. In both cases the pharmacist contributes to ensuring access to medicinal products and patient consultation. Tools to assess patient perceptions of pharmacists' interpersonal and communication skills are considered to be useful in supporting development of this professional skill. In 2007, Makoul et al. developed the Communication Assessment Tool (CAT) aimed to help physicians to reflect on their interpersonal and communication skills with the goal of reinforcing strengths and identifying areas that require more attention for improvement [13]. The CAT has been translated and cross-culturally adapted to many languages, including Italian [13–15].

Although the CAT is a validated tool intended to evaluate communication across different specialties and environments, there is no evidence of specific evaluation of pharmacists' communication skills.
The aim of this study were to adapt the original CAT instrument to the pharmacist profession (CAT-Pharm) and to test its validity and reliability in two different settings.

Ethics approval

The study was supported by the Italian Society of Hospital Pharmacy (SIFO). Ethics approval was obtained from the Ethics Committee of Cardarelli Hospital in Naples Italy (424/2017). This research was in conformity with the University of Malta's Research Code of Practice and Research Ethics Review Procedures.

Method

This was a pilot study carried out from June to December 2017 in Italy and from January to June 2018 in Malta. Twelve Italian hospital pharmacists selected from five Centers in the South, Center and North of Italy, and five community pharmacists selected by convenience sampling from each of the five districts of the island of Malta, were involved in this study. The enrolled pharmacists were responsible to administer the questionnaire to the volunteer patients. A reference pharmacist for Malta and one for Italy assumed responsibility for the final collection of all paper questionnaires.

Adaptation of CAT to pharmacist profession

An International working group (an instrument developer, pharmacists from English speaking countries, researchers with expertise in statistics and in patient reported outcomes, and pharmacists fluent in English with Italian as their native language) helped in development of the tool, adaptation and validation analyses of the instrument, and translation into English. This group consisted of A final modified version of CAT Tool, the CAT-Pharm, was obtained, and this version was translated into English and Maltese. The final version includes additional elements designed to collect self- reported demographic information (age, ethnicity, gender). As shown in Fig. 1, adaption to the pharmacist profession was achieved through five steps:

Step 1: An expert group composed of 4 Italian pharmacists reviewed the CAT giving suggestions about elimination, modification, addition of items.
Step 2: Consensus meeting to reach a harmonized version of the Italian CAT-Pharm that includes 15 items which measure patient perceptions of pharmacist communication, all measured on a 5-point response scale (1=poor; 2=fair; 3=good; 4=very good; 5=excellent). Compared to the original CAT, the harmonized version of the Italian CAT-Pharm consists of an additional item. Minor changes to the instructions were incorporated.
Step 3: Cognitive debriefing on 10 patients to assess if the questionnaire is easy to understand. Respondents were administered the harmonized version of the Italian CAT- Pharm and were systematically asked to identify what they think each question is asking, whether they can repeat the question in their own words, and what comes to mind when they hear a particular phrase or term. The patients were asked to explain how they selected their answer.
Step 4: Consensus meeting to reach a refined version of the Italian CAT-Pharm based on the analysis and discussion of information about comprehension of items and use of the tool in Step 3.
Step 5: The refined version was administered to an additional 10 patients in the same way as the previous version (step 3). Suggestions and comments expressed by respondents were collected and analyzed, yielding a final version Italian CAT-Pharm (Supplementary File 1).

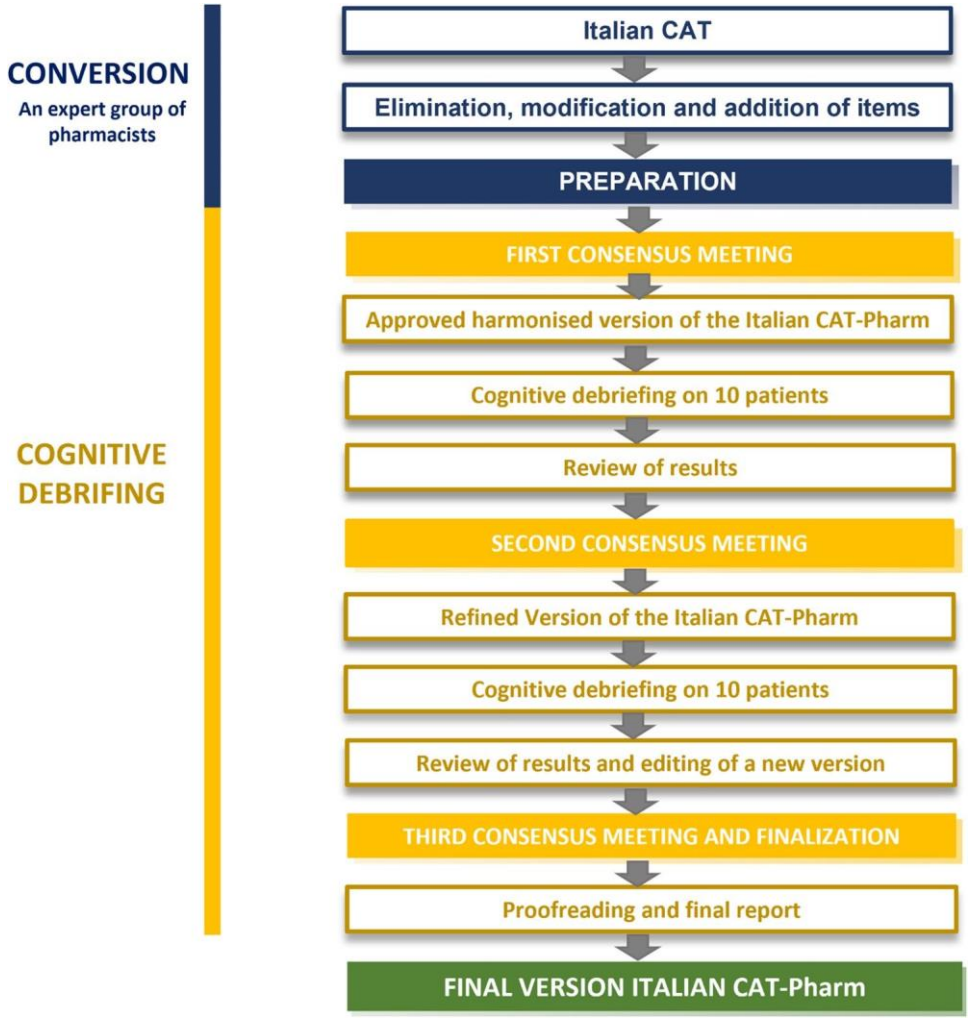

Fig. 1 Process flow chart for obtaining Italian CAT-Pharm

Information related to the process of CAT adaptation to the pharmacist profession (CAT-Pharm) are shown in Supplementary Files 2 and 3.
Subsequently, the following two steps were followed to obtain CAT-Pharm in English and Maltese.
Step 6: The final version of Italian CAT-Pharm was translated into English by an Italian mother tongue fluent in English (forward translation) and the following back translation was done by an English mother tongue. After a back translation review, a cognitive debriefing was done by three pharmacists and three laypersons. Final stages included proofreading and finalization of the English version (Supplementary file 4). The entire process of language adaptation and translation was carried out according to internationally accepted and recommended guidelines of International Society of Pharmacoeconomics and Outcome Research (ISPOR) and recommendations made by the WHO about the process of translation and adaptation of instruments [16–18].
Step 7: The English version of CAT-Pharm was translated to Maltese language by a Maltese linguist, back translated to English by an English mother tongue, and both versions were validated by two pharmacists and three laypersons. The process of language adaptation and translation was carried out according to the same guidelines [16–18]. Applicability testing of CAT-Pharm in English and Maltese was carried out in one community pharmacy with 10 patients.
These two steps are graphically represented in Fig. 2.

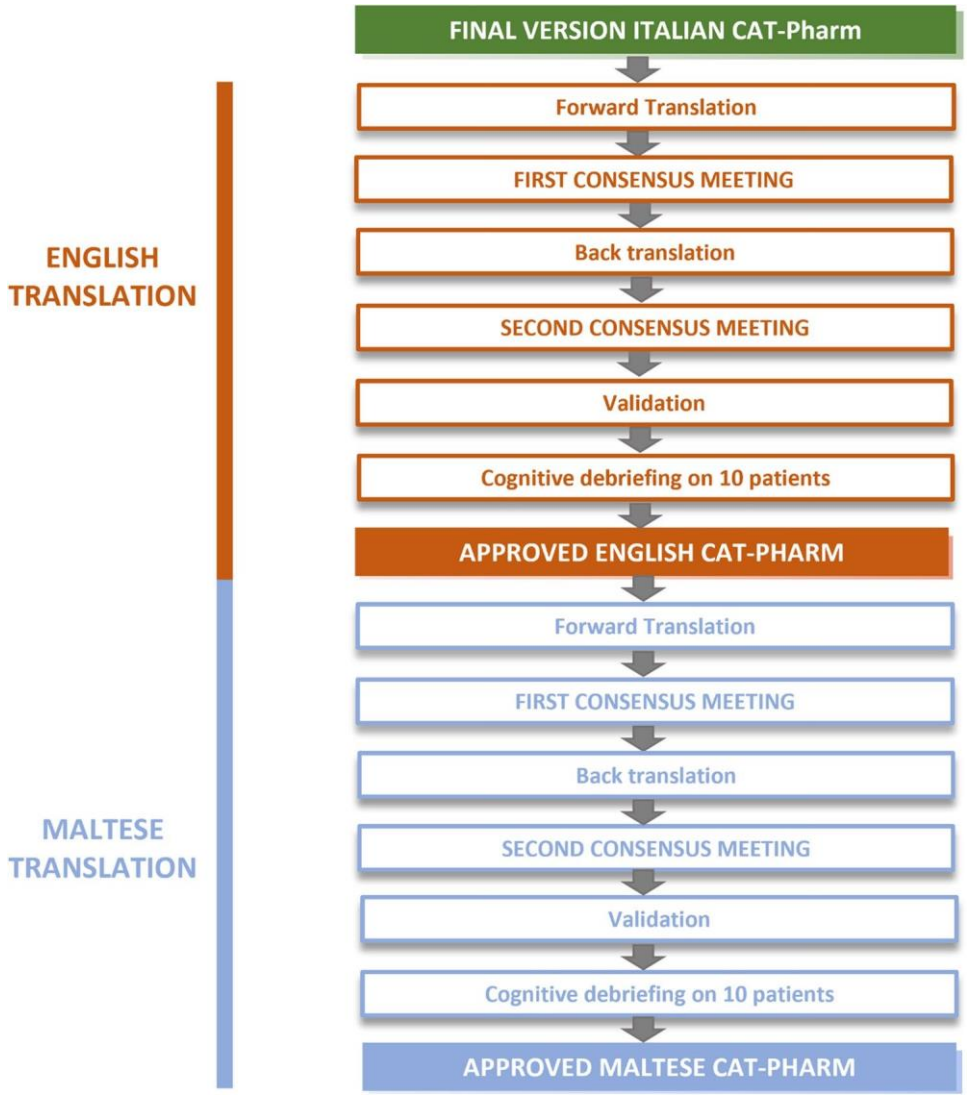

Fig. 2 Process flow chart for obtaining the English and Maltese CAT-Pharm

Setting, participants and eligibility criteria

CAT-Pharm was tested in Italy and Malta. In Italy, the set- ting was the hospital where pharmacists are involved in ensuring access to medicinal products, a consulting relationship with the patient and act as part of the multidisciplinary team. CAT-Pharm in Italy was applied to 97 outpatients recruited by convenience sampling in each of the five hospital pharmacies involved in the study. Patients inter- viewed and engaged by Italian

hospital pharmacists were not inpatients, hence, patients coming to the pharmacy after a visit and with a drug prescription were invited to fill the CAT-Pharm. CAT-Pharm in Malta was applied to 30 patients recruited by convenience sampling in each of the five com- munity pharmacies (N = 150). In each community pharmacy, 30 patients presenting a prescription to the same pharmacist, were handed the CAT-Pharm and invited to complete either the English or Maltese version. This process provided the opportunity to test the utility of applying the CAT-Pharm tool in community pharmacy setting.

In both Italian and Maltese settings, the pharmacist sub- mitted the questionnaire to the volunteer patients. Anonymity of the completion of the tool was ensured. One day was dedicated to data collection per pharmacy.

Statistical analyses

Validity (internal, external) and reliability assessments were required to determine the psychometric properties of the developed CAT-Pharm instrument. To investigate t validity of each item of the pharmacist-adapted CAT tool, a confirmatory factor analysis was performed. Sample adequacy was measured by Kaiser–Meyer–Olkin (KMO) and Bartlett's sphericity test. To confirm factor structure, a Oblimin direct rotation with Kaiser normalization was performed. Correlations between items were assessed using the Pearson's correlation test. The Chi-square test was used to compare the proportion of patients who rated a given item ‘Excellent’ between the two settings. A p-value < 0.05 was considered statistically significant. As questionnaire responses were structured with a 5-point Likert scale (poor; fair; good; very good; excellent), Cronbach’s alpha internal consistency reliability was performed to assess internal consistency for the translated CAT overall score. As in the original scale development, psychometric analysis indicated that ’Excellent’ maps onto ‘Yes’, and all the other response options (i.e. poor; fair; good; very good) map onto “No” [13]. Accordingly, and consistent with previous use of the CAT, results are presented as the percentage of participants who provided ratings of ‘Excellent’. Percentage of ‘Excellent’ responses was calculated from the total number of respondents to the individual question. Analyses were performed using SPSS Statistics for Windows, version 17.1 (SPSS Inc.Released 2008. Chicago, IL; USA).

Results

Developed CAT-Pharm Tool

The final version of CAT-Pharm was obtained by making minor changes to the original CAT (Table 1). References in the original CAT to ‘‘your doctor’’ or ‘‘the doctor’’ were changed to ‘‘your pharmacist’’ or ‘‘the pharmacist’’, and reference in the original CAT to “health” were changed to “prescribed therapy” (item 3).

Item 5 “Paid attention to me (looked at me, listened carefully)” was changed to “Explained how to correctly follow the prescribed therapy” and item 11 “Involved me in decisions as much as I wanted” was changed to “Discussed how to manage any side-effects of the prescribed therapy”. Item 13 “Showed care and concern” was changed to “Asked about my ability to follow the prescribed therapy” and an additional item (item 15) was added “Discussed possible interactions of the prescribed therapy with other drugs or foods”.

Validity of the CAT-Pharm items was assessed. Pearson’s correlation test showed significant positive correlations between CAT-Pharm items. The correlation coefficients ranged from 0.26 to 0.86.

The results of the Bartlett’s test of sphericity were KMO=0.92 and $\chi 2$=2969.34 (df =105, $p<0.01$), indicating that the correlation matrix was suitable for factor analysis. A two-factor solution was found identifying two questionnaires macro-areas. Factors 1 (the first six items) is focused on the confidential and familiar relationship pharmacist-patient. Factor 2 (items 7-15) is focused on investigating the correct activity of the pharmacist towards the patient. Results of confirmatory factor analysis are showed in the Supplementary File 5.

Reliability results indicated very high overall scale reliability for the 15 CAT-Pharm items (Cronbach’s alpha=0.95).

Table 1 Cross-cultural adaptation and translation of the CAT-Pharm

Item	Original Items	Adaptation for the pharmacists' profession	Changes compared to original CAT
Item 1	Greeted me in a way that made me feel comfortable	Greeted me in a way that made me feel comfortable	Not changed
Item 2	Treated me with respect	Treated me with respect	Not changed
Item 3	Showed interest in my ideas about my health	Showed interest in my ideas about the prescribed therapy	**Minor changes**
Item 4	Understood my main health concerns	Understood my main health concerns	Not changed
Item 5	Paid attention to me (looked at me, listened carefully)	Explained how to correctly follow the prescribed therapy	**Changed**
Item 6	Let me talk without interruptions	Let me talk without interruptions	Not changed
Item 7	Gave me as much information as I wanted	Gave me as much information as I wanted	Not changed
Item 8	Talked in terms I could understand	Talked in terms I could understand	Not changed
Item 9	Checked to be sure I understood everything	Checked to be sure I understood everything	Not changed
Item 10	Encouraged me to ask questions	Encouraged me to ask questions	Not changed
Item 11	Involved me in decisions as much as I wanted	Discussed how to manage any side effects of the prescribed therapy	**Changed**
Item 12	Discussed next steps, including any follow-up plans	Discussed next steps, including any follow-up plans	Not changed
Item 13	Showed care and concern	Asked about my ability to follow the prescribed therapy	**Changed**
Item 14	Spent the right amount of time with me	Spent the right amount of time with me	Not changed
Item 15	-	Discussed possible interactions of the prescribed therapy with other drugs or foods	**Added**

Applicability of the tool

The CAT-Pharm was tested on 97 patients in the Italian setting and 150 patients in the Maltese setting.

In the Italian setting, 51 patients (52.6%) were between 45-64 years of age, 50 participants (51.5%) were male and 90 (92%) were native Italian speakers. In Malta, 63 patients (42.0%) were between 65-84 years of age, 89 participants (59.3%) were female and 146 (97.3%) were Caucasian. In the Maltese setting 147 patients (98%) filled the questionnaire in English. Demographic characteristics of the two populations are shown in Table 2.

Table 2. Demographic characteristics of patients completing CAT-Pharm

Demographic characteristics	Italy N = 97		Malta N = 150	
	n	**%**	**n**	**%**
Gender				
Male	50	51.5	61	40.7
Female	47	48.5	89	59.3
Age *in years*				
≤24	1	1.0	2	1.3
25-44	18	18.6	48	32.0
45-64	51	52.6	36	24.0
65-84	25	25.8	63	42.0
≥85	-	-	1	0.7
Nationality/Ethnicity				
Native Italian speaker	90	92.0	-	-
Non-native Italian speaker	7	7.2	-	-
Caucasian	-	-	146	97.3
Hispanic or Latino	-	-	3	2.0
Asian	-	-	1	0.7
Language in which CAT-Pharm was completed				
Italian	97	100	-	-
English	-	-	147	98.0
Maltese	-	-	3	2.0
Had the patient seen the pharmacist before?				
No	65	67.0	10	6.7
Yes, but only once	19	19.6	16	10.7
Yes, more than once	13	13.4	124	82.7

Table 3 shows differences in ‘Excellent’ rating scores for each CAT-Pharm item in the two settings. The ‘Excellent’ scores of Italian CAT-Pharm items ranged from 12.4% to 55.7%. The highest-scoring items were ‘‘Talked in terms I could understand’’ (55.7%) and ‘‘Treated me with respect’’ and “Spent the right amount of time with me” (both 53.6%). The lowest-scoring item was ‘‘Discussed next steps, including any follow-up plans’’ (12.4%).

The ‘Excellent’ scores obtained from the Maltese setting using the English and Maltese versions of the tool ranged from 46.7% to 88%. The highest-scoring items were ‘‘Talked in terms I could understand” (88%) and “Treated me with respect ”and “Explained how to correctly follow the prescribed therapy” (both 86%). The lowest-scoring item was ‘‘Encouraged me to ask questions’’ (46.7%). A statistically significant difference in response between the Italian and Maltese setting was detected for all the items. Higher ratings were observed from the Maltese setting (Table 3).

Table 3. Percentage of Excellent ratings for individual CAT-Pharm items

Item	Statement	Excellent Ratings (%)		*Chi-square Test (P)Value*
		Italy	**Malta**	
		N=97	**N=150**	
Item 1	Greeted me in a way that made me feel comfortable	49.5	76.0	*<0.001*
Item 2	Treated me with respect	53.6	86.0	*<0.001*
Item 3	Showed interest in my ideas about the prescribed therapy	42.3	64.7	*0.001*
Item 4	Understood my main health concerns	36.1	67.3	*<0.001*
Item 5	Explained how to correctly follow the prescribed therapy	30.9	86.0	*<0.001*
Item 6	Let me talk without interruptions	45.4	68.0	*0.001*
Item 7	Gave me as much information as I wanted	38.1	81.3	*<0.001*
Item 8	Talked in terms I could understand	55.7	88.0	*<0.001*
Item 9	Checked to be sure I understood everything	48.5	65.3	*0.014*
Item 10	Encouraged me to ask questions	25.8	46.7	*0.001*
Item 11	Discussed how to manage any side effects of the prescribed therapy	26.8	60.7	*<0.001*
Item 12	Discussed next steps, including any follow-up plans	12.4	47.3	*<0.001*
Item 13	Asked about my ability to follow the prescribed therapy	32.0	60.7	*<0.001*
Item 14	Spent the right amount of time with me	53.6	75.3	*0.001*
Item 15	Discussed possible interactions of the prescribed therapy with other drugs or foods	21.6	63.3	*<0.001*

Discussion

The uniqueness of this study is that it presents a new tool to be used by patients to rate the communication with pharmacists related to prescribed medications. Items in the CAT and CAT-Pharm have the same communication tasks. The CAT-Pharm, compared to the original CAT, maintained 10 out of the 14 items, one item was slightly modified, three items have undergone changes to reflect the contribution of the pharmacist and one item was added to discuss possible interactions between prescribed therapy and other drugs or food. Although the CAT-Pharm is proposed as an assessment tool specific for pharmacist-patient relationship to reflect on their interpersonal and communication skills, the original purpose of the CAT-tool developed by Makoul et al in 2007 [13], was maintained and this was confirmed by the results of the factor analysis. The first six items are aimed at investigating the confidential relationship between the patient and the pharmacist and how comfortable the patient feels with the pharmacist. The remaining items are more focused on investigating the correct activity of the pharmacist towards the patient, i.e. including the patient in decisions, discussing next steps.

Given the usefulness of the tool specifically directed at the pharmacist-patient relationship, its applicability to all settings and contexts cannot be taken for granted. Relying on validated guidelines is crucial when carrying out modifications to psychometric questionnaires for adaptation to different professional groups or a different setting. CAT-Pharm reliability was confirmed by Cronbach's alpha values, validity confirmed by factor analysis, and internal validity assessed by administering and evaluating responses from a small sample of patients from the two different settings

CAT-Pharm external validity should be evaluated for the application to other settings which will require cross-cultural validation prior to implementation. Implementation of CAT-Pharm tool may be suggested as a method to assess patients' views of pharmacists' communication behavior and to identify areas that require more attention for improvement as part of professional development programs or as a competency development measurement tool for pharmacy students.

It is interesting to note that analysis of patient perceptions of communication with the pharmacist in Italy demonstrated differences from that in Malta. Usually, the community pharmacist has more frequent and direct contact with patients compared to the hospital pharmacist, which

explains why 67% of the patients who participated in Italy said they had never seen the pharmacist before, while in Malta only 6.7% of Maltese patients stated this. The largest difference was observed in the response to the question "Discussed next steps, including any follow-up plans" underlining how the community pharmacist has a continuous and frequent interaction with the same patient. Particularly, few patients in the Italian context rated as 'Excellent' the attitude of the pharmacist in discussing possible interactions of prescribed therapy with other drugs and food or the management of possible side-effects.

Notably, other significant differences were observed in patient perceptions of pharmacist communication methods, which were always greater in the Maltese community setting. It is to be understood that a high patient regard of community pharmacists' services including clinical services related to medication management has been reported for community pharmacy practice in Malta [19,20]. This is explained through the highly evolved patient-centered curriculum adopted in pharmacy education in Malta [21]. It is noteworthy that assessing the difference between Italy and Malta was not among the primary objectives of the study; however, significant differences emerged that warrant further investigation in a larger cohort of patients. The utility of the tool to detect differences in practice is an application of the tool to be investigated in terms of its use as a performance indicator for service development within pharmaceutical health systems [22-24].

Confirming results of previous studies, patients desire more opportunities to ask questions and for more active involvement in decisions regarding their care [13, 25-27]. The clinical relationship must serves to obtain information from the patient to identify their needs and understanding of the care plan as well as to provide the opportunity to patients to share their thoughts and questions. [28,29].

Limitations

A limitation of this study is the nature of assessment of validity where the tool was measuring communication with the pharmacist and seeking response by the participants availing themselves of the service to comment on the service received. Other limitations of the study included the small sample size and the adoption of expert group from two countries rather than a Delphi technique.

A limitation is that the study looked at content validity and did not assess construct validity. The high Cronbach's alpha values may indicate a redundancy of some items in the CAT-Pharm tool. In this study, the aim was to adapt the original CAT tool to the pharmacist profession and therefore the potential redundancy of items was not addressed in this paper. In further studies, the redundancy may be considered prior to undertaking construct validity and external validity. The next step will be to perform the study on a larger sample for external validity analyses and to ensure generalizability of the tool. During the external validation phase ethnicity questions will be added to all versions of the tool- together with the possibility of presenting the questionnaire in English to all patients.

Conclusion

This pilot study demonstrated that the developed CAT-Pharm tool may be applied to different pharmacy settings and is a valid and reliable tool that could be submitted for further psychometric testing to evaluate its contribution as an instrument to assess patient perception of the pharmacist's communication abilities. CAT-Pharm has the potential to be useful for pharmacists to reflect on their interpersonal and communication skills with the ideal goal of reinforcing strengths and identifying areas that would require more attention to improve patient empowerment.

Declarations

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Availability of data: The datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

Competing interest: The authors declare no competing interests

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4.3.2 Adaptation of communication assessment tool for community pharmacists in medication adherence and minor diseases management.

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Abstract: ***Aims***: To develop two versions of the Communication Assessment Tool (CAT) skilled for the setting of community pharmacy and to pilot test it on a selected sample. ***Methods***: Development of two versions of CAT-tool for community pharmacists. Validity and reliability assessments were required to determine the psychometric properties of developed tool versions. To investigate the construct validity of each adapted tool item, confirmatory factor analysis was performed. Reliability was assessed with the Cronbach's Alpha evaluation, internal validity by submitting tool versions to patients of eleven pharmacies from North, Center, and South of Italy for pilot testing. ***Results***: Two CAT versions were developed and tested: CAT-Pharm-community Adherence to therapy and Minor Disease Management versions. First to evaluate pharmacist-patient communication following the dispensing of a prescription drug, second a consultation for minor disease management. ***Conclusion***: Communication tools are useful to implement optimal management of chronic diseases to minimize non-adherence and patients' negative health outcomes.

Keywords: Communication assessment tool; Community pharmacy; Patient empowerment; Patient-pharmacist relationship.

Introduction

Patient communication is a key strategy for achieving better health outcomes and reducing the failure of physician-prescribed therapies. Information regarding the appropriate medication use together with other recommendations are an essential part of the pharmacist's profession at the time of prescription dispensing (Kerr et al 2021). Patients' understanding concerning prescribed pharmacological treatment is crucial to ensure a proper adherence to the therapy and/or an adequate management of their minor disease (Duffy et al 2021, Steininger et al 2020, Náfrádi et al 2017, De Geest et al 2018). Clearing up misunderstandings and confusion on this aspect should be a key task for the community pharmacist (Scala et al 2016, Menditto et al 2015, Scala et al 2018). Pharmacist recommendations could be better understood if they are conveyed effectively and appropriately to the patient's specific problem (Carter et al 2015, Ferranti et al 2010).

In this scenario, a psychometrically instrument, the Communication Assessment Tool (CAT), was already developed and validated for patient assessment of physician communication skills by Makoul et al in 2007 (Makoul et al 2017, Mercer et al 2008).

Albeit the community pharmacist plays a fundamental role in the prescribing-pharmacist-patient chain, to date, no specific assessment tools to detect the quality of communication between community pharmacist and patient during the dispensing of a prescription drug are available. Indeed, the community pharmacist can greatly contribute to the improvement of the patient's disease management. The pharmacist holds a key role in the relationship with the patient by providing useful information, acting as a facilitator, advising the patient on the use of medications and devices, with the ultimate goal of supporting patients and caregivers in the optimal management of the disease. There is now a worldwide recognition that the role of the community pharmacist should be directed towards the provision of advanced, high value-added services. The community pharmacist is an assurer of pharmaceutical care, which involves the active management of minor diseases, chronic conditions, verifying adherence, and monitoring drug therapies.

In this view, we recently developed a CAT tool skilled for the Pharmacist role: CAT-Pharm (Scala et al 2022). As a result, goals of this study were:

i) to develop two versions of a Communication Assessment Tool skilled for the setting of community pharmacy: CAT-Pharm-community Adherence to Therapy version and Minor Disease Management version; ii) to pilot testing a preliminary assessment of the communication between the clinical pharmacist and the patient following the dispensing of a prescription drug (Adherence to Therapy version) or a consultation for the management of a minor disease (Minor Disease Management version).

Materials and Methods

A pilot study was carried out in Italy from July to August 2019. Eleven pharmacies from North, Center and South of Italy were involved in the study by convenience sampling. Ethics approval was obtained by the Ethics Committee of Cardarelli Hospital in Naples, Italy (424/2017).

Adaptation of CAT to community pharmacist profession

The study was carried out through two different phases: i) development of two specific versions of the CAT-Pharm-community tool by adapting the original CAT to the community pharmacy setting; ii) evaluation of psychometric validity and reliability and pilot testing of the tools on a small sample of community pharmacies.

The original Communication Assessment Tool, developed by Makoul et al 2007, specifically focused on the assessment of the physicians interprofessional skills. This questionnaire was already adapted to the pharmacist role by developing a pharmacist-patients skilled tool, the CAT-Pharm. The new CAT-Pharm tool passed validity and reliability tests and was translated into Italian (Scala et al 2022). In this study, this CAT-Pharm tool was adapted specifically to the community pharmacy setting by developing the so-called CAT-Pharm-community in two different versions according to the two macro-activities covered by the community pharmacist role:

- CAT-Pharm-community – Adherence to Therapy version: This tool should be used to assess patient perceptions of the pharmacist's communication skills following the dispensing of a physician-prescribed medication.
- CAT-Pharm-community – Minor Disease Management version: This tool should be used to assess patient perceptions of the pharmacist's

communication skills following a consultation with the pharmacist for management of a minor disorder.

The design of the two CAT-Pharm-community versions was achieved through the following steps:

Step one: CAT-Pharm evaluation was performed by a working group composed of clinical pharmacists, hospital pharmacists, clinicians and researchers which indicated any items to be eliminated, modified or added;

Step two: Consensus meeting and drafting of a first CAT-Pharm-community for both versions by slightly modifying the items to be more focused on both adherence to therapy and minor disease management versions;

Step three: Cognitive debriefing on a sample of 6 patients to assess comprehensibility of the items of both versions. Respondents were asked to explain what is asked in each question, the meaning of each question, and to repeat the question in their own words. Respondents were also asked to explain the reason for their answer;

Step four: Final consensus meeting was done among by working group of the first stage and consisted in analysis and discussion of cognitive debriefing results and drafting of the final version of both CAT-Pharm-community versions.

Setting, Participants and Eligible criteria

The second part of the study consisted of internal validation and psychometric characterization of the two CAT-Pharm-community versions by pilot testing it on a selected sample. Eleven Italian community pharmacies participated in the pilot study, five from the North, two from the Center, and four from the South. Sample included in the pilot study consisted of both urban and rural community pharmacies on the Italian soil. Each pharmacy was asked to recruit approximately twelve patients to be surveyed based on the type of service provided to the patient: The Minor disease management version tool was proposed in the case of dispensing a medication after a consultation with the patient manifesting a minor disorder (~six patients per-pharmacy); while, the Adherence to therapy version tool was proposed in the case of dispensing a medication to treat a chronic condition, following a doctor's prescription (~six patients per-pharmacy).

Pilot study population consisted of patients aged 18 years or older visited the community pharmacies involved (inclusion criteria). Patients with cognitive impairment or receiving antipsychotics and foreign patients who did not understand the Italian language were not included in the study (exclusion criteria).

Tools used for the study and submitted to the volunteer patients were:

- CAT-Pharm-community TEST (Supplemental material S1): Original questionnaire in both developed versions adherence to therapy and minor disease management, structured in a 5 point Likert scale (poor; fair; good; very good; excellent).
- CAT-Pharm-community QUEST (Supplemental material S2): Two questionnaires with the same items of the two versions developed to require an evaluation of the importance of each specific item, structured in a rating grade (very important; important; slightly important; not important)

Moreover, a specific questionnaire was also directed to pharmacist requiring personal and demographic information, named as Pharmacist profiling questionnaire (Supplemental material S3):

Patients enrollment process followed a systematic approach. The person responsible for inviting the patient to complete the CAT-Pharm-community was different from the pharmacist who dispensed the medications for which the patient expresses perceptions about communication/relational skills. This served to eliminate background bias as the patient could be conditioned in providing their opinion. Patients were informed of the study purpose and signed an Informed Consent. Moreover, they were asked to give an evaluation of their communication with the pharmacist, adding suggestions for any unclear or incomprehensible questions. After acceptance to participate, patients received the CAT-Pharm specific version based on their counselling with the pharmacist. Patients who had a consultation for a minor disease received the Minor Disease Management version, while those who asking for a dispensation of a prescription drug received the Adherence to Therapy version. After completion of one of the CAT-Pharm-community versions, the patient was also asked to complete a second questionnaire (QUEST) to assess the importance of the CAT-Pharm items.

Finally, the pharmacist who performed the consultation with the patient completed the pharmacist profiling questionnaire attaching it to the patient's file.

Statistical analysis

Validity (internal, external, and construct validity) and reliability assessments were required to determine the psychometric properties of the developed CAT-Pharm-community tool in both versions. Confirmatory factor analysis was performed to investigate construct validity of each item of the community pharmacist-adapted CAT tool. Sample adequacy was measured by Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity test. To confirm factor structure, a Oblimin direct rotation with Kaiser normalization was performed. Correlations between items were assessed using the Pearson's correlation test. The Chi-square test was used to compare the proportion of patients who rated a given item 'Excellent' between the two settings. A p-value <0.05 was considered statistically significant. As both questionnaire versions' responses were structured in a 5 point Likert scale (poor; fair; good; very good; excellent), Cronbach's alpha was performed to assess internal consistency for the translated CAT overall score. As in the original scale development, psychometric analysis indicated that 'Excellent' maps onto 'Yes', and all the other response options (i.e. poor; fair; good; very good) map onto "No" (Makoul et al 2007). Accordingly, and consistent with previous CAT tool uses, results were presented as the percentage of participants who provided ratings of 'Excellent'. Percentage of 'Excellent' responses was calculated from the total number of respondents to the individual question. Analyses were performed using SPSS Statistics for Windows, version 17.1 (SPSS Inc. Released 2008. Chicago, IL; USA).

Results

Both CAT-Pharm-community versions consisted of 16 items and explored several areas of communication at the time of drug dispensing. For each of the 16 items, the patient completing the test could assign a score from 1 (poor) to 5 (excellent).

Regarding the *CAT Pharm-community Test - Adherence to Therapy version*, items' construct validity was assessed. Pearson's correlation test showed significant positive correlations between CAT-Pharm items. The

correlation coefficients ranged from -0.142 to 0.797 (Supplemental table S4.1). The results of the Bartlett's test of sphericity showed a KMO of 0.818 and $\chi 2$=583.141 (df =120, p<0.01), indicating that the correlation matrix was suitable for factor analysis. A four-factor solution was found identifying four questionnaires macro-areas (Supplemental table S4.2). Factors 1 (items 1-5) was focused on the understanding of patient clinical needs; Factor 2 (items 6-10) was focused on communication about therapy to the patient; Factor 3 (items 11-13) was focused on the evaluation of patient understanding; Factor 4 (items 14-16) was focused on the building of a trust relation between pharmacist and patient. Results of confirmatory factor analysis are showed in the Supplemental material S4. Moreover, reliability results indicated very high overall scale reliability for the 16 items of the Adherence to therapy version (Cronbach's Alpha = 0.88).

To assess the tool's internal validity, the CAT Pharm-community Adherence to Therapy version was tested on 67 patients, 70% of these were women. Overall, mean age recorded was 59 years (standard deviation: ±14.9). Characteristics of these patients is showed in Table 1. Overall, Majority of patients considered as excellent the respectful attitude of the pharmacist (92%, item 2) and the pharmacist's welcome (85%, item 1). A minor percentage of patients (42%) considered excellent the manner in which the pharmacist discussed future interventions, including any examinations and follow-up visits. (item 14) (Table 2). In addition, approximately 80% of patients considered as very important the attitude and communication methods adopted by the pharmacist, whereas 20.9% didn't find very useful the information received about future interventions such as examinations and follow-up visits (Table 3).

Regarding the *CAT Pharm-community Test - Minor Diseases Management version*, item's construct validity was assessed. Pearson's correlation test showed significant positive correlations between CAT-Pharm items. The correlation coefficients ranged from 0.115 to 0.761 (Supplemental table S4.3). The results of the Bartlett's test of sphericity recorded a KMO of 0.750 and $\chi 2$=581.129 (df =120, p<0.01), indicating that the correlation matrix was suitable for factor analysis. A four-factor solution was found in this tool's version identifying the same four macro-areas (Supplemental tables S4.4 and S4.5). Moreover, reliability results indicated very high

overall scale reliability for the 16 items of the Adherence to therapy version (Cronbach's Alpha = 0.87).

To assess the tool’s internal validity, the CAT Pharm-community Minor Diseases Management version was tested in 65 patients, of which 73.8% were women. Overall, mean age was 57.5 years (standard deviation: ± 13.9) (Table 1). Majority of patients (93.8%) rated as excellent the pharmacist's respectful attitude (item 2), and 90.8% of patients also considered excellent the pharmacist's welcome (item 1). Only 47.7% of patients adequately received encouragement from the pharmacist to ask questions (item 13) (Table 4). In addition, about 80% of patients rated very important the communication attitude adopted by the pharmacist, while 15% consider not very useful to receive information about possible interactions of the prescribed therapy with other drugs and foods (Table 5).

Table 1. Demographic characteristic of patients completing CAT- Pharm-community Test

Demographic information	**Adherence to Therapy *version***	**Minor Disesase *version***
	N = 67 (%)	**N = 65 (%)**
Gender		
Male	20 (29.9%)	17 (26%)
Female	47 (70.1%)	48 (73.8%)
Age		
Mean (± SD)	58.6 (±14.9)	57.5 (±13.9)
Educational level		
Primary school graduation	31 (46.3%)	7 (10.8%)
Secondary school graduation	14 (20.9%)	15 (23.1%)
High school graduation	9 (13.4%)	28 (43.1%)
Degree graduatin	13 (19.4%)	15 (23.1%)
Occupation		
Unemployed	2 (3.0%)	1 (1.54%)
Housewife	7 (10.4%)	7 (10.8%)
Retired	23 (34.3%)	20 (30.8%)
Employed	30 (44.8%)	32 (49.3%)
Student	1 (1.5%)	1 (1.54%)
Other	4 (6.0%)	4 (6.2%)
Marital Status		
Single	15 (22.4%	13 (20.0%)
Married	41 (61.2%)	40 (61.5%)
Widower	6 (9.0%)	7 (10.8%)
Divorced	5 (7.5%)	5 (7.7%)
Had the patient seen the pharmacist before?		
No	1 (1.5%)	-
Yes, but only one	5 (7.5%)	1 (1.54%)
Yes more than once	61 (91.0%)	64 (98.5%)

Abbreviations: SD, Standard Deviation

Table 1. Percentage of excellent ratings for individual CAT-Pharm-community items (Adherence to Therapy version)

CAT-Pharm-community TEST *Adherence to Therapy version*	**Rating (% Excellent) N = 67**	
	N	**%**
1. Greeted me in a way that made me feel comfortable	57	85.1
2. Treated me with respect	62	92.5
3. Understood my main health concerns	46	68.7
4. Let me talk without interruptions	46	68.7
5. Showed interest in my ideas about the prescribed therapy	40	59.7
6. Explained how to correctly follow the prescribed therapy	54	80.6
7. Asked about my ability to follow the prescribed therapy	47	70.1
8. Discussed how to manage any side effect of the prescribed therapy	34	50.7
9. Discussed possible interactions of the prescribed therapy with other drugs or foods	35	52.2
10. Gave me as much information as I wanted	50	74.6
11. Talked in terms I could understand	54	80.6
12. Checked to be sure I understood everything	52	77.6
13. Encouraged me to ask questions	31	46.3
14. Discussed next steps, including any follow-up plans	28	41.8
15. Spent the right amount of time with me	52	77.6
16. Respected my privacy	52	77.6

Table 3. Patients reporting importance of the CAT-Pharm-community items to asses adherence to therapy

CAT-Pharm-community QUEST *Adherence to Therapy version*	**Very important**		**Important**		**Not very important/ Important**	
	N	**%**	**N**	**%**	**N**	**%**
1. Greeted me in a way that made me feel comfortable	55	82.1	11	16.4	1	1.5
2. Treated me with respect	53	79.1	13	19.4	1	1.5
3. Understood my main health concerns	50	74.6	15	22.4	2	3.0
4. Let me talk without interruptions	41	61.2	24	35.8	2	3.0
5. Showed interest in my ideas about the prescribed therapy	42	62.7	20	29.9	4	6.0
6. Explained how to correctly follow the prescribed therapy	51	76.1	15	22.4	1	1.5
7. Asked about my ability to follow the prescribed therapy	47	70.1	18	26.9	2	3.0
8. Discussed how to manage any side effect of the prescribed therapy	38	56.7	19	28.4	10	14.9
9. Discussed possible interactions of the prescribed therapy with other drugs or foods	41	61.2	19	28.4	7	10.4
10. Gave me as much information as I wanted	54	80.6	12	17.9	1	1.5
11. Talked in terms I could understand	55	82.1	12	17.9	-	-
12. Checked to be sure I understood everything	54	80.6	12	17.9	1	1.5
13. Encouraged me to ask questions	34	50.7	25	37.3	8	11.9
14. Discussed next steps. including any follow-up plans	27	40.3	26	38.8	14	20.9
15. Spent the right amount of time with me	46	68.7	21	31.3	-	-
16. Respected my privacy	45	67.2	21	31.3	1	1.5

Table 4. Percentage of excellent ratings for individual CAT-Pharm-community items (Minor disease Management version)

CAT-Pharm-community TEST *Minor disease Management version*		**Rating (% Excellent) N = 67**	
		N	**%**
1.	Greeted me in a way that made me feel comfortable	59	90.8%
2.	Treated me with respect	61	93.8%
3.	Understood my main health concerns	48	73.8%
4.	Let me talk without interruptions	44	67.7%
5.	Asked if I had consulted the doctor about this problem or taken some medication before the consultation	44	67.7%
6.	Gave me right therapy and advice for my problem	55	84.6%
7.	Explained how to correctly follow the prescribed therapy	47	72.3%
8.	Discussed how to manage any side effect of the prescribed therapy	32	49.2%
9.	Discussed possible interactions of the prescribed therapy with other drugs or foods	36	55.4%
10.	Gave me as much information as I wanted	51	78.5%
11.	Talked in terms I could understand	52	80.0%
12.	Checked to be sure I understood everything	48	73.8%
13.	Encouraged me to ask questions	31	47.7%
14.	Discussed next steps, including any follow-up plans	42	64.6%
15.	Spent the right amount of time with me	48	73.8%
16.	Respected my privacy	54	83.1%

Table 5. Patient reporting importance of the CAT-Pharm-community items to assess the management of minor diseases

CAT-Pharm-community QUEST *Minor disease Management version*	**Very important**		**Important**		**Not very important/ Important**	
	N	**%**	**N**	**%**	**N**	**%**
1. Greeted me in a way that made me feel comfortable	50	76.9	14	21.5	1	1.5
2. Treated me with respect	53	81.5	11	16.9	1	1.5
3. Understood my main health concerns	51	78.5	14	21.5	-	-
4. Let me talk without interruptions	36	55.4	28	43.1	1	1.5
5. Asked if I had consulted the doctor about this problem or taken some medication before the consultation	44	67.7	20	30.8	1	1.5
6. Gave me right therapy and advice for my problem	49	75.4	16	24.6	-	-
7. Explained how to correctly follow the prescribed therapy	50	76.9	15	23.1	-	-
8. Discussed how to manage any side effect of the prescribed therapy	37	56.9	18	27.7	10	15.4
9. Discussed possible interactions of the prescribed therapy with other drugs or foods	40	61.5	17	26.2	8	12.3
10. Gave me as much information as I wanted	48	73.8	15	23.1	2	3.1
11. Talked in terms I could understand	49	75.4	16	24.6	-	-
12. Checked to be sure I understood everything	47	72.3	17	26.2	1	1.5
13. Encouraged me to ask questions	32	49.2	27	41.5	6	9.2
14. Discussed next steps. including any follow-up plans	39	60.0	22	33.8	4	6.2
15. Spent the right amount of time with me	45	69.2	20	30.8	-	-
16. Respected my privacy	47	72.3	16	24.6	2	3.1

Discussion

Ineffective communication between health professionals and patients is recognized to be one of the main causes of medical errors and damage to patients' health. To overcome this gap, implementation strategies for better communication in healthcare have been investigated for more than a decade (Haley et al 2021). In this scenario, the main strength of this study lies in the introduction of two specific tools that patients can use to assess communication with community pharmacists in relation to prescribed medication. The two CAT-Pharm-community tools available in Italian language, have proven their potential to be implemented in all community pharmacies. The two tools, compared to the original Italian CAT (Scala et al 2016) and CAT-Pharm (Scala et al 2022), are more specific for the patients' needs. Indeed, the Adherence to Therapy version is exclusively aimed at investigating the level of communication between the community pharmacist and the patient with a specific treatment plan to be followed, while, the Minor Disease Management version investigates the level of communication with the patient following counselling for the management of a minor disease. Several differences can be detected in the two versions, especially in 3 items: "Showed interest in my ideas about the prescribed therapy" for the Adherence to therapy version instead "Asked if I had consulted the doctor about this problem or taken some medication before the consultation" for the Minor Disease Management version; the same for the item "Explained how to correctly follow the prescribed therapy" instead "Gave me right therapy and advice for my problem" and for "Asked about my ability to follow the prescribed therapy" instead "Explained how to correctly follow the prescribed therapy".

The results of the present study prove that, regardless of the type of consultation required by the patient, information regarding a treatment plan to be followed or a minor disease to manage, the most important aspect for the patient seems to be the confidentiality assured by the pharmacist. To prove it, items considered most important in a patient perspective were: "Greeted me in a way that made me feel comfortable", "Treated me with respect" and "Understood my main health concerns". These same items were also rated as excellent in both CAT-Pharm-community versions, hence, generally the patients seem satisfied from the interaction with the community pharmacist. This may be explained by the circumstance that the majority of patients who received the Adherence to

Therapy and Minor Disease Management versions (91% and 98%, respectively) had had a consultation with the community pharmacist more than once.

Notably, in the Adherence to therapy version, less than half of patients rated excellent the item “Discussed next steps, including any follow-up plans”. Therefore, in the Italian context, enhancing the pharmacist’s role as a driver of proper medication adherence seems to be a key aspect. The pharmacist is a pivotal figure in the prescriber-pharmacist-patient chain to ensure adherence to the prescribed treatment and the achievement of favorable health outcomes. In this sense, several recent studies have investigated and confirmed the positive impact of the pharmacist services on patient medication adherence (Gautier et al 2021, Bunchuailua et al 2021, Bruggmann et al 2021).

This role is crucial to encourage adherence to a specific prescribed treatment plan, but also, as demonstrated by the use of the Minor Disease Management version tool, to improve clinical outcomes and promote health status of patients following a minor disease consultation. Corroborating to our evidences, a recent systematic review underlined the role of the clinical pharmacist services in improving patient outcomes and medication therapy management. Clinical pharmacist interventions showed a positive impact on therapeutic, humanistic, and safety outcomes (Ahmed et al 2021).

Another recent systematic review (Falch and Alves 2021) investigated on impact of pharmacists as health professionals with the opportunity to act on medication regimen complexity reduction, particularly for older patients. Moreover, results of this review confirmed that pharmacists' active role in this sense has not been studied in depth so far.

Finally, our results indicated that patients need to be actively involved in decisions about their care, regardless of the type of minor or major health problem. This is also confirmed by the finding that few patients felt encouraged to ask questions (item 13) and this issue was also previously revealed by the pilot study conducted for the development and validation of the CAT-Pharm. The pharmacist-patient relationship seems to be crucial to obtain information from the patient about their needs, their ability to follow the prescribed treatment, and to support them so that they

understand their minor disorder or the prescribed treatment plan (Osuna et al 2018, Ilardo and Speciale 2020).

Limitations

The present study have several limitations. First, a limitation is strictly related to the nature of the internal validity assessment where the questionnaire measured communication with the pharmacist and sought the response of participants using the service to comment on the service received. Second, the small sample size should be considered; however, this is a pilot study with the aim of developing and translating an ad hoc instrument for assessing community pharmacist-patient communication in two different situation of the consultation and evaluating the reliability and construct and internal validity of the tool. Although the study did not cover the assessment of external validity, the next step will certainly be to carry out the study on a larger and more heterogeneous sample for external validity analyses and to ensure the generalizability of the communication tool in both versions.

Conclusions

Communication Assessment Tool (CAT) adapted to the community pharmacy setting (CAT-Pharm-community) could be a useful aid for the pharmacist in evaluating the patient's perception of the approach to the problem they reported. Feedback obtained from the questionnaire may be useful in taking corrective action to improve the quality of pharmacy service during counseling for management of a minor disorder. Moreover, the communication tool could be useful for the implementation of an optimal management of chronic diseases to minimize non-adherence treatment and consequently patient’s negative health outcomes.

Conflict of Interest: The author(s) declare that there are no conflicts of interest

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4.4 STAGE 4 Innovative DU-model to measure medication adherence in chronic patients

Based on what has hitherto been discussed in this dissertation, the Final Stage involved the implementation and adaptation of an **ML/AI based algorithm applied to Big data** in healthcare within the national setting for later validation across different EU countries. This algorithm is based on the assumption that medication adherence can be assessed through the use of longitudinal data to avoid returning a dichotomous value of adherence/non-adherence. It is also based on the use of clustering of subjects with common characteristics (determinants/predictors of an adherence level). Hence, **clustering** differs from the **group-based trajectory modeling** as for the longitudinal nature of the Real World Data analyzed. **Longitudinal data** are data in which each variable is measured repeatedly over time. One possibility for the analysis of such data is to cluster them. Reason why, clustering on longitudinal adherence trajectories was performed as offers advantages over simple clustering on group means distinct longitudinal adherence patterns and also allows classification accuracy for different scenarios [20].

Moreover, an ML/AI-based algorithm was implemented and adapted based on the already created by Dima A et al. [21,22] for medication adherence visualization and evaluation on RWD. This algorithm is used in the context of longitudinal cluster analysis. Working jointly with the algorithm creators, we implemented among RWD in the Italian Healthcare sector functions to facilitate reproducible adherence calculations in the statistical environment R (version 4.1.2).

The development and implementation of the AI algorithm (**Stage 4**) was carried out through two phases:

i) First phase in which the algorithm was implemented with computational methods on the library AdhereR of R and tested to Big Data health in the Italian context specifically of a chronic disease such as heart failure (*4.4.1 Longitudinal trajectory modeling to assess adherence to Sacubitril/Valsartan among patients with Heart Failure*);

ii) Second phase of testing and validation instead consisted in applying the algorithm among different health related databases across EU (*4.4.2 Adherence trajectories during the first year of T2DM treatment: a population-based longitudinal study in the Netherlands.).*

4.4.1 Longitudinal trajectory modeling to assess adherence to Sacubitril/Valsartan among patients with Heart Failure.

i) First phase in which the algorithm was implemented with computational methods on the library AdhereR of R and tested to Big Data health in the Italian context specifically of a chronic disease such as heart failure

Implementation and feasibility of AI algorithm

The algorithm appears as an Artificial Intelligence (AI) script for data mining on Big Data for the evaluation of adherence clusters and has been for the first time developed in an **R package (*library*): AdhereR** (https://www.adherer.eu/). Its core functionality is written in R language and is optimized for various use scenarios, being able to effectively scale up from the analysis and displaying of a few patients on a consumer grade laptop to the batch processing of millions of records on parallel heterogeneous compute clusters [21, 22]. The AdhereR package was developed in order to compute and visualize adherence estimates from EHD but based on the principles that the ideal measurement of the therapeutic adherence process would involve recording the time of prescription and each medication intake with an exact time stamp [18,19]. This would make it possible to describe in the greatest detail the adherence to a drug treatment prescribed with a given posology set and defined upstream. Therefore, ideally it would be necessary to know a range of information to get a complete picture of the patient, such as: the actual intake of the drug, the timing with which it is taken daily (exact time), errors in doses taken, omissions or over-takes [21, 22]. While this level of detail can be achieved with careful use of electronic monitoring devices, electronic health records usually include much less information. On this basis, **EHD-based algorithms** estimate medication based on the availability of *current supply*, under four main assumptions:

- the regimen requires the use of a fixed daily dosage of medication (if medication is to be taken as needed, a ratio cannot be computed)
- all medication supplied for that patient in that period of time is recorded and the patient does not use medication from other sources (if the patient uses other medication, adherence and/or persistence will be underestimated)
- the medication supplied is used by the patient it has been supplied for

(if other subjects use the medication, adherence and/or persistence will be overestimated)

- medication is supposed to be supplied at least two times during that period (if all medication is supplied once at the beginning of the treatment, there are no differences between patients regarding the supply patterns and all patients would be 100% covered for the whole treatment period)

In a practical perspective, the following terms and definitions are used in the AdhereR library [21, 22]:

Adherence (implementation) = the extent to which a patient's medication use corresponds to prescribed use,

CMA = continuous multiple-interval measures of medication availability/gaps, representing various indicators of the quality of implementation,

Medication event = prescribing or dispensing record of a given medication for a given patient; usually includes the patient's unique identifier, an event date, and a duration,

Duration = number of days the quantity of supplied medication would last if used as recommended,

Quantity = number of doses supplied at a medication event,

Daily dosage = number of doses recommended to be taken daily,

Medication type = classification performed by the researcher depending on study aims, e.g. based on therapeutic use, mechanism of action, chemical molecule or pharmaceutical formulation,

Follow-up window (FUW) = the total period for which relevant medication events are recorded for included patients,

Observation window (OW) = the period within the FUW for which adherence or persistence is computed,

Persistence = the length of time during which the patient continues to use medication, before discontinuing for a time period longer than a pre-specified permissible gap,

Treatment episode = a period of active medication use, represented by the number of consecutive days between a first medication supply event and the moment when the supply of the last medication event was finished (in a row of consecutive medication events where the interval between any two consecutive events is lower than the duration of the first plus a

researcher-defined permissible gap),

Permissible gap = a researcher-defined value representing the maximum number of days between the end of the supply from one medication event and the start of the following one that can be considered as continuous medication use.

In a practical perspective, the library can use data stored in various formats and can assess level of medication adherence by using longitudinal data based on the **3-component consensus taxonomy** for medication adherence [4] by building separate algorithm functions for distinct phases of adherence process: *initiation, implementation* and *persistence*.

The algorithm distinguishes three main classes of functionalities implemented by AdhereR. First, prescription, dispensation and hospitalization data can be pre-processed to extract the type of information used by the subsequent steps, namely the patient unique ID, the date and the duration of each event, and possibly its medication class and dosage (*compute_event_durations*). Second, these data can be used for the estimation of initiation (*time_to_initiation*), (non-)persistence (*compute.treatment.episodes*), and various types of implementation estimates: simple, per-episode, and sliding window **Continuous Medication Availability (CMA) functions.**

Vollmer et al [23] already defined CMA measures from 1 to 8. The first CMA measures (**CMA1-4**) do not consider supply gaps and operate on the dispensed supply only. For this reason CMA1-4 are similar to the MPR, hence also defined as *MPR-like* measures and they do not consider oversupply. The other CMAs measures (**CMA5–8**) belong to the group that compute supply gaps in the measurement window and may consider oversupply. CMA 5-8 are related to PDC measure, so also called *PDC-like* measures.Hence, among the simple eight numeric CMAs, one more (**CMA9**) was originally developed by Dima et al [18,19]. Description and differences of CMA indicators are detailed in **Table 1**.

Table 1. The nine CMAs implemented in AdhereR library (from Dima et al [21]).

CMA	Description	2-year simple CMA	1-year simple CMA	CMA per episode	Sliding window CMA
1	total number of days of medication supplied in the OW, excluding the last event; thedurations of all events are added up, possibly resulting in an estimate > 1.0	67.4%	140.0%	100.3%	85.2%
	# days supply excluding last event / first to last event			33.3%	30.6%
2	total number of days of medication supplied in the OW, including the last event; thedurations of all events are added up, possibly resulting in an estimate > 1.0	65.8%	77.9%	87.7%	98.6%
	# days supply including last / first event to OW end			39.5%	33.7%
3	CMA1, capped at 1	67.4%	100%	100.0%	85.2%
				33.3%	30.6%
4	CMA2, capped at 1	65.8%	77.9%	87.7%	98.6%
				39.5%	33.7%
5	number of gap days for all event intervals are extracted from the total time interval;(accounting for carry over within OW and excluding the supply left)	67.4%	100%	84.8%	83.2%
	# days of theoretical use / first to last event			33.3%	30.6%
6	number of gap days for all event intervals are extracted from the total time interval;(accounting for carry over within OW and excluding the supply left)	65.8%	77.9%	87.7%	83.8%
	# days of theoretical use / first event to OW end			39.5%	33.7%
7	number of gap days for all event intervals extracted from the total time interval;(accounting for carry over from before the OW and within OW, and excluding thesupply left at the OW end)	65.8%	69.0%	87.7%	83.8%
	# days of theoretical use/OW start to OW end			39.5%	47.7%
8*	number of gap days for all event intervals extracted from the total time interval; (accounting for carry over within OW and excluding the supply left at the OW end); theperiod covered by the supply carried-over from before the OW is excluded by a lagged start of the OW	65.8%	68.0%	87.7%	83.8%
	# days of theoretical use / lagged OW start to OW end			39.5%	38.6%
9#	Similar to CMA7 and CMA8, except how carryover from before the OW and supply leftat the OW end are treated: the supply of each medication event is evenly spread until the next event (ratio days supply up to 100%); oversupply is carried over to the next event	65.8%	70.6%	87.7%	83.8%
	# OW days; each weighted by its ratio days supply/ OW start to OW end			39.5%	47.7%

Notes:

CMA: continuous multiple-interval measures of medication availability/gaps; OW: observation window; FUW: follow-up window;

***CMA8 is designed for when an event with a hypothesized causal effect on adherence happens at the OW start (e.g. enrolment in an intervention study); in this case, it may be that the existing supply is not part of the relationship under study (e.g. it delays the actual start of the study for that participant) and needs to be excluded by shortening the time interval examined;*

[#] In longitudinal studies with multiple adherence measures, the assumption of 100% adherence until current supply ends (used in CMA7) may introduce additional variation in adherence estimates depending on where the OW start is located between last event before OW start and the first event in the OW: an OW start closer to the first event in the OW generates lower estimates for the same number of gap days between the two events. To address this, CMA9first computes a ratio of days' supply for each event in the FUW (until the next event or FUW end), then weighs all days in the OW by their corresponding ratio to generate an average CMA value for the OW.

AdhereR can generate various real-time interactive plots that allow the easy exploration of individual patients. The **event patterns** based on a simple **"CMA0"** is showed in Figure 1. referred to two patients (with IDs "1" and "5", printed on the vertical axis and distinguished by alternating bands of white and light gray backgrounds). In this example each patient receiving a prescription of a specific pharmacological treatment defined with the labels "medA" and "medB" and marked with a red and light blue line [21]. The prescribed periods are solid lines and the line width, and the numbers printed below each line represent the actual prescribed doses; the gaps are showed as dotted horizontal lines (**Figure 1**).

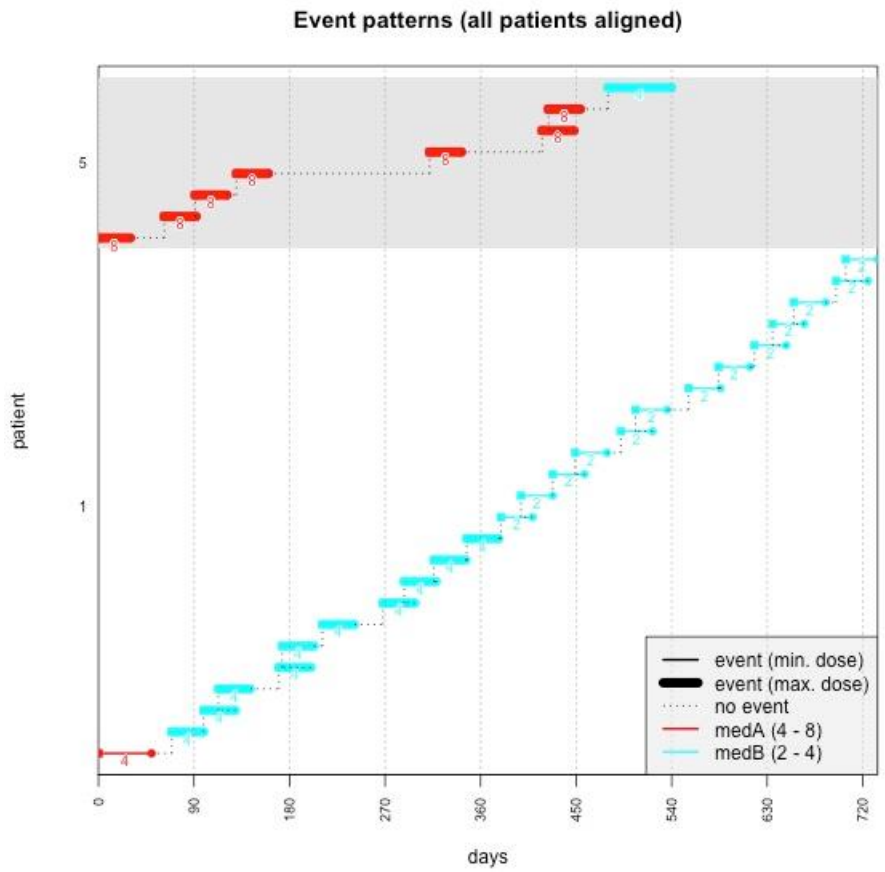


Figure 1. Example of patients' visualization with a basic CMA-0
Source Dima et al Source Dima et al, https://www.adherer.eu/features/

Below in Figure 2 is showed an adherence estimate by using **CMA9** for the same two patients. The yellow rectangles are the **observations windows (OWs)** and dashed rectangles are **follow-up windows** (**FUWs**). Each **small rectangle** represents a period between the start of an event (or the start of the OW) and the start of the next event (or the end of the observation window) colored by treatment type; the solid color (and solid line) represents periods with prescription, while the hashed transparent ones lack prescription; the numbers to the left are the doses. The percent and green bars represent the **overall adherence estimates** [21] (Figure 2).

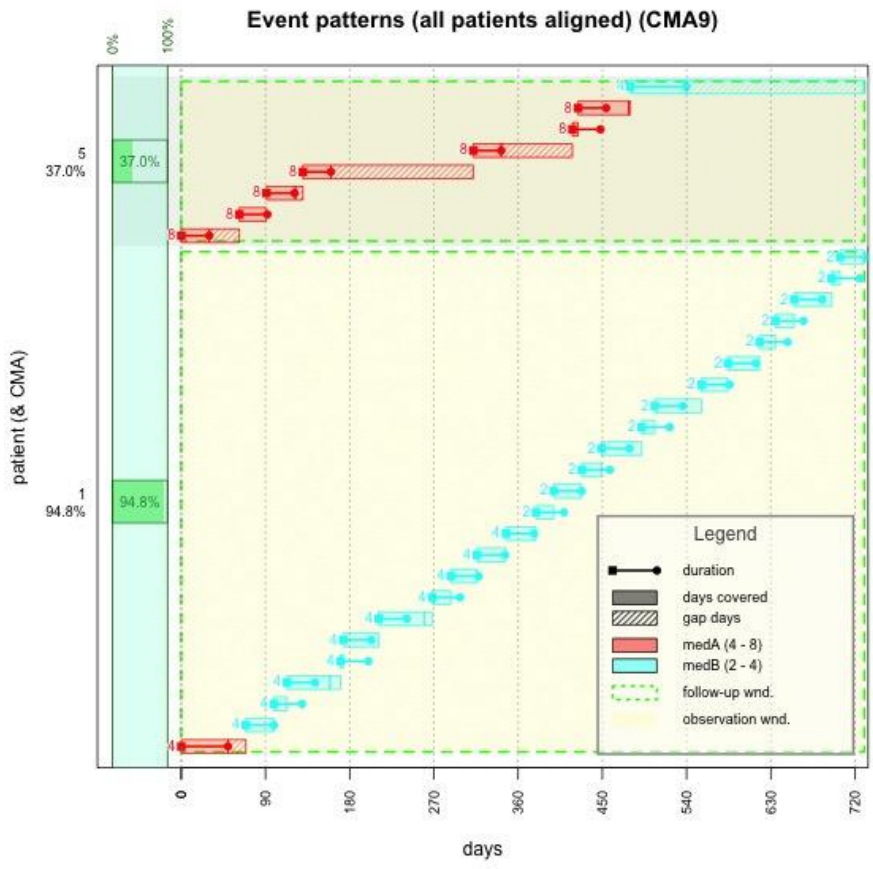


Figure 2. Example of patients' visualization with CMA9
Source Dima et al Source Dima et al, https://www.adherer.eu/features/

Finally, Figure 3 below exemplifies the **CMA9 estimates for each individual treatment episode** visible through the gray bars at the top of each patient showing the estimated adherence for each treatment episode.

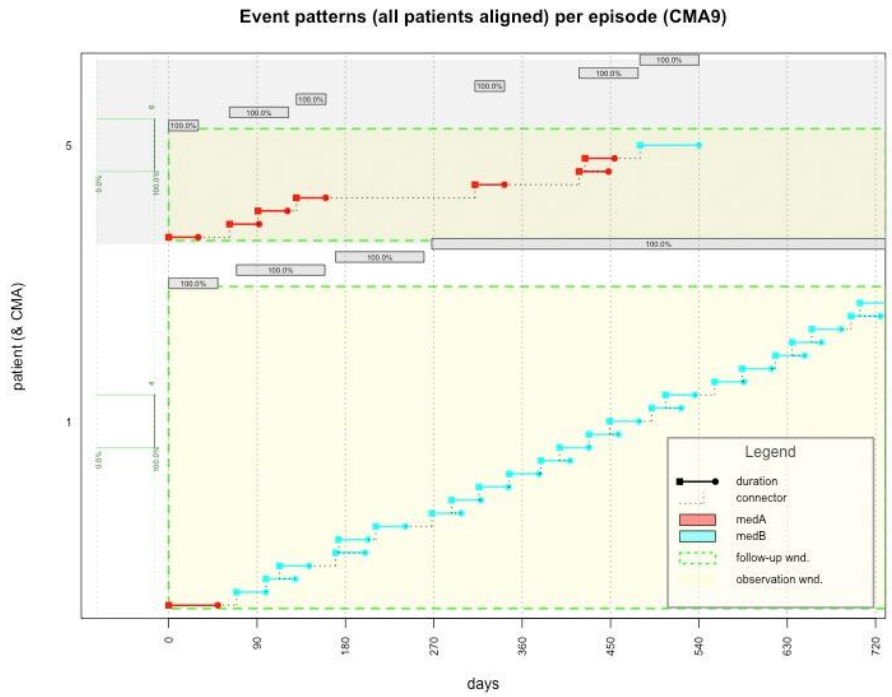
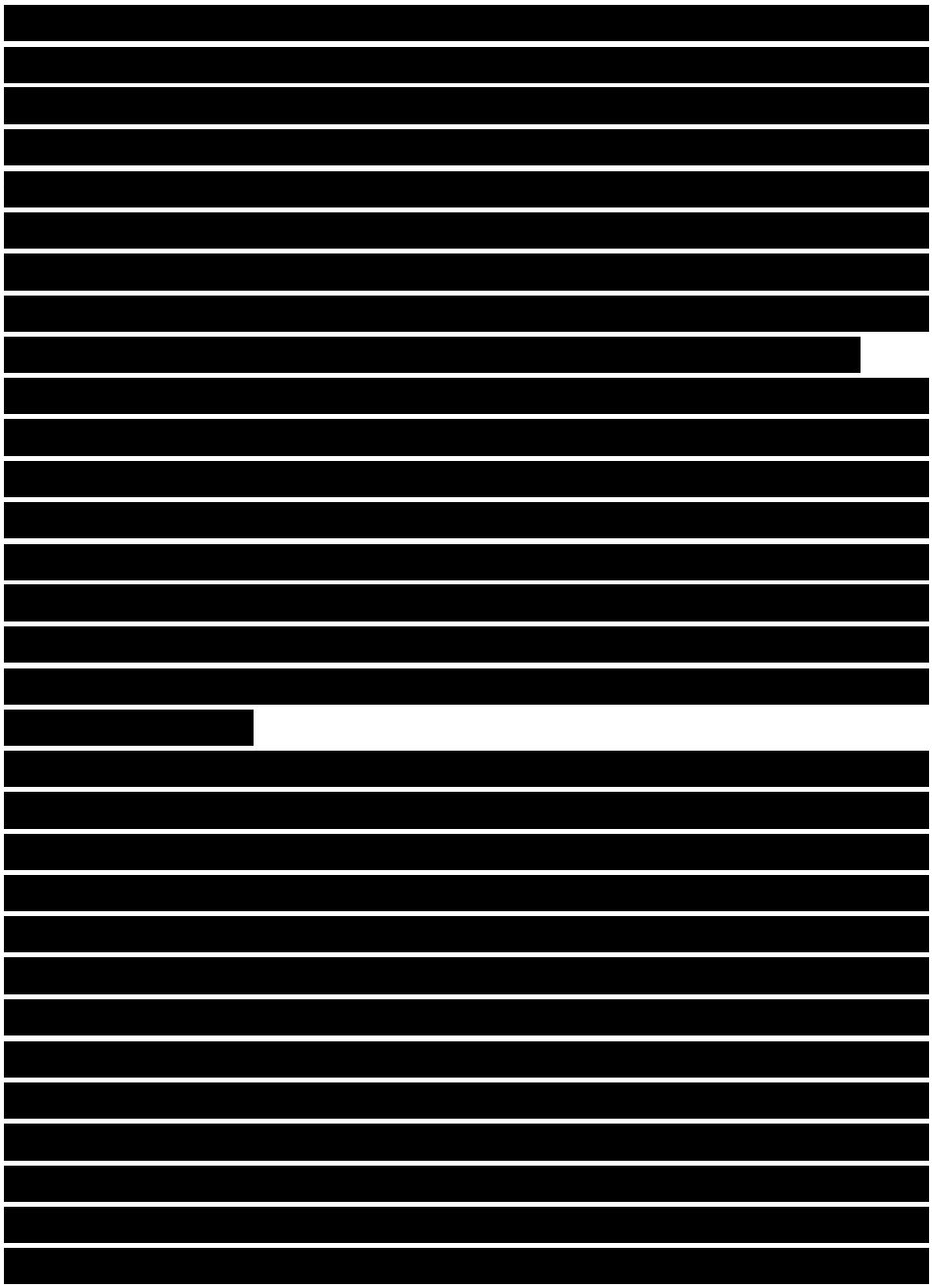


Figure 3. Example of patients visualization with CMA9 per episode
Source Dima et al, https://www.adherer.eu/features/

Given this exemplification, these estimates are made to administrative databases with large populations, which is why these estimates are repeated for all patients in the considered population [24]. Overall mean values are then shown by **grouping or clustering patients with similar adherence estimates** and evaluating their common characteristics and identifying them as determinants of adherence or poor adherence. Therefore, once implemented the CMA indicator, patients were clustered into groups following the principals of clustering into groups as widely above discussed into *Paper 4.2.3* of this thesis. Hence, to identify groups and classify individuals based on adherence trajectories, the R package "**kml**" (version 4.1.2) was used, which provides an implementation of **k-means** designed to work specifically on longitudinal data. The algorithm does not require prior information about groups, allows for the clustering of trajectories that do not follow polynomial or parametric functions, and

avoids issues related to model selection. It features an implementation of the algorithm optimized for increased speed with default settings (Euclidean distance and 20 re-rolls with different starting conditions).

Algorithm testing on heart failure treatment



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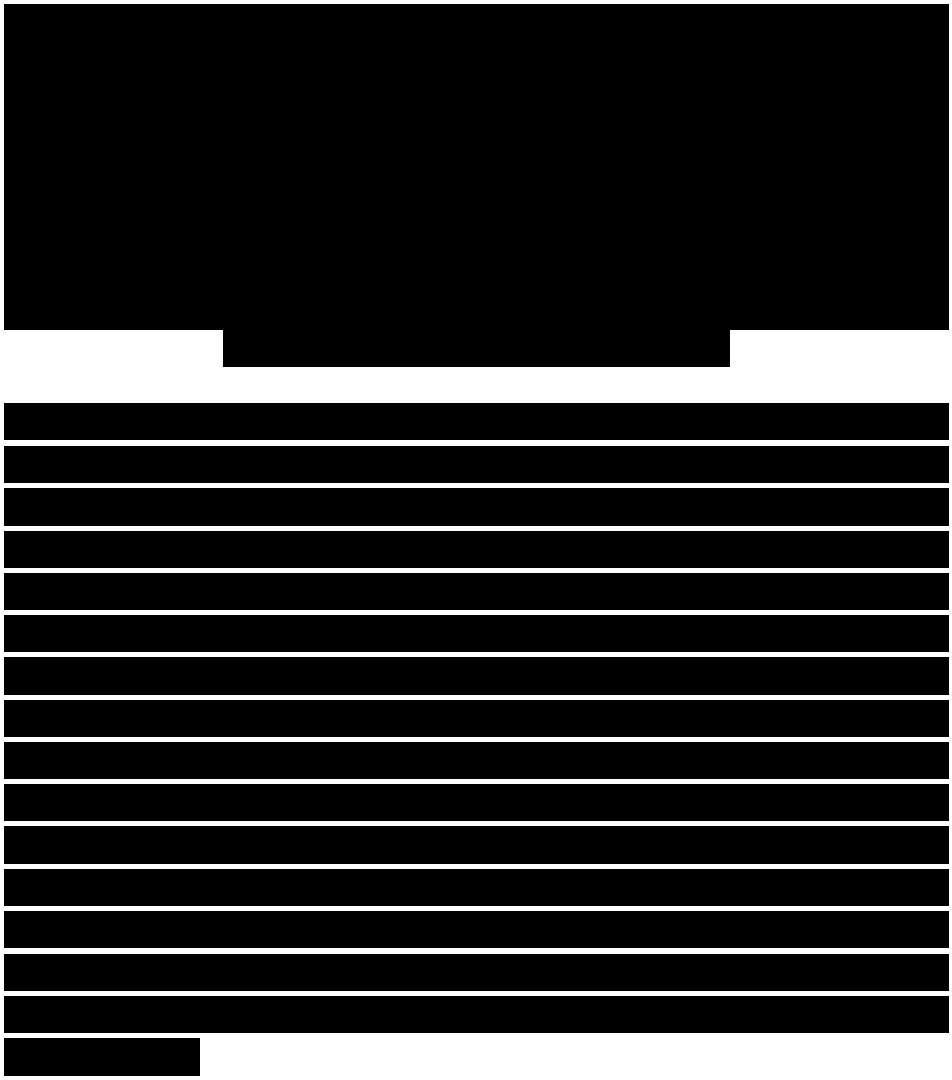

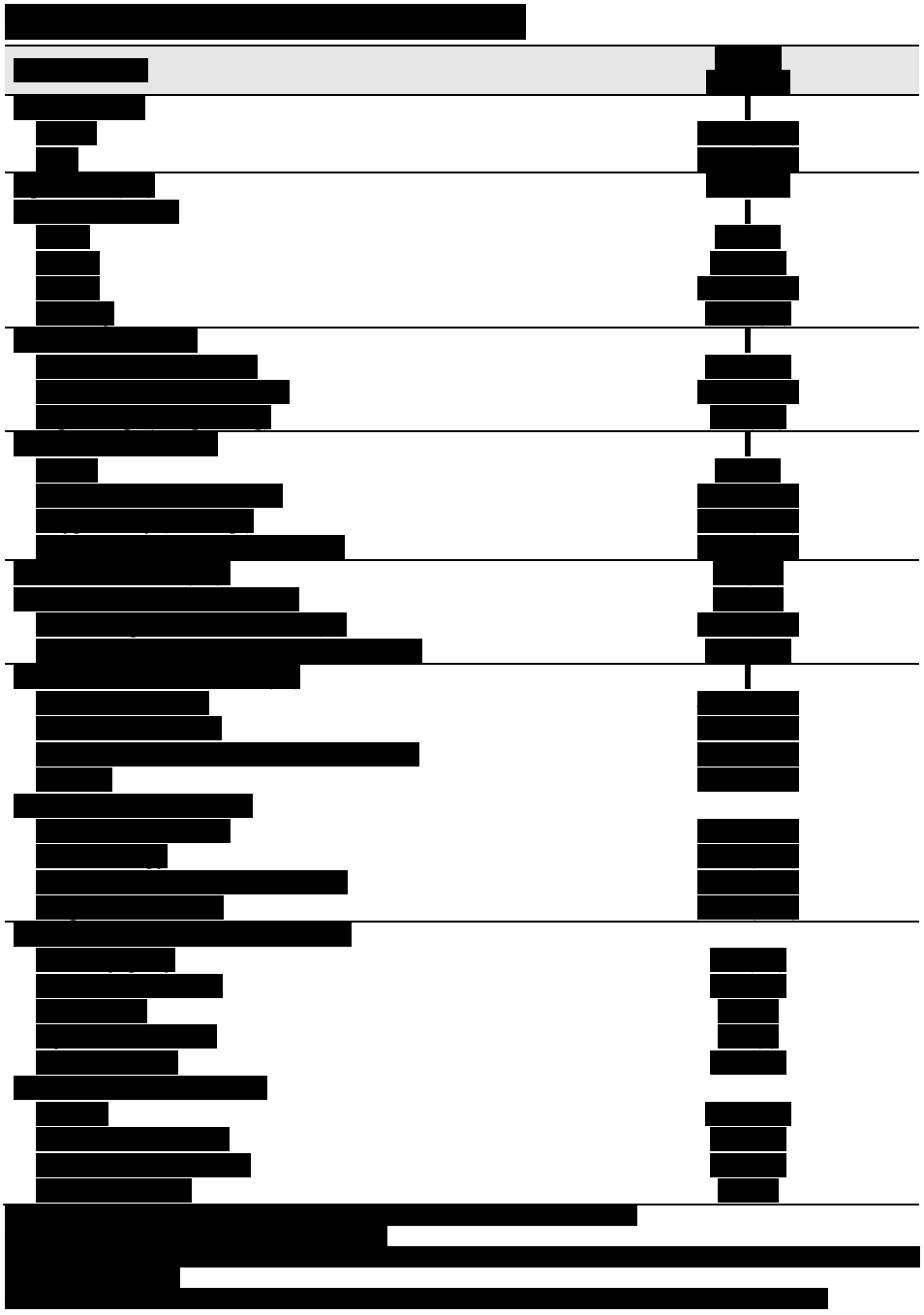

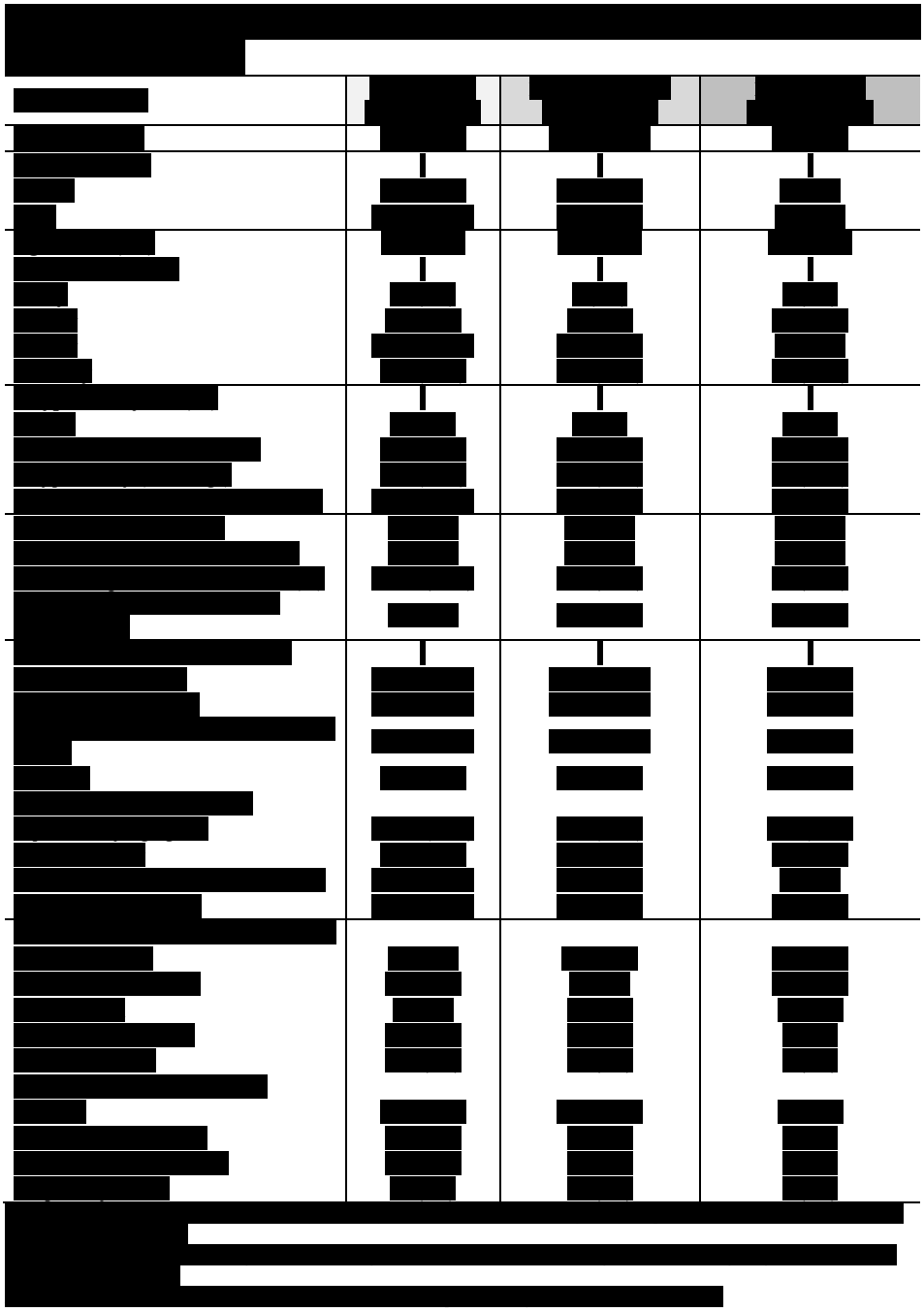

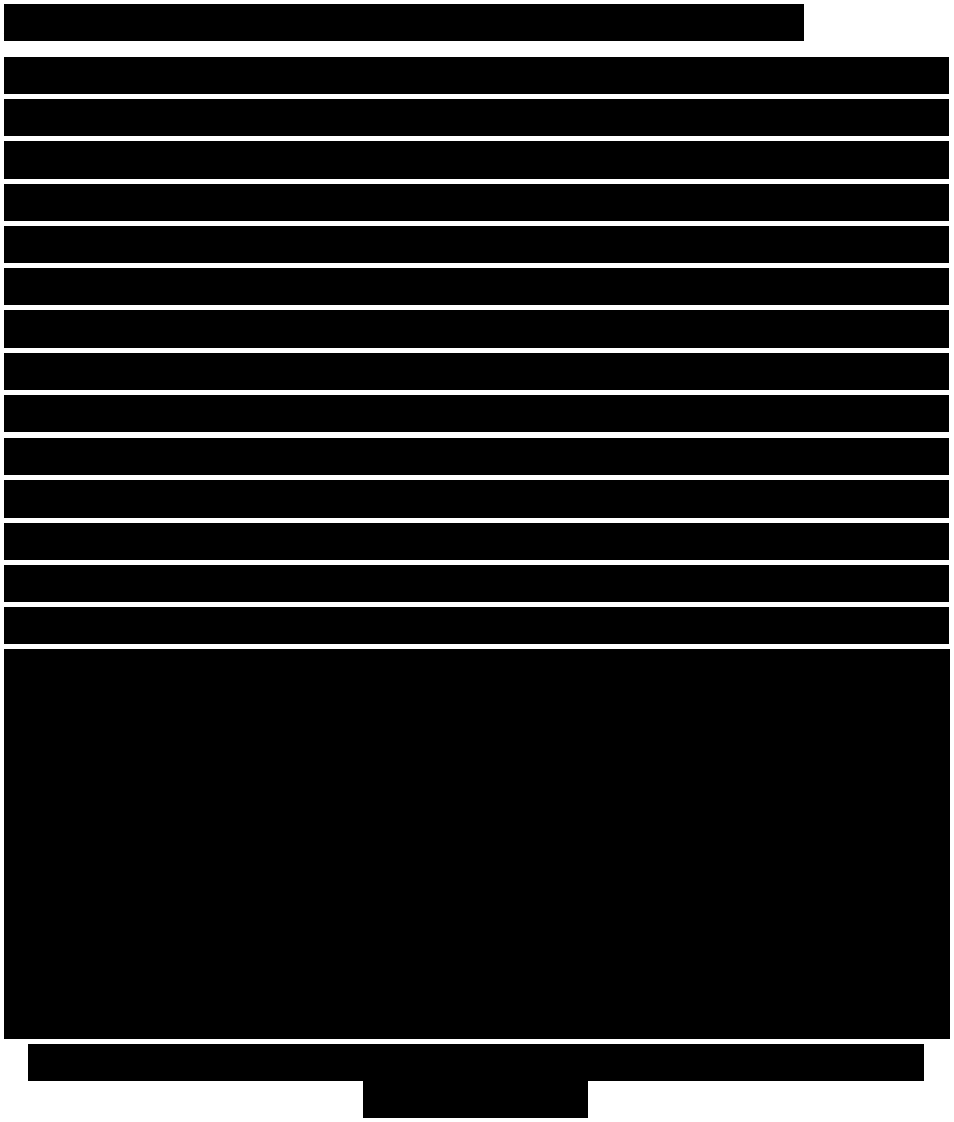

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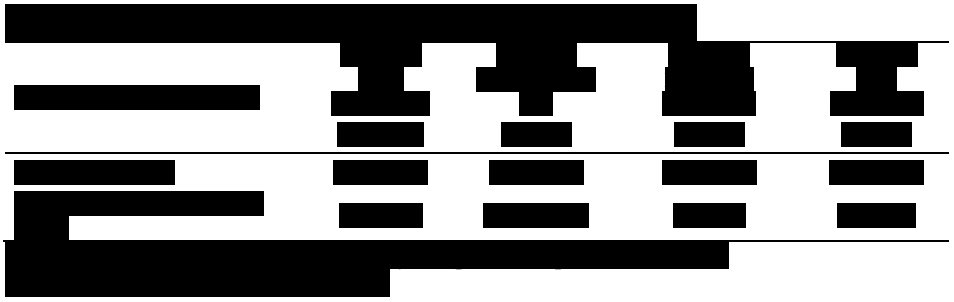

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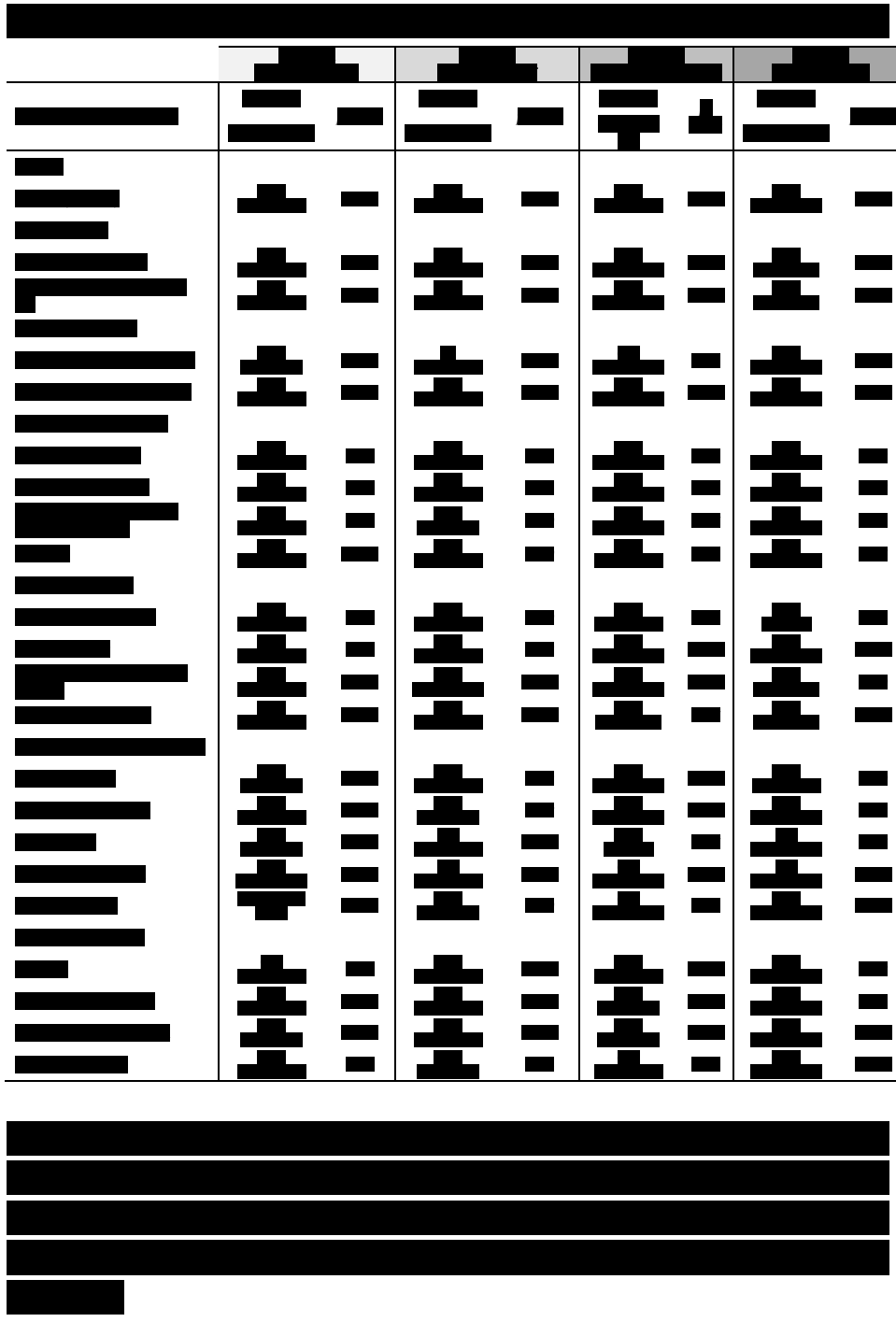

4.4.2 Adherence trajectories during the first year of T2DM treatment: a population-based longitudinal study in the Netherlands.

ii) Second phase of testing and validation instead consisted in applying the algorithm among different health related databases across EU.

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patients into adherence trajectories based on patterns of oral antidiabetics (OADs) prescriptions in the year following therapy initiation.

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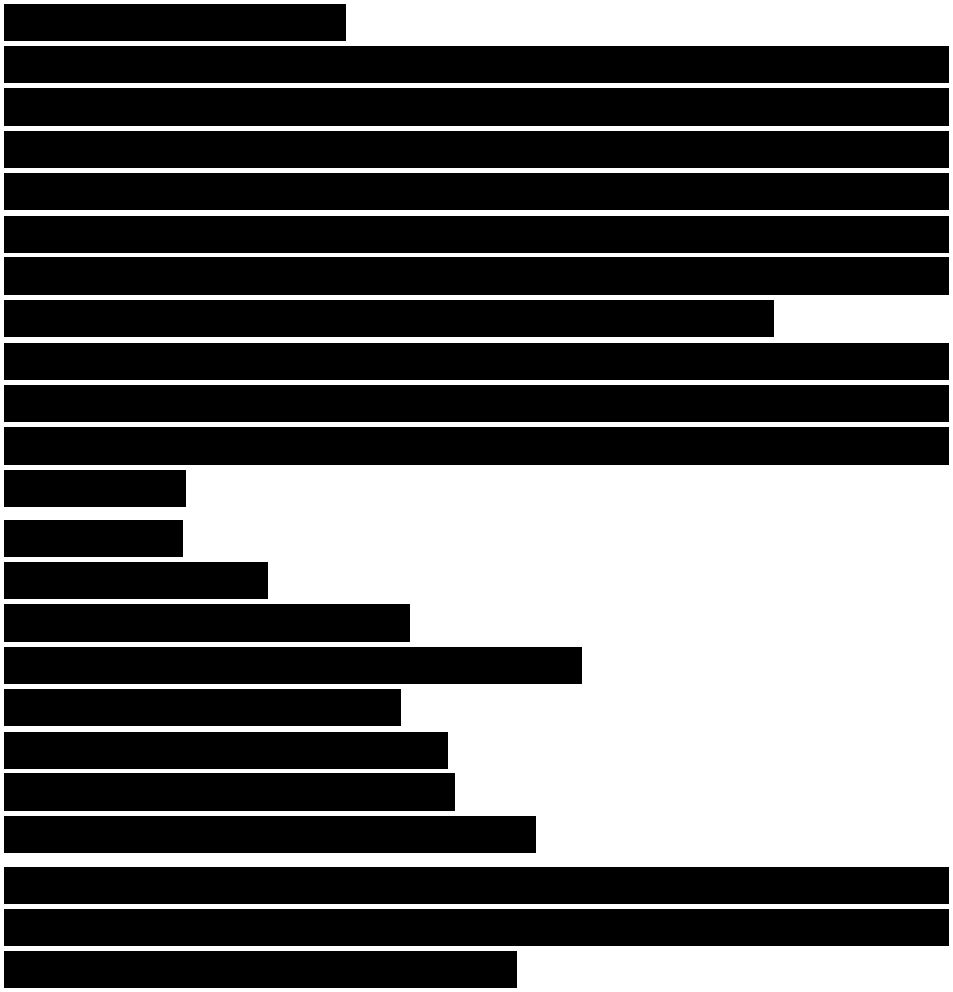

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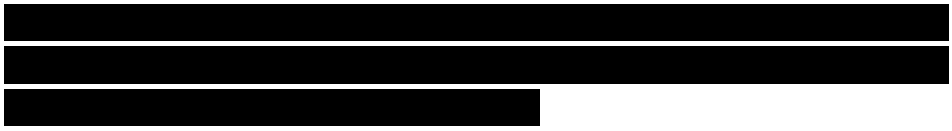

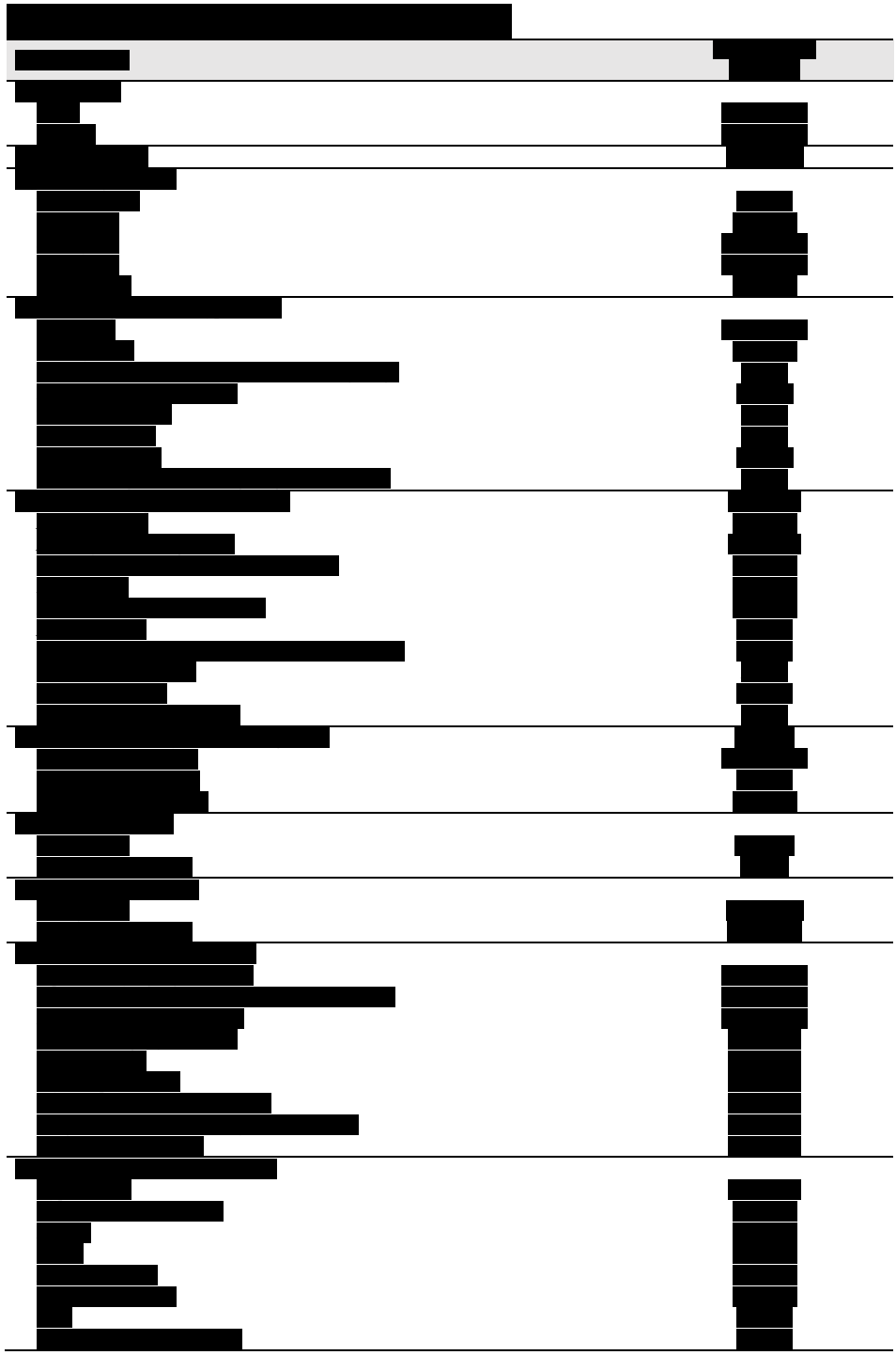

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patients into adherence trajectories based on patterns of oral antidiabetics (OADs) prescriptions in the year following therapy initiation.

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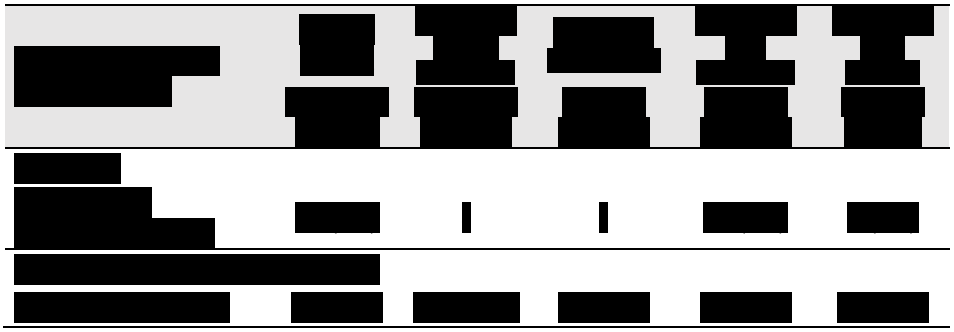

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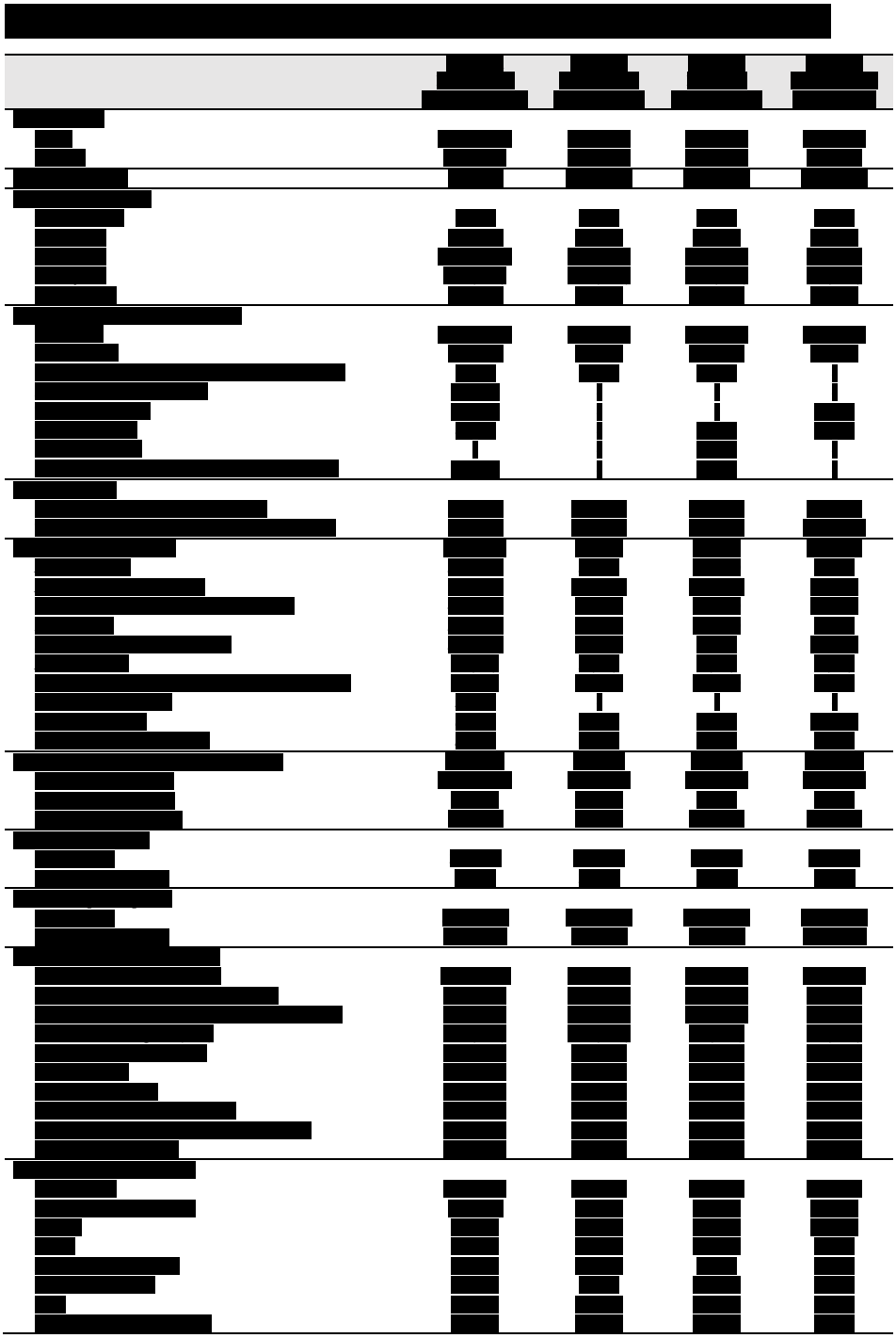

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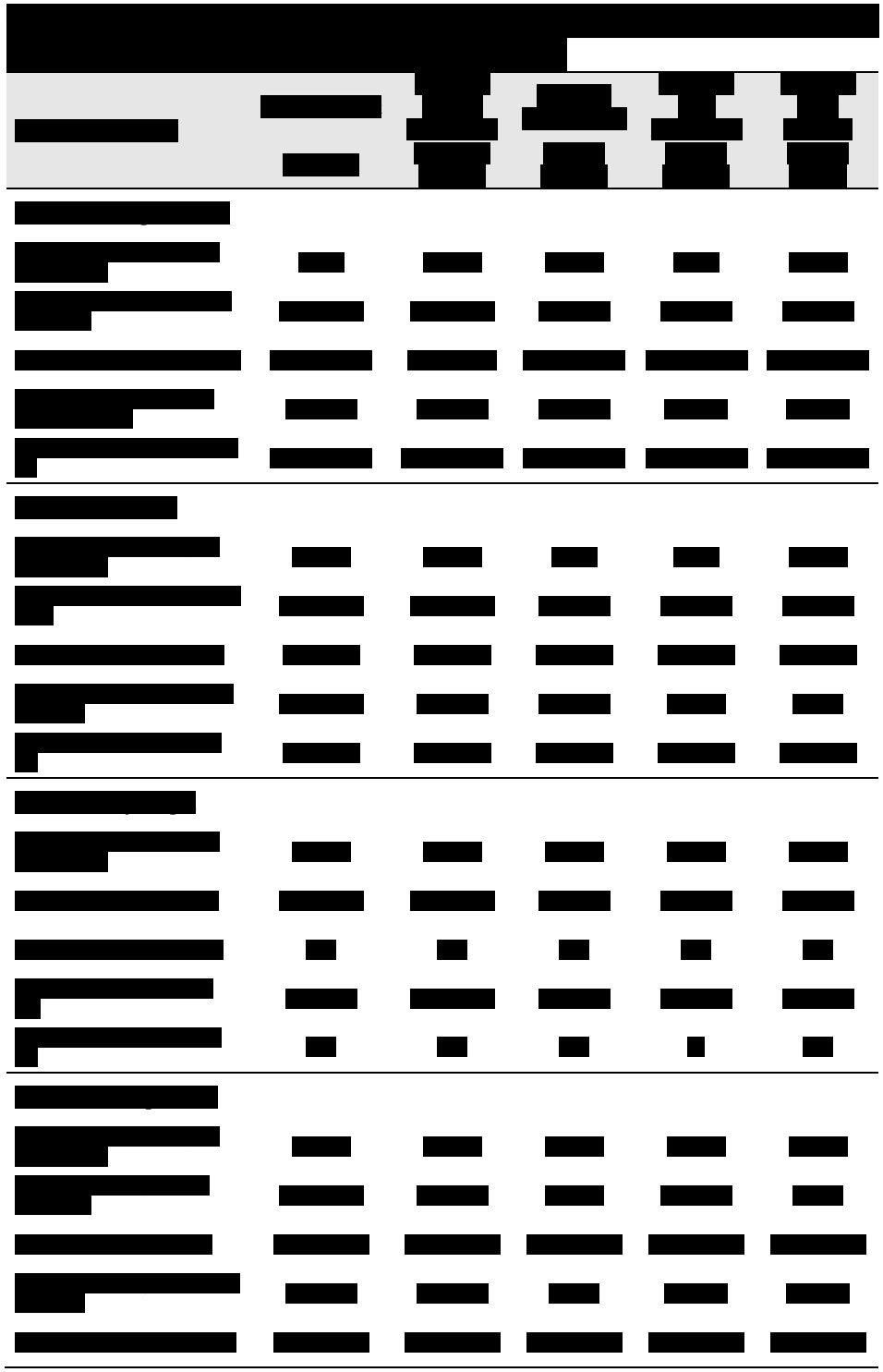

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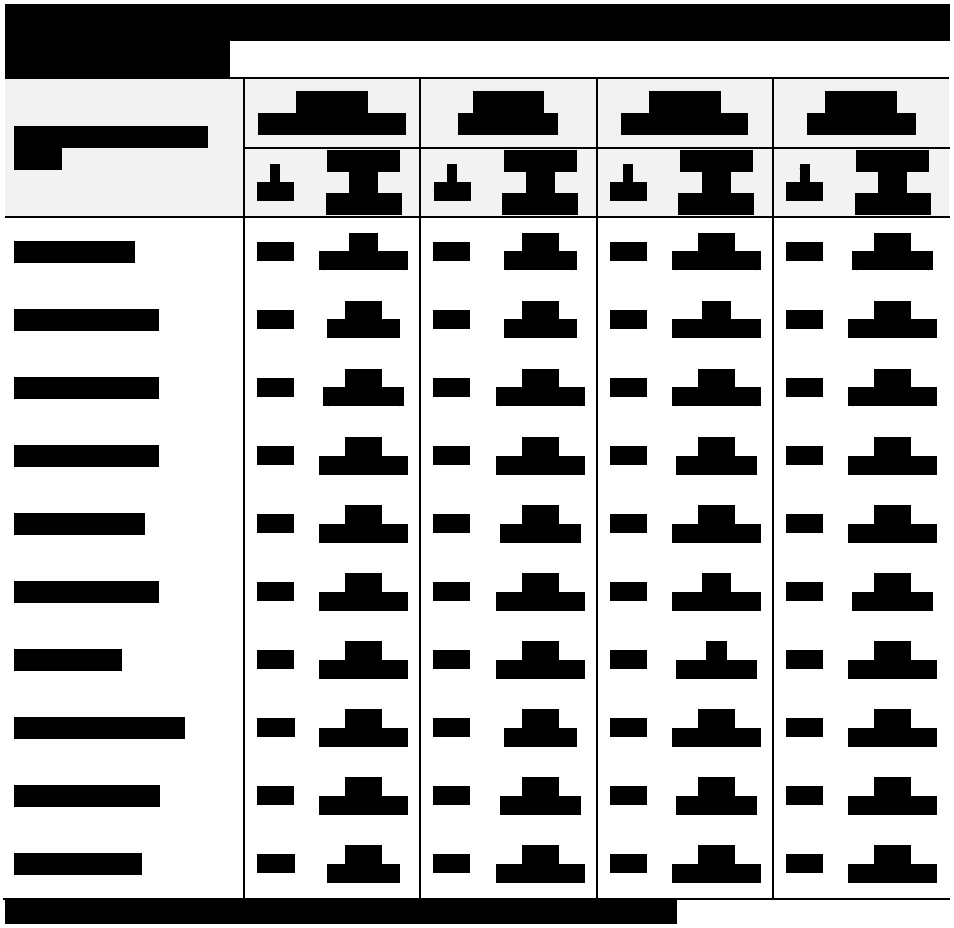

AI Algorithm final remarks

Investigating the adherence dynamics over time in a real world population reflected the adherence behavior of patients more accurately than summarizing adherence as a single average measure over time. Studying medication adherence phenomenon on selected chronic populations, such as patients diagnosed with diabetes and heart failure, by using an already developed AI/ML algorithm allowed the identification of groups within a population that share similar medication adherence trajectories and behaviors over time using a new dynamic indicator, the CMA9, computed through the use of the AdhereR developed by Dima and colleagues. AdhereR was developed to facilitate flexible and comprehensive analyses of medication adherence from electronic health data. All objects included in the package (*compute.treatment.episodes*, CMA1 to CMA9 and their versions *CMA_per_episode* and *CMA_sliding_window*) were developed to be adapted to different research questions and designs depending on the type of medication, the study population, and the length of follow-up. The application, adaptation and implementation on two databases of different origins, administrative and clinical, and in different population settings, Italy and The Netherlands, of an AI/ML algorithm used various alternative parameterizations leading to the identification of longitudinal adherence trajectories.

Medication adherence was estimated under three conditions: per observation window (assuming persistence), within each treatment episode (accounting for persistence), and for consecutive sliding windows (with or without overlaps). This was carried out both in the implementation phase on the population of subjects with heart failure treated with sac/val and in the testing and validation phase in the population with T2DM treated with OADs.

The first implementation phase, designed and conducted in the population with heart failure treated with sac/val, demonstrated the applicability of the algorithm on real-world data from administrative databases. The results showed the different characteristics of subjects belonging to different adherence groups, confirming the association of determinants of specific adherence behavior. The determinants of belonging to a low medication adherence behavior were related to high rates of polypharmacy

and multimorbidity regimen as the frequency of previous hospitalization/s in the case of patients with heart failure.

The second testing and validation phase, designed and conducted in the population with T2DM treated with OADs, confirmed the findings described above. The validation phase was conducted on a clinical database allowing a further evaluation, namely the association between adherence levels and clinical outcomes in chronic patients. Findings on the population with T2DM founded that the clinical monitoring parameters of diabetic patients, such as glycated hemoglobin and LDL levels, reached normal levels by the end of follow-up are in the groups with high medication adherence.

The results of the computerization of an AI algorithm for the assessment of adherence to drug therapies in populations with chronic conditions both revealed: i) on the one hand the complex challenge of clustering subjects with similar adherence trajectories in choosing the correct number of adherence clusters that may influence the assessment of predictive factors for belonging to one adherence cluster (behavior) rather than another; ii) on the other hand the identification of the correlation between clinical complexity of chronic patients, intended as multimorbidity and polypharmacy regimens, was identified and confirmed over time.

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General Considerations

This PhD Project is based on the assumption that medication adherence is a key factor associated with the effectiveness of all pharmacological therapies but is particularly critical for medications used for chronic conditions.

From findings and assumptions of this dissertation, medication adherence represents a complex and multifaceted process, and its understanding and improvement are an urgent imperative in the present and future health care landscape. A gold standard in terminology and measurements are essentials to fully understand the medication adherence phenomenon in whole and to enable a reproducible process during measurements and an unique communication in real clinical practice. To reach this aim, an unambiguous and univocal communication is necessary. Ineffective communication between health care professionals and chronically ill patients could further compromise the patients' understanding of their disease, influencing their adherence behavior leading to potential complications too. To respond to this need, the ABC Taxonomy first proposed from Vrijens et al in 2012 aimed to promote consistency and quantification of the terms used to describe adherence. Hence, in a research perspective, medication adherence should be evaluated as a multifaceted process composed of three different phases over time, which may totally or partially fail because of late initiation or non-initiation (initiation), suboptimal pursuance and perdurance (implementation and persistence, respectively) or early interruption (discontinuation) of a certain drug treatment. Thanks to its growing interest in scientific research and to its implications for improving medication adherence in the daily practice, the ABC Taxonomy may be considered a promising and useful model to conceptualize and study medication adherence.

This dissertation also explored the challenges in the lack of a standard for measuring adherence as an indicator of quality of care. Hence, measuring quality of care in disease management has become an increasingly important part of health care evaluation and improvement. In this scenario, measuring performance indicators such as medication adherence allow policy priorities to be made explicit, responsibilities/expectations to be defined, accountability to be facilitated, and resources to be focused. Albeit this, medication adherence as healthcare quality indicator can be difficult to operationalize due to its nature as quantitative measure of

quality, and, quality is a multidimensional construct based on numerous, sometimes conflicting, approaches.

In this scenario, this dissertation has explored and faced challenges in medication adherence research and its relation with patient complexity in terms of multimorbidity and polypharmacy by implementing an innovative drug-utilization models to measure medication adherence based on ML/AI principals.

Main findings of this thesis address all the developments and discoveries observed to date regarding the measurement of medication adherence through indirect methods, namely the use of Big Data. For about two decades, DU methods have been used to assess levels of adherence to drug therapies prescribed by such methods, but such measurements have always been much debated as they are sometimes discordant and based on dichotomous principles (adherent/non-adherent) that are not fully applicable to real-world clinical practice settings. Therefore, this thesis project implemented methods based on longitudinal calculation of medication adherence by exploiting the crasis between: DU research, ML/AI models (Data science applications) and medication adherence to major chronic diseases. Such joining tract between disciplines has enabled the implementation of a recently developed open source algorithm for medication adherence analysis, which, when applied to administrative health databases, ensures a measurement and visualization of all adherence profiles of patients treated with specific drug therapies throughout the entire pharmacological treatment period. This algorithm was implemented by characterizing patients with similar medication adherence estimates and evaluating their baseline and clinical characteristics as potential determinants of nonadherence. Therefore, the results of this dissertation show that the complexity of chronic patients with multimorbidity and polypharmacy strongly affects medication adherence levels by negatively impacting clinical and economic outcomes.

On the other hand, analyzing the limitations of such research, from the data analysis perspective, evaluation of refill adherence using administrative databases is prone to methodological pitfalls, affecting the resulting adherence values. Hence, pitfalls to be taken into account are differences in the definition of medication adherence and refill adherence measures, Handling missing, incorrect or duplicate records and linkage of different

data sources as well as data selection for analysis. Efforts have been undertaken to alleviate problems by a systematization of terminology, definitions, and guidelines as well as computation examples of refill adherence.

Therefore, these findings address the problem of inconsistencies in medication adherence assessment through data analysis, focusing, promoting and implementing the new frontiers in medication adherence research based on harmonization adherence definitions and measurements.

In conclusion, medication nonadherence is a complex problem rooted in a multitude of interconnected factors some of them modifiable and predictable upstream. Future studies are needed to understand the underlying complexity and guide future interventions in real clinical practice. Future research in the field should be based on more comprehensive models that include not only patient-related factors but also provider-, prescribing-, and system-related factors. Accordingly, given the emerging digitization of the health care systems and the increased demand for Real World Evidence, administrative databases, as a cost-effective resource for information on medication adherence, serve a key role as indicators of quality of care, opening up new avenues for improving clinical outcomes through targeted interventions and the resulting reduction in health care costs and utilization.

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Appendix of Chapter *4.1*

Supplementary Table 1. **Criteria for the assessment of the Charlson Comorbidity Index (CCI) overall value**

Comorbid condition	ICD-9 codes	Weight
Ischemic heart disease	410, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 412	1
Congestive heart failure	398.91, 402.01, 402.11,402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428.0, 428.1, 428.9	1
Peripheral vascular disease	093.0, 437.3, 440.0, 440.1, 440.2, 440.3, 440.8, 440.9, 441.0, 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, 441.9, 443.1, 443.8, 443.9, 557.1, 557.9, V43.4	1
Cerebrovascular disease	362.34, 430, 431, 432, 432.0, 432.1, 432.9, 433, 433.0, 433.1, 433.2, 433.3, 433.8, 433.9, 434, 434.0, 434.1, 434.9, 435, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438, 438.0, 438.1, 438.2, 438.3, 438.4, 438.5, 438.8, 438.9	1
Dementia	290.0, 290.1, 290.2, 290.3, 290.4, 290.8, 290.9, 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.9, 294.1, 331.2	1
Chronic pulmonary disease	416.8, 416.9, 490, 491, 491.0, 491.1, 491.2, 491.8, 491.9, 492.0, 492.8, 493.0, 493.1, 493.2, 493.9, 494.0, 494.1, 495.0, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8, 495.9, 496, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8	1
Rheumatologic disease	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 714.0, 714.1, 714.2, 714.8, 725	1
Peptic ulcer disease	531.0, 531.1, 531.2, 531.3, 531.4, 531.5, 531.6, 531.7, 531.9, 532.0, 532.1, 532.2, 532.3, 532.4, 532.5, 532.6, 532.7, 532.9, 533.0, 533.1, 533.2, 533.3, 533.4, 533.5, 533.6, 533.7, 533.9, 534.0, 534.3, 534.4, 534.5, 534.6, 534.7, 534.9	1
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9, 573.3, 573.4, 573.8, 573.9, V42.7	1
Diabetes mild to moderate	250.0, 250.1, 250.2, 250.3, 250.8, 250.9	1

Comorbid condition	ICD-9 codes	Weight
Diabetes with chronic complications	250.4, 250.5, 250.6, 250.7	2
Hemiplegia or paraplegia	334.1, 342.0, 342.1, 342.8, 342.9, 343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 344.0, 344.1, 344.2, 344.3, 344.4, 344.5, 344.6, 344.9	2
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.0, 582.1, 582.2, 582.4, 582.8, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 585, 586, 588.0, V42.0, V45.1, V56.0, V56.1, V56.2, V56.3, V56.8	2
Any malignancy, including lymphoma and leukemia	140.0, 140.1, 140.3, 140.4, 140.5, 140.6, 140.8, 140.9, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.0, 147.1, 147.2, 147.3, 147.8, 147.9, 148.0, 148.1, 148.2, 148.3, 148.8, 148.9, 149.0, 149.1, 149.8, 149.9, 150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9, 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 152.0, 152.1, 152.2, 152.3, 152.8, 152.9, 153.0, 153.1, 153.2, 153.3, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 154.2, 154.3, 154.8, 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 156.8, 156.9, 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 158.0, 158.8, 158.9, 159.0, 159.1, 159.8, 159.9, 160.0, 160.1, 160.2, 160.3, 160.4, 160.5, 160.8, 160.9, 161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 163.0, 163.1, 163.8, 163.9, 164.0, 164.1, 164.2, 164.3, 164.8, 164.9, 165.0, 165.8, 165.9, 170.0, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.8, 171.0, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172.0, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 176.0, 176.1, 176.2, 176.3, 176.4, 176.5, 176.8, 176.9, 180.0, 180.1, 180.8, 180.9, 182.0, 182.1, 182.8, 183.0, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9, 184.0, 184.1, 184.2, 184.3, 184.4, 184.8, 184.9, 186.0, 186.9, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187.9, 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 189.0, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9, 190.0, 190.1, 190.2, 190.3, 190.4, 190.5, 190.6, 190.7, 190.8, 190.9, 191.0, 200.0, 200.1, 200.2, 200.8, 201.0, 201.1, 201.2, 201.4, 201.5, 201.6, 201.7, 201.9, 202.0, 202.1, 202.2, 202.3, 202.4, 202.5, 202.6, 202.8, 202.9, 203.0, 203.1, 204.0, 204.1, 204.2, 204.8, 204.9, 205.0, 205.1, 205.2, 205.3, 205.8, 205.9, 206.0, 206.1, 206.2, 206.8, 206.9, 207.0, 207.1, 207.2, 207.8, 208.0, 208.1, 208.2, 208.8, 208.9, 238.6	2

Comorbid condition	ICD-9 codes	Weight
Moderate or severe liver disease	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8	3
Metastatic solid tumor	196.0, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197.0, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198.0, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.8, 199.0, 199.1	6
AIDS	0.42	6

Supplementary Table 2. **Criteria for the identification of chronic diseases using administrative health-related databases.**

ID		ICD-9 CM code	ATC code
	Infectious and parasitic diseases		
1	HIV infection	042.x-044.x	J01FA09, J05AF01, J05AR01, J05AR04, J05AR05, J05AF02, J05AF03, J05AE01, J05AE08, J05AF11, J05AG01, J05AG02, J05AG03, J05AR06, J05AX07, P01CX01, P01AX06
2	Tuberculosis	010.x - 018.x	J04AB
	Neoplasms		
3	Neoplasms	140.x-165.x, 170.x-176.x, 179.x-199.x, 200.x-208-x	L01, L03AC, L02BA01, L02BA02, L02BG02, L02BG03, L02BG04, L02BG06, L02BB01, L02BB03, L02AE02, L02AE04, L02AB01
	Endocrine, nutritional and metabolic diseases, and immunity disorders		
4	Thyroid disorders	240.x-246.x, 252.1, 252.0	H03A, H03B
5	Diabetes	250.x	A10
6	Hyperlipidaemia	272.2, 272.4	C10
7	Obesity	278.0x	-
8	Weight loss	260-263.x	-
9	Disorders of fluid, electrolyte, and acid-base balance	276.x	-
10	Hyperuricemia/Gout	274.x	M04AC01, M04AA, M04AB

ID		ICD-9 CM code	ATC code
11	Disorders involving the immune mechanisms	279.x	-
	Diseases of the blood and blood-forming organs		
12	Coagulation defects	286.x	B02B
13	Anaemias	280.x-285.x	B03A, B03B, B03XA01, L03AA
	Mental disorders		
14	Dementia / Alzheimer	290.x, 331.0x	N06DA, N06DX01
15	Psychosis	295.x, 296.1x-298.x	N05AD, N05AA, N05AB, N05AC, N05AX, N05AE, N05AF, N05AG N05AH, N05AL
16	Depression	300.4, 301.12, 309.0x, 309.1x, 311.x	N06A
17	Bipolar disorders	296.0x	N05AN01
18	Anxiety	300.0x	N05BA, N05BB01, N05CD, N05BC01, N05BC51, N05BX, N05CF, N05CX01, N06BX
19	Alcohol abuse	291.1, 291.2, 291.5, 291.8x, 291.9, 303.9, 305.0x, V11.3x	N07BB01
20	Drug addiction	292.0x, 292.82-292.89, 292.9x, 304.x, 305.2x305.9x	N07BB04

ID		ICD-9 CM code	ATC code
	Diseases of the nervous system and sense organs		
21	Parkinson's disease	332.x	N04
22	Multiple sclerosis	340	L03AB07, L03AB08, L04AA23, L04AA27, L03AX13, L04AA31, L04AA34, L03AB13, L04AX07
23	Epilepsy	345.x	N03AA, N03AB02, N03AB05, N03AB52, N03AX, N03AB01, N03AB04, N03AB54, N03AC01, N03AC02, N03AC03, N03AD01, N03AD02, N03AD03, N03AD51, N03AE01, N03AF01, N03AF02, N03AG01, N03AG02, N03AG03, N03AG04, N03AG05, N03AG06, N03AF03, N03AF04
24	Glaucoma	365.x	S01E
	Diseases of the circulatory system		
25	Ischaemic Heart Disease/Angina	410.x – 414	C01DA, C01DX
26	Heart failure	428.x, 402.11, 402.91	C01AA, C01BA93, C01BA02, C01BA01, C01BA51, C01BA71, C01DA, C03CA01
27	Arrhythmia	426.x, 427.x, 785.0x,	C01BC, C01BD, C01BA, C07AA07
28	Valvular diseases	093.20-093.24, 394.0x-397.1x, 424.00-424.91, 746.3x-746.6x	-
29	Vascular diseases	440.x, 441.2, 441.4, 441.7, 441.9, 443.1x-443.9x, 447.1, 557.1x, 557.9x, 785.4x	-

ID		ICD-9 CM code	ATC code
30	Cerebrovascular diseases	430.x-438.x	-
31	Hypertension	401.x-405.x	C03AA, C03AB, C03AH, C03AX01, C02CA04, C03BA02, C03BA03, C03BA04, C03BA05, C03BA07, C03BA08, C03BA09, C03BA10, C03BA11, C03DB01, C03DB02, C03EA, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA08, C09BA09, C09BB, C09DB, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C02AB01, C02AB02, C02AC01, C02AC02, C02AC04, C02AC05, C02DB02, C02DB03, C02DB04, C02DC01, C02DD01, C02DG01, C02KA01, C02KB01, C02KC01, C02KD01, C02KX01, C09XA
	Diseases of the respiratory system		
32	Chronic Obstructive Pulmonary Disease	490-492.x, 494.x, 496	R03AA, R03AB, R03AC, R03DA, R03DB, R03DA20, R01AC01, R03BC01, R01AC51, S01GX01, S01GX51, R03BA
33	Asthma	493.x	
34	Cystic Fibrosis	277.0	R05CB, R05FB01, R05FA01, A09AA02, R07AX02, R07AX30, R07AX31
	Diseases of the digestive system		
35	Liver cirrhosis and other liver chronic diseases	571.x, 573.x	J05AP08, J05AP09, J05AP51, J05AP53, J05AP54, J05AP55, J05AP56, J05AP57, B05AA01
36	Inflammatory bowel diseases	555.x-556.x	A07EC01, A07EC02, A07EC03, A07EC04
37	Chronic and acute pancreatitis	577.0-577.1	-

ID		ICD-9 CM code	ATC code
	Diseases of the genitourinary system		
37	Kidney disease without dialysis	582.x, 583.0, 583.1, 583.4, 583.7, 583.8, 584.6, 585.x, 586.x, 588.x	V03AE
39	Kidney dialysis with dialysis	V45.1, V56.x	-
	Diseases of the skin and subcutaneous tissues		
40	No rheumatoid psoriasis	696.1	D05BB01, D05BB02, D05AX
	Diseases of the musculoskeletal system and connective tissue		
41	Rheumatologic conditions (rheumatic fever, rheumatoid arthritis, Felty's syndrome, juvenile chronic polyarthritis, inflammatory spondylopathies, polymyalgia rheumatica)	390.x, 391.x, 699.0, 714.0x, 714.1, 714.3, 714.9x, 720.0x-720.9x, 725.x	M01BA, M01CB, P01BA02
42	Anchylosing spondylitis	720.0	-
43	Systemic sclerosis	710.1x	-
44	Systemic lupus erythematosus	710.0x	-

ID		ICD-9 CM code	ATC code
Other conditions			
45	Transplantation	V42	L04AA01, L04AA02, L04AA03, L04AA04, L04AA05, L04AA06, L04AA08, L04AA09, L04AA10, L04AA11, L04AA12, L04AA14, L04AA15, L04AA16, L04AA17, L04AA18, L04AA19, L04AA21, L04AD01, L04AD02, L04AX01
46	Chronic pain	338.2, 338.4	N02A
47	Inflammation, not elsewhere specified	-	M01A

Appendix of Chapter 4.2

Supplementary material of Paper *4.2.1:* Italian translation and validation of the original ABC Taxonomy for Medication Adherence

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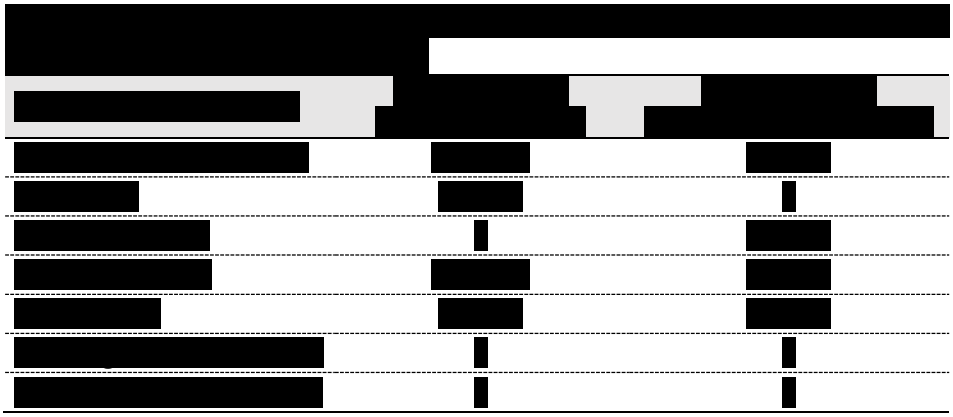

Supplementary material of Paper *4.2.2:* Treatment patterns and medication adherence among newly diagnosed patients with migraine: a drug utilization study

Supplementary Table 1. List of study drugs

Migraine treatment	ATC code	Active substance	Redeemability	Route of Administration	DDD
Treatment with acute medications					
Specific acute treatment					
Triptans	N02CC01	Sumatriptan	A	oral, parenteral	50 mg/6 mg
	N02CC03	Zolmitriptan	A	oral	2.5 mg
	N02CC04	Rizatriptan	A	oral	10 mg
	N02CC05	Almotriptan	A	oral	12.5 mg
	N02CC06	Eletriptan	A	oral	40 mg
	N02CC07	Frovatriptan	A	oral	2.5 mg
Non-specific acute treatment					
Opioids	N02AX02	Tramadol	A	oral, parenteral, rectal	0.3 g
	N02AJ06	Codeine + Paracetamol	A	oral	30 mg/0.5 g
NSAIDs	M01AB05	Diclofenac	A	oral, parenteral, rectal	0.1 g
	M01AE09	Flurbiprofen	A	oral, rectal	0.2 g
	M01AE01	Ibuprofen	A	oral, parenteral, rectal	1.2 g
	M01AB01	Indometacin	A	oral, parenteral, rectal	0.1 g
	M01AE03	Ketoprofen	A	oral, parenteral, rectal	0.15 g
	M01AB15	Ketorolac	A	oral, parenteral	30 mg
	M01AE02	Naproxen	A	oral, rectal	0.5 g
	M01AX17	Nimesulide	A	oral	0.2 g
	M01AC01	Piroxicam	A	oral, parenteral, rectal	20 mg
	N02BA01	Aspirin	A	parenteral	1 g
Propulsives	A03FA01	Metoclopramide	A	oral, parenteral	30 mg
Antiemetics	A04AA01	Ondansetron	A/H	oral, parenteral, rectal	16 mg
Treatment with prophylactic medications					
Specific prophylactic treatment					
Antiserotoninergic	N02CX01	Pizotifen	A	oral	1.5 mg
Non-specific prophylactic treatment					
Beta-blockers	C07AB02	Metoprolol	A/H	oral, parenteral	0.15 g
	C07AA05	Propranolol	A	oral, parenteral	0.16 g
Antidepressants	N06AA09	Amitriptyline	A	oral, parenteral	75 mg
	N06AX11	Mirtazapine	A	oral	30 mg
Antiepileptics	N03AX11	Topiramate	A	oral	0.3 g
Other anticonvulsants	N03AG01	Valproic Acid	A/H	oral, parenteral	1.5 g
	N03AX09	Lamotrigine	A	oral	0.3 g

Abbreviations: ATC, Anatomical Therapeutic Chemical; DDD, Definited Daily Doses; NSAIDs, Nonsteroidal anti-inflammatory drugs.

Supplementary Table 2. Algorithms used for the identification of comorbidities

Comorbidities	ICD-9 code
Autoimmune disease	420.0, 424.91, 517.8, 583.81, 710.0, 340, 357.1, 359.6, 714.0-714.2, 714.81, 714.89, 714.9, 720.0, 555, 569, 556, 560, 569, 694.3, 696.0, 696.1, 390, 391.0- 391.2, 391.8, 391.9
Chronic kidney disease	250.41, 250.40, 582, 583, 590.00-590.01, 583.89, 583.81, 585-587, 753.12-753.15
Chronic obstructive pulmonary disease (COPD)	490-493, 496
Diabetes	249-250, 648, 362
Hypertension	401-405, 437.2
Liver disease	571.0, 571.2, 573.3, 571.40, 571.41, 571.49, 571.5, 571.6, 571.9, 571.8, 070.32, 070.33, 070.54, 070.59, 456.0, 456.1, 456.20, 456.21
Obesity	278.1, 278.00- 278.03

Supplementary Table 3. Algorithms used for the identification of comedications

Comedications	ATC code
Anticonvulsants	N03 except N03AX11, N03AG01, N03AX09
Antidepressants	N06A except N06AA09, N06AX11
Beta-blockers	C07 except C07AB02, C07AA05
Cardiovascular medications	C01-C10
Drugs for respiratory system	R01-R03

Appendix of Chapter 4.3

Supplementary material of *4.3.1:* Developing and piloting a communication assessment tool assessing patient perspectives on communication with pharmacists (CAT-Pharm)

Supplementary Table 1 Short description of modifications from CAT to CAT-Pharm Italian version

Section/Item	Harmonized Italian Version		Refined Italian Version		Final Italian version	
Title	**Discussion**	**Consensus**	**Discussion**	**Consensus**	**Discussion**	**Consensus**
Items' numeration was changed in adapting the CAT to pharmacists' context according to a logical temporal sequence						
Instruction	Phisician	*Changed to* Pharmacist				
CAT Item 3	"Ha mostrato interesse per le mie idee sulla mia salute"	*Changed to* "Ha mostrato interesse per le mie idee sulla terapia prescritta"				
CAT Item 5	"Mi ha prestato attenzione (mi ha guardato, mi ha ascoltato con attenzione)"	*Eliminated*				
CAT Item 11	"Mi ha coinvolto nelle decisioni sulla mia salute nella misura da me desiderata"	*Eliminated*				
CAT Item 13	"Ha mostrato attenzione e interesse"	*Eliminated*				
CAT-Pharm Item 5		*New* "Mi ha dato informazioni su come seguire la terapia prescritta dal medico"	"Mi ha dato informazioni su come seguire la terapia prescritta dal medico"	*Changed to* "Mi ha spiegato come seguire correttamente lo schema terapeutico prescritto dal medico"		

Section/Item	Harmonized Italian Version		Refined Italian Version		Final Italian version	
Title	**Discussion**	**Consensus**	**Discussion**	**Consensus**	**Discussion**	**Consensus**
CAT-Pharm Item 13		*New* "Mi ha chiesto se ero in grado di seguire correttamente la terapia prescritta dal medico"	"Mi ha chiesto se ero in grado di seguire correttamente la terapia prescritta dal medico"	*Changed to* "Mi ha chiesto se ero in grado di seguire correttamente lo schema terapeutico prescritto dal medico"		
CAT-Pharm Item 11		*New* "Ha discusso con me come gestire gli eventuali effetti collaterali provocati dalla terapia"			"Ha discusso con me come gestire gli eventuali effetti collaterali provocati dalla terapia"	*Changed to* "Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia"
CAT-Pharm Item 12			"Ha discusso sulle prossime cose da fare, incluso eventuali programmi di esami e visite di controllo"	*Changed to* "Ha discusso degli interventi futuri, incluso eventuali programmi di esami e visite di controllo"		
CAT-Pharm Item 15		*New* "Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci e alimenti"				

Supplementary Table 2 Short description of modifications - English version

Section/Item	Reconciled English Version		Back Translation Review		Harmonized English Version		Refined English Version		Final English version	
Title	**Discussion**	**Consensus**	**Discussion**	**Consensus**	**Discussion**	**Consensus**	**Discussion**	**Consensus**	**Discussion**	**Consensus**
CAT-Pharm Item 12							Discussed with me how to correctly follow the prescribed therapy	*Changed to* Explained how to correctly follow the prescribed therapy		
CAT-Pharm Item 13	Asked me if I am able to follow the prescribed therapy	*Changed to* Asked about my ability to follow the prescribed therapy								
CAT-Pharm Item 11					Discussed about side effects of the prescribed therapy and how to manage them	*Changed to* Discussed how to manage any side effects of the prescribed therapy				
Demographic Question 1	Age	*Changed to* How old are you?								
Demographic Question 2	Gender	*Changed to* Whati is your gender?								
Demographic Question 4	Nationality	*Changed to* How would you describe your race or ethnicity?								

Supplementary Figure 1 Italian CAT-Pharm

Appendix
Ownerships: the questionnaire as well as its translation, adaptations, computer programs, and scoring of the CAT are intellectual property of Gregory Makoul, Gregory Makoul, PhD, MS
Director, Connecticut Institute for Primary Care Innovation, Hartford, CT, USA
Professor of Medicine, University of Connecticut School of Medicine, Farmington, CT, USA and can be obtained through a license agreement with the Developer/Owner

Nome del Farmacista:

Strumento di Valutazione della Comunicazione

La comunicazione con i pazienti è una componente molto importante della qualità dell'assistenza sanitaria. Gradiremmo conoscere le sue impressioni sul modo con cui il suo farmacista comunica con lei. **Le sue risposte sono del tutto confidenziali, per cui Le saremo grati se sarà il più possibile sincero ed obiettivo**.
La sua partecipazione è volontaria e non influirà in alcun modo sull'assistenza sanitaria.

Per favore dia un punteggio al modo di comunicare del suo farmacista.
Segni con una X la sua risposta per ciascuna domanda mostrata di seguito.
Grazie molto

Il Farmacista…	**Scarso**	**Sufficiente**	**Buono**	**Molto Buono**	**Eccellente**
1. Mi ha accolto in un modo che mi ha fatto sentire a mio agio	1	2	3	4	5
2. Mi ha trattato con rispetto	1	2	3	4	5
3. Ha mostrato interesse per le mie idee sulla terapia prescritta	1	2	3	4	5
4. Ha capito le mie principali preoccupazioni di salute	1	2	3	4	5
5. Mi ha spiegato come seguire correttamente lo schema terapeutico prescritto dal medico	1	2	3	4	5
6. Mi ha lasciato parlare senza interrompermi	1	2	3	4	5
7. Mi ha fornito tutte le informazioni che volevo	1	2	3	4	5
8. Ha verificato che avessi capito ogni cosa	1	2	3	4	5
9. Ha parlato con parole per me facili da capire	1	2	3	4	5
10. Mi ha incoraggiato a fare domande	1	2	3	4	5
11. Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia	1	2	3	4	5
12. Ha discusso degli interventi futuri incluso eventuali esami e visite di controllo	1	2	3	4	5
13. Mi ha chiesto se ero in grado di seguire correttamente lo schema terapeutico prescritto dal medico	1	2	3	4	5
14. Mi ha dedicato il giusto tempo	1	2	3	4	5
15. Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci e alimenti	1	2	3	4	5

Commenti:

****

Queste informazioni servono per scopi statistici e rimarranno anonime. Per favore segni una sola risposta per ogni domanda.

1. Età ____

2. Sesso
   ☐1 Maschio
   ☐2 Femmina

3. Ha mai avuto contatti con questo farmacista prima? ☐1 No
   ☐2 Si, ma solo una volta
   ☐3 Si, più di una volta

4. Nazionalità:
   ☐1 Italiana
   ☐2 Non Italiana

5. Oggi era lei il paziente?
   ☐1 Si
   ☐2 No, ho accompagnato il paziente

Grazie

Supplementary Figure 2 English CAT-Pharm

Pharmacist's Name:

Communication Assessment Tool

Communication with patients is a very important part of health care. We would like to know how you feel about the way your pharmacist communicated with you. **Your answers are completely confidential, so please be as open and honest as you can**.

Your participation is completely voluntary and will not affect your medical treatment in any way.

Please rate the pharmacist's communication about your prescribed medication therapy. Mark your answer for each item below. Thank you very much.

The pharmacist…	Poor	Fair	Good	Very Good	Excellent
1. Greeted me in a way that made me feel comfortable	1	2	3	4	5
2. Treated me with respect	1	2	3	4	5
3. Showed interest in my ideas about the prescribed therapy	1	2	3	4	5
4. Understood my main health concerns	1	2	3	4	5
5. Explained how to correctly follow the prescribed therapy	1	2	3	4	5
6. Let me talk without interruptions	1	2	3	4	5
7. Gave me as much information as I wanted	1	2	3	4	5
8. Talked in terms I could understand					
9. Checked to be sure I understood everything	1	2	3	4	5
10. Encouraged me to ask questions	1	2	3	4	5
11. Discussed how to manage any side effects of the prescribed therapy	1	2	3	4	5
12. Discussed next steps, including any follow-up plans	1	2	3	4	5
13. Asked about my ability to follow the prescribed therapy	1	2	3	4	5
14. Spent the right amount of time with me	1	2	3	4	5
15. Discussed possible interactions of the prescribed therapy with other medicines or foods	1	2	3	4	5

Comments:

****

This set of questions about the patient is for statistical purposes. Your own responses are completely confidential. Please mark one answer for each question.

1. How old are you?
   - ☐1 24 or younger
   - ☐2 25-44
   - ☐3 45-64
   - ☐4 65-84
   - ☐5 85 or older

2. What is your gender?
   - ☐1 Male
   - ☐2 Female
   - ☐3 Other _____

3. Have you seen this pharmacist before?
   - ☐1 No
   - ☐2 Yes, but only once
   - ☐3 Yes, more than once

4. How would you describe your race or ethnicity?
   - ☐1 Caucasian
   - ☐2 African
   - ☐3 African-American
   - ☐4 Hispanic or Latino
   - ☐5 Aasian
   - ☐6 Other _____

5. Were you the patient today?
   - ☐1 Yes
   - ☐2 No, I was with the patient today

Thank you very much.

Supplementary material of *4.3.2:* Adaptation of communication assessment tool for community pharmacists in medication adherence and minor diseases management

Supplementary Figure 1a CAT-Pharm-Community TEST Adherence to therapy version

Strumento di Valutazione della Comunicazione
ADERENZA ALLA TERAPIA

La comunicazione con i pazienti è una componente molto importante della qualità dell'assistenza sanitaria. Gradiremmo conoscere le sue impressioni sul modo con cui il farmacista ha comunicato con lei. Le sue risposte sono del tutto confidenziali, per cui Le saremo grati se sarà il più possibile sincero ed obiettivo.
La sua partecipazione è volontaria e non influirà in alcun modo sull'assistenza sanitaria.
Per favore dia un punteggio al modo di comunicare del suo farmacista.
Segni con una X la sua risposta per ciascuna domanda mostrata di seguito.
Grazie molto

Il farmacista…	Scarso	Sufficiente	Buono	Molto Buono	Eccellente
1. Mi ha accolto in un modo che mi ha fatto sentire a mio agio	1	2	3	4	5
2. Mi ha trattato con rispetto	1	2	3	4	5
3. Ha capito le mie principali preoccupazioni di salute	1	2	3	4	5
4. Mi ha lasciato parlare senza interrompermi	1	2	3	4	5
5. Ha mostrato interesse per le mie idee sulla terapia prescritta	1	2	3	4	5
6. Mi ha spiegato come seguire correttamente lo schema terapeutico prescritto dal medico	1	2	3	4	5
7. Mi ha chiesto se ero in grado di seguire correttamente lo schema terapeutico prescritto dal medico	1	2	3	4	5
8. Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia	1	2	3	4	5
9. Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci, integratori e alimenti	1	2	3	4	5
10. Mi ha fornito tutte le informazioni che volevo	1	2	3	4	5
11. Ha parlato con parole per me facili da capire	1	2	3	4	5
12. Ha verificato che avessi capito ogni cosa	1	2	3	4	5
13. Mi ha incoraggiato a fare domande	1	2	3	4	5
14. Ha discusso degli interventi futuri incluso eventuali esami e visite di controllo	1	2	3	4	5
15. Mi ha dedicato il giusto tempo	1	2	3	4	5
16. Mi ha parlato mettendomi in condizioni di rispettare la mia privacy	1	2	3	4	5

Commenti:
_____
_____

****

Queste informazioni servono per scopi statistici e rimarranno anonime.
Per favore segni una sola risposta per ogni domanda.

Sesso:
- ☐ M
- ☐ F

Età: _____

Titolo di studio:
- ☐ Nessun titolo
- ☐ Scuola elementare
- ☐ Scuola media
- ☐ Scuola superiore
- ☐ Laurea specialistica

Professione:
- ☐ Occupato/a
- ☐ Disoccupato/a
- ☐ Casalinga/o
- ☐ Pensionato
- ☐ Studente
- ☐ Altro

Stato civile:
- ☐ Single
- ☐ Coniugato/a
- ☐ Divorziato/a
- ☐ Vedovo/a

Ha mai visto prima il Farmacista?
- ☐ No
- ☐ Si, ma solo una volta
- ☐ Si, più di una volta

Supplementary Figure 1b CAT-Pharm-Community TEST Minor disease management version

Strumento di Valutazione della Comunicazione
GESTIONE MINOR DISEASE

La comunicazione con i pazienti è una componente molto importante della qualità dell'assistenza sanitaria. Gradiremmo conoscere le sue impressioni sul modo con cui il farmacista ha comunicato con lei. Le sue risposte sono del tutto confidenziali, per cui Le saremo grati se sarà il più possibile sincero ed obiettivo.
La sua partecipazione è volontaria e non influirà in alcun modo sull'assistenza sanitaria.
Per favore dia un punteggio al modo di comunicare del suo farmacista.
Segni con una X la sua risposta per ciascuna domanda mostrata di seguito.
Grazie molto

Il farmacista...	Scarso	Sufficiente	Buono	Molto Buono	Eccellente
1. Mi ha accolto in un modo che mi ha fatto sentire a mio agio	1	2	3	4	5
2. Mi ha trattato con rispetto	1	2	3	4	5
3. Mi ha rivolto delle domande specifiche sulla mia problematica	1	2	3	4	5
4. Mi ha lasciato parlare senza interrompermi	1	2	3	4	5
5. Mi ha chiesto se avessi consultato il medico per questo problema o assunto qualche farmaco prima della consulenza	1	2	3	4	5
6. Mi ha fornito una terapia e dei consigli mirati alla mia problematica	1	2	3	4	5
7. Mi ha spiegato come seguire correttamente lo schema terapeutico indicatomi	1	2	3	4	5
8. Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia	1	2	3	4	5
9. Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci, integratori e alimenti	1	2	3	4	5
10. Mi ha fornito tutte le informazioni che volevo	1	2	3	4	5
11. Ha parlato con parole per me facili da capire	1	2	3	4	5
12. Ha verificato che avessi capito ogni cosa	1	2	3	4	5
13. Mi ha incoraggiato a fare domande	1	2	3	4	5
14. Mi ha incoraggiato a ritornare per verificare la risoluzione del mio problema	1	2	3	4	5
15. Mi ha dedicato il giusto tempo	1	2	3	4	5
16. Mi ha parlato mettendomi in condizioni di rispettare la mia privacy	1	2	3	4	5

Commenti:
_____
_____.
****

Queste informazioni servono per scopi statistici e rimarranno anonime.
Per favore segni una sola risposta per ogni domanda.

Sesso:
□ M
□ F

Età: _____

Titolo di studio:
□ Nessun titolo
□ Scuola elementare
□ Scuola media
□ Scuola superiore
□ Laurea specialistica

Professione:
□ Occupato/a
□ Disoccupato/a
□ Casalinga/o
□ Pensionato
□ Studente
□ Altro

Stato civile:
□ Single
□ Coniugato/a
□ Divorziato/a
□ Vedovo/a

Ha mai visto prima il Farmacista?
□ No
□ Si, ma solo una volta
□ Si, più di una volta

Supplementary Figure 2a CAT-Pharm-Community QUEST Adherence to therapy version

Strumento di Valutazione della Comunicazione
ADERENZA ALLA TERAPIA

Indichi quanto ritiene siano importanti queste domande per valutare la qualità della comunicazione del farmacista.
Segni con una X la sua risposta per ciascuna domanda mostrata di seguito. Grazie molto

Il farmacista…	Molto Importante	Importante	Poco Importante	Non Importante
1. Mi ha accolto in un modo che mi ha fatto sentire a mio agio				
2. Mi ha trattato con rispetto				
3. Ha capito le mie principali preoccupazioni di salute				
4. Mi ha lasciato parlare senza interrompermi				
5. Ha mostrato interesse per le mie idee sulla terapia prescritta				
6. Mi ha spiegato come seguire correttamente lo schema terapeutico prescritto dal medico				
7. Mi ha chiesto se ero in grado di seguire correttamente lo schema terapeutico prescritto dal medico				
8. Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia				
9. Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci, integratori e alimenti				
10. Mi ha fornito tutte le informazioni che volevo				
11. Ha parlato con parole per me facili da capire				
12. Ha verificato che avessi capito ogni cosa				
13. Mi ha incoraggiato a fare domande				
14. Ha discusso degli interventi futuri incluso eventuali esami e visite di controllo				
15. Mi ha dedicato il giusto tempo				
16. Mi ha parlato mettendomi in condizioni di rispettare la mia privacy				

Per favore indichi se sono state omesse domande importanti ai fini della valutazione della qualità della comunicazione del farmacista

Commenti:

Supplementary Figure 2b CAT-Pharm-Community QUEST Minor disease management version

Strumento di Valutazione della Comunicazione

GESTIONE MINOR DISEASE

Indichi quanto ritiene siano importanti queste domande per valutare la qualità della comunicazione del farmacista.
Segni con una X la sua risposta per ciascuna domanda mostrata di seguito.
Grazie molto

Il farmacista…	Molto Importante	Importante	Poco Importante	Non Importante
1. Mi ha accolto in un modo che mi ha fatto sentire a mio agio				
2. Mi ha trattato con rispetto				
3. Mi ha rivolto delle domande specifiche sulla mia problematica				
4. Mi ha lasciato parlare senza interrompermi				
5. Mi ha chiesto se avessi consultato il medico per questo problema o assunto qualche farmaco prima della consulenza				
6. Mi ha fornito una terapia e dei consigli mirati alla mia problematica				
7. Mi ha spiegato come seguire correttamente lo schema terapeutico indicatomi				
8. Ha discusso con me come gestire gli eventuali effetti indesiderati provocati dalla terapia				
9. Ha discusso con me delle possibili interazioni della terapia prescritta con altri farmaci, integratori e alimenti				
10. Mi ha fornito tutte le informazioni che volevo				
11. Ha parlato con parole per me facili da capire				
12. Ha verificato che avessi capito ogni cosa				
13. Mi ha incoraggiato a fare domande				
14. Mi ha incoraggiato a ritornare per verificare la risoluzione del mio problema				
15. Mi ha dedicato il giusto tempo				
16. Mi ha parlato mettendomi in condizioni di rispettare la mia privacy				

Per favore indichi se sono state omesse domande importanti ai fini della valutazione della qualità della comunicazione del farmacista

Commenti:

Supplementary Figure 3 Pharmacist characteristics

CARATTERISTICHE DEL FARMACISTA

La prego di compilare il seguente questionario, indicando con una X le risposte corrette. Le informazioni che fornirà saranno totalmente confidenziali e usate solo per gli scopi della ricerca. Grazie per la collaborazione.

Sesso:

☐ M
☐ F

Età: _____

Anni dalla laurea:

☐ Meno di 5
☐ 5-10
☐ 11-20
☐ 21-30
☐ Più di 30

Titolo di studio:

☐ Laurea
☐ Specializzazione
☐ Dottorato di ricerca

Contesto della Farmacia in cui lavora:

☐ Farmacia urbana
☐ Farmacia rurale
☐ Farmacia sub-urbana

Numero di consultazioni al giorno in Farmacia*:

☐ <= 25
☐ Tra 26 e 49
☐ >=50

*(1) consultazioni/dispensazioni secondo dati federfarma 2016: ogni giorno circa 800.000 italiani si recano in farmacia per una **consulenza con il farmacista** (4 mln al giorno di pazienti che entrano in farmacia). Le farmacie sul territorio italiano sono circa 18.500. Dividendo il numero le 18.500 farmacie vuol dire 43 consulenze al giorno di media. Mediamente una farmacia è costituita da circa due farmacisti che vi operano. Pertanto mediamente un farmacista dovrebbe erogare almeno 25 consulenze al giorno. Possiamo così ipotizzare che <= 25 consulenze rientri in un numero basso di consulenze. Tra le 26 e 49 rientri nella media (se consideriamo che alcune farmacie sono costituite da un solo farmacista) più di 50 consulenze lo consideriamo come un numero elevato di consulenze per singolo farmacista.

1. Federfarma. La Farmacia Italiana 2016 [Internet]. 2016. Available from: https://www.federfarma.it/Documenti/farmaci_italiana2016.aspx

Supplemental table S4.1. CAT-Pharm Community Test – Adherence to Therapy version – Pearson's correlation (N°=67)

CAT-Pharm-community Test Adherence to Therapy Items		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16
Item 1	**Pearson correlation**	1	.583**	.515**	.415**	.372**	.286*	.340**	.274*	.289*	.592**	.334**	.661**	.305*	.307*	.416**	.340**
	Two-tailed significance		0.000	0.000	0.000	0.002	0.019	0.005	0.025	0.018	0.000	0.006	0.000	0.012	0.012	0.000	0.005
Item 2	**Pearson correlation**	.583**	1	.316**	.358**	.284*	0.090	0.167	0.003	-0.012	0.200	.278*	.283*	0.076	-0.003	.283*	.285*
	Two-tailed significance	0.000		0.009	0.003	0.020	0.467	0.177	0.978	0.924	0.106	0.023	0.020	0.543	0.983	0.020	0.019
Item 3	**Pearson correlation**	.515**	.316**	1	.307*	.564**	.515**	.636**	.374**	0.220	.445**	.279*	.506**	.459**	.439**	.291*	.274*
	Two-tailed significance	0.000	0.009		0.011	0.000	0.000	0.000	0.002	0.074	0.000	0.022	0.000	0.000	0.000	0.017	0.025
Item 4	**Pearson correlation**	.415**	.358**	.307*	1	0.211	.309*	.287*	-0.142	-0.141	.245*	.499**	.342**	0.198	0.030	.295*	0.205
	Two-tailed significance	0.000	0.003	0.011		0.087	0.011	0.018	0.252	0.256	0.046	0.000	0.005	0.109	0.809	0.015	0.096
Item 5	**Pearson correlation**	.372**	.284*	.564**	0.211	1	.457**	.615**	.448**	.290*	.500**	0.149	.456**	.506**	.340**	.342**	0.180
	Two-tailed significance	0.002	0.020	0.000	0.087		0.000	0.000	0.000	0.017	0.000	0.227	0.000	0.000	0.005	0.005	0.145
Item 6	**Pearson correlation**	.286*	0.090	.515**	.309*	.457**	1	.717**	.391**	.266*	.370**	0.002	.300*	.304*	.267*	0.169	0.209
	Two-tailed significance	0.019	0.467	0.000	0.011	0.000		0.000	0.001	0.030	0.002	0.990	0.014	0.012	0.029	0.171	0.090
Item 7	**Pearson correlation**	.340**	0.167	.636**	.287*	.615**	.717**	1	.350**	0.185	.384**	0.066	.353**	.451**	.343**	0.232	0.153
	Two-tailed significance	0.005	0.177	0.000	0.018	0.000	0.000		0.004	0.133	0.001	0.594	0.003	0.000	0.005	0.059	0.217
Item 8	**Pearson correlation**	.274*	0.003	.374**	-0.142	.448**	.391**	.350**	1	.764**	.490**	-0.052	.349**	.430**	.544**	.378**	0.172
	Two-tailed significance	0.025	0.978	0.002	0.252	0.000	0.001	0.004		0.000	0.000	0.678	0.004	0.000	0.000	0.002	0.164
Item 9	**Pearson correlation**	.289*	-0.012	0.220	-0.141	.290*	.266*	0.185	.764**	1	.480**	0.053	.342**	.453**	.586**	.394**	.360**
	Two-tailed significance	0.018	0.924	0.074	0.256	0.017	0.030	0.133	0.000		0.000	0.672	0.005	0.000	0.000	0.001	0.003
Item 10	**Pearson correlation**	.592**	0.200	.445**	.245*	.500**	.370**	.384**	.490**	.480**	1	.318**	.797**	.396**	.337**	.628**	.372**
	Two-tailed significance	0.000	0.106	0.000	0.046	0.000	0.002	0.001	0.000	0.000		0.009	0.000	0.001	0.005	0.000	0.002
Item 11	**Pearson correlation**	.334**	.278*	.279*	.499**	0.149	0.002	0.066	-0.052	0.053	.318**	1	.457**	.289*	0.226	.457**	.313**
	Two-tailed significance	0.006	0.023	0.022	0.000	0.227	0.990	0.594	0.678	0.672	0.009		0.000	0.018	0.066	0.000	0.010
Item 12	**Pearson correlation**	.661**	.283*	.506**	.342**	.456**	.300*	.353**	.349**	.342**	.797**	.457**	1	.416**	.347**	.635**	.333**
	Two-tailed significance	0.000	0.020	0.000	0.005	0.000	0.014	0.003	0.004	0.005	0.000	0.000		0.000	0.004	0.000	0.006
Item 13	**Pearson correlation**	.305*	0.076	.459**	0.198	.506**	.304*	.451**	.430**	.453**	.396**	.289*	.416**	1	.561**	.471**	0.204
	Two-tailed significance	0.012	0.543	0.000	0.109	0.000	0.012	0.000	0.000	0.000	0.001	0.018	0.000		0.000	0.000	0.097
Item 14	**Pearson correlation**	.307*	-0.003	.439**	0.030	.340**	.267*	.343**	.544**	.586**	.337**	0.226	.347**	.561**	1	.435**	0.150
	Two-tailed significance	0.012	0.983	0.000	0.809	0.005	0.029	0.005	0.000	0.000	0.005	0.066	0.004	0.000		0.000	0.226
Item 15	**Pearson correlation**	.416**	.283*	.291*	.295*	.342**	0.169	0.232	.378**	.394**	.628**	.457**	.635**	.471**	.435**	1	.333**
	Two-tailed significance	0.000	0.020	0.017	0.015	0.005	0.171	0.059	0.002	0.001	0.000	0.000	0.000	0.000	0.000		0.006
Item 16	**Pearson correlation**	.340**	.285*	.274*	0.205	0.180	0.209	0.153	0.172	.360**	.372**	.313**	.333**	0.204	0.150	.333**	1
	Two-tailed significance	0.005	0.019	0.025	0.096	0.145	0.090	0.217	0.164	0.003	0.002	0.010	0.006	0.097	0.226	0.006	

** Correlation is significant at the 0.01 level (two-tailed); * Correlation is significant at the 0.05 level (two-tailed); ° Total sample interviewed with CAT-Pharm-community Test Adherence to Therapy version

Supplemental table S4.2. CAT-Pharm Community Test – Adherence to Therapy version – Confirmatory factor analysis (N*=67)

CAT-Pharm-community Test Adherence to Therapy version Items		**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Item 1	Greeted me in a way that made me feel comfortable	**0.748**	0.303	0.227	0.143
Item 2	Treated me with respect	**0.738**	0.164	0.114	-0.230
Item 3	Understood my main health concerns	**0.282**	0.712	0.230	0.179
Item 4	Let me talk without interruptions	**0.297**	0.340	0.620	-0.330
Item 5	Showed interest in my ideas about the prescribed therapy	**0.228**	0.682	0.116	0.279
Item 6	Explained how to correctly follow the prescribed therapy	0.124	**0.812**	-0.065	0.135
Item 7	Asked about my ability to follow the prescribed therapy	0.075	**0.896**	0.076	0.125
Item 8	Discussed how to manage any side effect of the prescribed therapy	0.155	**0.319**	-0.186	0.803
Item 9	Discussed possible interactions of the prescribed therapy with other drugs or foods	0.220	**0.075**	-0.093	0.872
Item 10	Gave me as much information as I wanted	0.563	**0.276**	0.241	0.494
Item 11	Talked in terms I could understand	0.264	-0.042	**0.837**	0.028
Item 12	Checked to be sure I understood everything	0.566	0.258	**0.433**	0.365
Item 13	Encouraged me to ask questions	-0.052	0.420	**0.461**	0.539
Item 14	Discussed next steps, including any follow-up plans	-0.070	0.282	0.308	**0.703**
Item 15	Spent the right amount of time with me	0.392	0.056	0.538	**0.490**
Item 16	Respected my privacy	0.603	0.017	0.098	**0.223**
Explained Variance (%)		*16.556*	*19.877*	*13.254*	*19.910*
Cumulative Variance (%)		*56.344*	*39.787*	*69.597*	*19.910*
KMO		*0.818*			
χ2 (df)		*583.141 (120)*			
p-value		*<0.01*			

*Total sample interviewed with CAT-Pharm-community Test Adherence to Therapy version
Abbreviations: df, Degrees of freedom; KMO, Kaiser-Meyer-Olkin.
Notes: Extraction method: Principal component analysis; Rotation method: Oblimin with Kaiser normalisation.

Supplemental table S4.3. CAT-Pharm Community Test – Minor Disease version – Pearson's correlation (N° = 65)

CAT-Pharm-community Test Minor Disease item		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16
Item 1	Pearson correlation	1	.739**	.406**	.334**	0.224	0.160	.349**	0.195	0.186	.372**	.320**	.396**	.263*	0.242	.413**	.482**
	Two-tailed significance		0.000	0.001	0.006	0.073	0.202	0.004	0.120	0.137	0.002	0.009	0.001	0.034	0.052	0.001	0.000
Item 2	Pearson correlation	.739**	1	.425**	.436**	.304*	.322**	.371**	0.116	0.142	.463**	.317*	.338**	0.230	.335**	.422**	.480**
	Two-tailed significance	0.000		0.000	0.000	0.014	0.009	0.002	0.357	0.259	0.000	0.010	0.006	0.065	0.006	0.000	0.000
Item 3	Pearson correlation	.406**	.425**	1	.541**	.592**	.499**	.273*	.365**	.495**	.397**	0.023	0.078	.485**	.338**	0.237	0.241
	Two-tailed significance	0.001	0.000		0.000	0.000	0.000	0.028	0.003	0.000	0.001	0.857	0.539	0.000	0.006	0.058	0.053
Item 4	Pearson correlation	.334**	.436**	.541**	1	.343**	.443**	.247*	0.117	0.082	.656**	0.227	.302*	0.241	.431**	.468**	.279*
	Two-tailed significance	0.006	0.000	0.000		0.005	0.000	0.047	0.352	0.517	0.000	0.070	0.015	0.054	0.000	0.000	0.024
Item 5	Pearson correlation	0.224	.304*	.592**	.343**	1	.573**	.318**	.373**	.467**	.462**	0.144	0.147	.489**	.346**	.292*	.300*
	Two-tailed significance	0.073	0.014	0.000	0.005		0.000	0.010	0.002	0.000	0.000	0.252	0.242	0.000	0.005	0.018	0.015
Item 6	Pearson correlation	0.160	.322**	.499**	.443**	.573**	1	.477**	.294*	.274*	.474**	0.170	.268*	.494**	.305*	.548**	0.239
	Two-tailed significance	0.202	0.009	0.000	0.000	0.000		0.000	0.017	0.027	0.000	0.176	0.031	0.000	0.014	0.000	0.055
Item 7	Pearson correlation	.349**	.371**	.273*	.247*	.318**	.477**	1	.361**	0.180	.282*	.479**	.519**	.454**	.314*	.576**	.421**
	Two-tailed significance	0.004	0.002	0.028	0.047	0.010	0.000		0.003	0.152	0.023	0.000	0.000	0.000	0.011	0.000	0.000
Item8	Pearson correlation	0.195	0.116	.365**	0.117	.373**	.294*	.361**	1	.761**	0.197	-0.004	0.222	.543**	.318**	0.170	0.186
	Two-tailed significance	0.120	0.357	0.003	0.352	0.002	0.017	0.003		0.000	0.115	0.972	0.075	0.000	0.010	0.175	0.138
Item 9	Pearson correlation	0.186	0.142	.495**	0.082	.467**	.274*	0.180	.761**	1	.309*	-0.035	0.042	.502**	.424**	0.116	.287*
	Two-tailed significance	0.137	0.259	0.000	0.517	0.000	0.027	0.152	0.000		0.012	0.782	0.742	0.000	0.000	0.356	0.020
Item 10	Pearson correlation	.372**	.463**	.397**	.656**	.462**	.474**	.282*	0.197	.309*	1	.320**	.382**	.417**	.483**	.617**	.481**
	Two-tailed significance	0.002	0.000	0.001	0.000	0.000	0.000	0.023	0.115	0.012		0.009	0.002	0.001	0.000	0.000	0.000
Item 11	Pearson correlation	.320**	.317*	0.023	0.227	0.144	0.170	.479**	-0.004	-0.035	.320**	1	.590**	.266*	0.096	.477**	.359**
	Two-tailed significance	0.009	0.010	0.857	0.070	0.252	0.176	0.000	0.972	0.782	0.009		0.000	0.032	0.448	0.000	0.003
Item 12	Pearson correlation	.396**	.338**	0.078	.302*	0.147	.268*	.519**	0.222	0.042	.382**	.590**	1	.412**	0.176	.704**	.429**
	Two-tailed significance	0.001	0.006	0.539	0.015	0.242	0.031	0.000	0.075	0.742	0.002	0.000		0.001	0.162	0.000	0.000
Item 13	Pearson correlation	.263*	0.230	.485**	0.241	.489**	.494**	.454**	.543**	.502**	.417**	.266*	.412**	1	.474**	.415**	.247*
	Two-tailed significance	0.034	0.065	0.000	0.054	0.000	0.000	0.000	0.000	0.000	0.001	0.032	0.001		0.000	0.001	0.047
Item 14	Pearson correlation	0.242	.335**	.338**	.431**	.346**	.305*	.314*	.318**	.424**	.483**	0.096	0.176	.474**	1	.404**	.399**
	Two-tailed significance	0.052	0.006	0.006	0.000	0.005	0.014	0.011	0.010	0.000	0.000	0.448	0.162	0.000		0.001	0.001
Item 15	Pearson correlation	.413**	.422**	0.237	.468**	.292*	.548**	.576**	0.170	0.116	.617**	.477**	.704**	.415**	.404**	1	.485**
	Two-tailed significance	0.001	0.000	0.058	0.000	0.018	0.000	0.000	0.175	0.356	0.000	0.000	0.000	0.001	0.001		0.000
Item 16	Pearson correlation	.482**	.480**	0.241	.279*	.300*	0.239	.421**	0.186	.287*	.481**	.359**	.429**	.247*	.399**	.485**	1
	Two-tailed significance	0.000	0.000	0.053	0.024	0.015	0.055	0.000	0.138	0.020	0.000	0.003	0.000	0.047	0.001	0.000	

** Correlation is significant at the 0.01 level (two-tailed); * Correlation is significant at the 0.05 level (two-tailed); ° Total sample interviewed with CAT-Pharm-community Test Minor Disease version

Supplemental table S4.4. CAT-Pharm Community Test – Minor Disease version – Confirmatory factor analysis (N* = 65)

CAT-Pharm-community Test Minor Disease version Items		**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Item 1	Greeted me in a way that made me feel comfortable	**0.854**	0.112	0.228	0.122
Item 2	Treated me with respect	**0.798**	0.320	0.196	0.026
Item 3	Understood my main health concerns	**0.316**	0.641	-0.133	0.425
Item 4	Let me talk without interruptions	**0.291**	0.791	0.136	-0.102
Item 5	Asked if I had consulted the doctor about this problem or taken some medication before the consultation	**0.074**	0.615	0.068	0.464
Item 6	Gave me right therapy and advice for my problem	-0.108	**0.729**	0.318	0.260
Item 7	Explained how to correctly follow the prescribed therapy	0.140	**0.183**	0.697	0.309
Item 8	Discussed how to manage any side effect of the prescribed therapy	0.052	**0.048**	0.122	0.883
Item 9	Discussed possible interactions of the prescribed therapy with other drugs or foods	0.160	**0.150**	-0.085	0.884
Item 10	Gave me as much information as I wanted	0.318	**0.687**	0.300	0.093
Item 11	Talked in terms I could understand	0.209	0.037	**0.763**	-0.085
Item 12	Checked to be sure I understood everything	0.206	0.084	**0.844**	0.068
Item 13	Encouraged me to ask questions	-0.004	0.355	**0.389**	0.643
Item 14	Discussed next steps, including any follow-up plans	0.262	0.446	0.127	**0.375**
Item 15	Spent the right amount of time with me	0.202	0.450	0.733	**0.038**
Item 16	Respected my privacy	0.594	0.144	0.398	**0.193**
Explained Variance (%)		*16.556*	*14.154*	*19.677*	*18.664*
Cumulative Variance (%)		*56.344*	*69.735*	*19.677*	*38.341*
KMO		*0.750*			
χ2 (df)		*581.129 (120)*			
p-value		*<0.01*			

*Total sample interviewed with CAT-Pharm-community Test Minor Disease version
Abbreviations: df, Degrees of freedom; KMO, Kaiser-Meyer-Olkin.
Notes: Extraction method: Principal component analysis; Rotation method: Oblimin with Kaiser normalisation.

Supplemental table S4.5. Common Factors of CAT-Pharm Community Test – Adherence to Therapy and Minor Disease versions

FACTORS	CAT-Pharm-community TEST	
	Adherence to Therapy version	**Minor Disease Management version**
F1 *Understanding of patient clinical needs*	**item1** Greeted me in a way that made me feel comfortable	**item1** Greeted me in a way that made me feel comfortable
	item2 Treated me with respect	**item2** Treated me with respect
	item3 Understood my main health concerns	**item3** Understood my main health concerns
	item4 Let me talk without interruptions	**item4** Let me talk without interruptions
	item5 Showed interest in my ideas about the prescribed therapy	**item5** Asked if I had consulted the doctor about this problem or taken some medication before the consultation
F2 *Communication about therapy*	**item6** Explained how to correctly follow the prescribed therapy	**item6** Gave me right therapy and advice for my problem
	item7 Asked about my ability to follow the prescribed therapy	**item7** Explained how to correctly follow the prescribed therapy
	item8 Discussed how to manage any side effect of the prescribed therapy	**item8** Discussed how to manage any side effect of the prescribed therapy
	item9 Discussed possible interactions of the prescribed therapy with other drugs or foods	**item9** Discussed possible interactions of the prescribed therapy with other drugs or foods
	item10 Gave me as much information as I wanted	**item10** Gave me as much information as I wanted
F3 *Evaluate patient understanding*	**item11** Talked in terms I could understand	**item11** Talked in terms I could understand
	item12 Checked to be sure I understood everything	**item12** Checked to be sure I understood everything
	item13 Encouraged me to ask questions	**item13** Encouraged me to ask questions
F4 *Building a trust with patient*	**itme14** Discussed next steps, including any follow-up plans	**Item14** Discussed next steps, including any follow-up plans
	item15 Spent the right amount of time with me	**item15** Spent the right amount of time with me
	item16 Respected my privacy	**item16** Respected my privacy

Appendix of Chapter *4.4*

Supplementary material 1. Implementation of the ML/AI Algorithm for MA assessment and visualization.