Polypharmacy in the elderly: data, models, and strategies

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CEXS DEPARTMENT

Gábrielnek és Joannak

In appreciation

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Abstract

The demographic shift toward an aging population is increasing the burden of public health. On average, a person of 70 years can combine the intake of up to seven medications. The administration of multiple drugs at the same time is known as polypharmacy. The often unnecessary use of more drugs that would be strictly necessary is the cause of many problems for the patient such as drug interactions, serious side effects, and lack of adherence to treatment. The increasing use of polypharmacy leads to an increase in morbidity and mortality. The national health agencies are clearly interested in the reduction of polypharmacy, given the enormous cost of associated side effects and consequent hospitalizations.

To try to deepen some of the most important aspects associated with the practice of polypharmacy, this thesis focused on three main lines of research: on the one hand, the identification, extraction and storage of relevant data in polypharmacy, which led to to the construction of two databases, Drug Metabolites database (DMdb) and Drug-Drug Interactions database (DDIdb); on the other hand, the exploitation of the collected data for the development of models that allow to anticipate possible secondary effects; and finally, the analysis and review of the different polypharmacy approach strategies in various countries as an approach to a coordinated strategy proposal in the face of this increasingly important challenge for the health management of aging populations.

Resum

El canvi demogràfic cap a una població envellida està augmentant la carga de la salut publica. De mitja, una persona de 70 anys pot arribar a combinar la ingesta de fins a set medicaments. El consum de diversos fàrmacs al mateix temps es coneix com a polifarmàcia. L'ús, normalment innecessari, de més medicaments de què seria estrictament necessaris és la causa de molts problemes pel pacient com interaccions farmacològiques, efectes secundaris greus i falta d'adherència al tractament. L'augment de l'ús de la polifarmàcia comporta l'augment de la morbiditat i mortalitat. Les agències nacionals de salut estan clarament interessades en la reducció de la polifarmàcia, donat l'enorme cost que suposen els efectes secundaris associats i les hospitalitzacions.

Per intentar profunditzar en alguns dels expectes més importants associats a la pràctica de la polifarmàcia, la present tesi es va focalitzar en tres línies d'investigació principals: per una part la identificació, extracció i emmagatzematge de dades rellevants en polifarmàcia, el que va donar lloc a la construcció de dos bases de dades, Drug Metabolites Database (Dmdb) i Drug-Drug Interactions Database (DDIdb): per una altre part, l'explotació de les dades recollides pel desenvolupament de models que permetin anticipar possibles efectes secundaris, i finalment les anàlisis i revisió de les diferents estratègies d'abordatge de la polifarmàcia en diversos països, com a aproximació a una proposta d'estratègia coordinada davant d'aquest repte d'augment importància per la gestió en salut de poblacions cada dia més envellides.

Preface

Today, the average 70-year-old takes seven different prescription medications. With a high possibility to experience unpleasant and harmful adverse drug reactions, there is an urgent need to understand and handle better drug interactions. In addition, currently, three times more people die because of prescription drugs than from a motorcycle accident.

Polypharmacy continues to increase and is known to be an important risk factor for morbidity and mortality, especially for elderly people. Nearly one in 25 older people are at risk of serious health problems such as bleeding and muscle weakness because they take unwise combinations of drugs, which often includes non-prescription medications. In older Europeans' and Americans' the use of prescription drugs and over-the-counter medications and dietary supplements has increased during the past decade.

Potential interactions can happen within prescription, over-the-counter and dietary supplements. For example, taking warfarin (a prescription blood thinner) together with simvastatin (a prescription cholesterol-lowering drug) increases the risk of bleeding and rhabdomyolysis (a severe muscle tissue injury). Taking lisinopril (a prescription anti-hypertension drug) with potassium (a food supplement) produces a higher risk of abnormally high blood levels of potassium. Taking both niacin (a non-prescription cholesterol-lo-

wering medication) and garlic (a dietary supplement) also produces a higher risk of rhabdomyolysis.

With around 3000 existing prescription drugs, 300 dietary supplements, and some 600 herbal products currently available, it is extremely difficult for physicians to take into account polypharmacy problems for patients for whom little history is known and who often cannot recount the medicines and supplements that they are already taking. Naturally, doctors do their best to avoid adverse drug interactions. Nonetheless, for patients taking two medications, the risk of a drug interaction is 15%. This risk rises to 40% for those taking five medications and to an alarming 80% for patients taking seven or more. The risk of a toxic medication interaction is very real, considering that more than one half of non-institutionalized adults older than 65 years take five or more different medications, and 12% use 10 or more.

Indeed, in hospitalized patients, adverse drug interactions are estimated to be the fourth leading cause of death. According to the Agency for Healthcare Research and Quality, more than 770,000 people are injured or die each year in hospitals from adverse drug reactions and other adverse drug events, which may cost up to $5.6 million per hospital.

Unfortunately, while national governments and health insurance companies are equally interested in reducing polypharmacy, there remains a gap in the literature regarding the polypharmacy and its

developmental course. More research is needed to examine the extent of simultaneous poly-drug use as well as the factors and consequences associated with multiple drug use. For many applications including drug discovery, drug re-purposing, and the definition of pharmacogenomic modulators, we need a molecular-level understanding of drug effects, but this is often either missing or incomplete. There are significant gaps in our understanding of the pathways by which drugs act. This incomplete knowledge limits our ability to use rational mechanistic molecular information to re-purpose drugs, to understand their interactions with other drugs, and to predict both positive clinical outcomes, i.e. the desired therapeutic effects of drugs (often referred to as "indications") and negative clinical outcomes, usually known as drug side effects.

Understanding the "magic triangle" of drugs, targets, and their side effects have become a "holy grail" of the pharmaceutical industry. In this thesis, I will analyze the approach of quantitatively predicting polypharmacological relationships between drug classes, metabolites, targets, and their side effects. This will allow the biological relevance of combinations of drugs to be evaluated in terms of related pathways, molecular functions, and disease-gene relationships.

Table of contents

1. INTRODUCTION

1.1 Adverse drug reactions

An adverse drug reaction (ADR) is a harmful reaction followed by the administration of one or more drugs. Differently, a side-effect (SE) in an expected reaction. It is listed normally in the drug label of the drug's package. If a patient experience an SE, often it can continue with the therapy, however in the case of ADR, it may require discontinuation of the treatment or the dose reduced[1]. Frequently, taking a combination of drugs may lead to serious, life-threatening ADRs.[1].

ADR has become an important problem globally. According to the federal agency of the United States; Food and Drug Administration (FDA), there are well over 2 million ADRs reported yearly, of which 100,000 cases result in patient death[2]. Because of this, ADRs have become the 4th leading cause of death in the US and are associated with a financial cost of 136 million dollars per year[3]. In 1994 an estimated 106 000 deaths were caused by ADRs in the United States. In 2014 the number of deaths associated with adverse drug reactions was 128.000 [4]. However there are articles that say the number of deaths caused by drugs is much lower[3], [5]. It is also difficult to get the correct number, as in public databases the deaths by a drug reaction, overdose, household products, poisons, and acci-

dents are all put together[6]. Other research indicates that globally 83.700 people die because of adverse effects of medical treatment[7].

Nonetheless, for patients taking two medications, the risk of a drug interaction is 15%. This risk increases to 40% for those using five prescriptions and to a dangerous 80% for patients taking seven or more medications. The ADR related toxicity is a high priority concern, considering that the world generation is getting older, and the elderly take five or more different medications daily, and 12% of them use 10 or more[8,9]. Due to gender differences in hormonal and immunological physiology, the woman has a higher risk to develop ADR compared with man[10].

On the one hand when the patient does not take the prescribed dose, mixing with other medications the number of ADRs increase. The increasing variety of over the counter (OTC) drugs, herb supplements the number of unexpected ADRs exponentially increases.

On the other hand, a lack of knowledge among doctors concerning newly discovered dangerous combinations may also put patients life at risk (table 1). Approximately 50% of the older generation takes at least one more medication that is not medically necessary[10]. The process of identification of ADR and the causing drug is tedious and can be mistaken by allergy, side effect, and intolerance[11].

Type of drug interaction	Examples	ADR of the interaction
Drug-drug	Warfarin and Sulfadiazine	may increase the plasma concentrations and hypoprothrombinemic effects of coumarin anticoagulants
Drug-disease	NSAID use in renal disease	may impair renal function, inhibition of prostaglandin synthesis
Drug-herbal	St. John's Wort and fluoxetine	may potentiate the risk of serotonin syndrome, hyperstimulation of brainstem 5-HT1A and 2A receptors
Drug-alcohol	Metronidazole and ethanol	may result in a disulfiram-like reaction
Drug-food	Calcium and levothyroxine	may decrease the effects of levothyroxine
Drug-nutritional status	Ventricular tachycardia and CCBs	can precipitate cardiac arrest
Drug duplication	ACE inhibitor and ARB	high risk of vascular events or renal dysfunction

Table 1. Types of drug interactions and their ADRs.

OTC drugs sold directly to a consumer without a prescription needed. They are popular, and usually, patients use prescriptions and

OTC medicines together. However, the effect of recent regulatory and market forces on these patterns is so far not known. Lately, the use of no-prescription-needed drugs has raised, which puts 15% of elderly at risk for major drug interaction[12].

The main reason to use OTC drugs is to calm pain and inflammation, lower cholesterol and blood sugar and treatment of gastroesophageal reflux disease[12]. The most common ADRs due to co-medication leads to gastric, hepatic and skin damage[13–15]. ADRs associated drugs are antithrombotic agents, diabetes-related drugs, and diuretics[13]. Misused OTC medication is also associated with addiction, euphoria, irritation, economic cost, accidents and effects on job and relationships[15]. Patients are not aware of the recommended doses of OTC drugs and herbal products. A study showed that one-third of adults are unable to identify the correct dose of ibuprofen, the time between doses and contraindications[16].

The use of dietary supplements raised globally[14,17]. They are not only used as nutritional supplements but also in the prevention and treatment of diseases[17]. Interestingly, in many cases, patients don´t tell their doctor that they use supplementations[14], as they are not aware that supplements can interact with medicines, and it could drive to dangerous ADR[17]. Additionally, more than 60 herbs, herbal drugs, and herbal supplements are associated with hepatotoxicity[18], Elderly people often take multivitamins, vitamin B and C, calcium, iron, zinc, coenzyme Q10, and vitamin D supplements, while a low intake of vitamin E, folic acid, zinc and saw palmetto[12,17].

The most common ADRs in older adults are dizziness (may cause falling), orthostatic hypotension, delirium, renal failure, gastrointestinal and intracranial hemorrhage. These ADRs are strongly linked to diuretics, NSAIDs, antiplatelet, antidepressants and antidiabetic drugs. It is not surprising that twice as many elderly adults are hospitalized because of ADRs than adults younger than 65, and have a median stay of 8 days. ADRs have significant economic and clinical costs, as they usually lead to hospital admission, prolongation of hospital stay and emergency department visits. The consequences and control of ADRs, only in the USA cost up to 30.1 billion dollars annually.

Considering that more than half of ADR related admissions are preventable, it is an enormous economic burden. Pharmacovigilance is intended at identifying drug safety signals as early as possible, thus minimizing potential consequences of ADRs[19].

Most drugs are associated with ADRs, sometimes discovered late in drug development or only during the extended course of clinical use. ADRs are linked to the therapeutic target, pathway or could arise as an outcome of an off-target effect of a drug-drug combinations[20].

A toxic effect is always dosage related. They use the same mechanism as the therapeutic effect, while unforeseen ADRs use separate

mechanisms[1]. The risk of such effects ranges from low (duloxetine and omeprazole) to high (aspirin and warfarin).

Around 80% of ADRs are type A, typically dose-related and predictable, while type B is not dose-related, unpredictable and idiosyncratic[10]. Idiosyncratic reactions can affect many different organ systems, either as -an isolated event (e.g., hepatitis) or as part of a syndrome (e.g., drug hypersensitivity syndrome).

Type	Type of effect	Characteristics	Example
A	Augmented	Dose dependent, predicted from known pharmacology of the drug	Hypoglycaemia - insulin
B	Bizarre	Dose independent, unpredictable, idiosyncratic	Anaphylaxis to penicillin
C	Cronic	Prolong treatment	Analgestic neuropathy
D	Delayed	After years of treatment	Antipsycotic - turdive dyskinesia
E	End of use	Withdrawal effect	GC withdrawal, adrenocortical

Table 2. Types of ADRs and their characteristics.

Formation of reactive metabolites of compounds in combination with a reduced capacity for detoxification may be the initiating step in many idiosyncratic reactions[21]. However, not all ADRs fit into type A and type B categories; therefore, additional categories have been developed. These include type C (continuing), type D (delayed use), and type E (end of use) reactions (table 2). Sensitivity to

ADRs is determined by age, gender, health status, ethnicity, and polypharmacy[22].

ADRs are a major public health concern and are among the top causes of morbidity and mortality. The principal reasons for ADRs are drug metabolites, drug-drug interactions, and polypharmacy.

1.2 Drug metabolites

Drug metabolism is the enzymatic transformation of one chemical compound into another. The drug metabolism mainly occurs in the liver, and some metabolic processes occur in the lungs, kidney, epithelial cells of the gastrointestinal tract, or in the skin[23].
Overall, the metabolic system converts lipophilic, water-insoluble and nonpolar drugs into more polar and water-soluble metabolites. This step is crucial for the excretion of the drug by body liquids. A few compounds can be excreted, without being metabolized, e.g. vancomycin .

The liver hepatocytes contain the essential enzymes for the metabolism of both endogenous and exogenous compounds. The main enzymes in metabolism are part of the cytochrome P450 group. They are localized mainly in the smooth endoplasmic reticulum of the cell[24]. The speed of the metabolism defines the duration and intensity of a compound's pharmacological action. Altogether, the drugs therapeutic effect diminishes as they are metabolized, The process may result in pharmacologically active, inactive, or toxic metabolite.

Drug metabolism is classified into two phases of biochemical reactions - phase 1 and phase 2[25] (Figure 1).

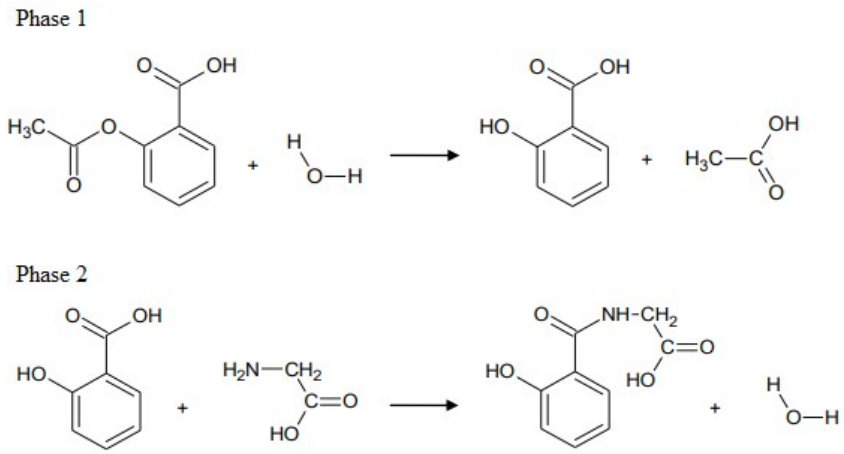

Figure 1: Metabolism of Aspirin. Aspirin undergoes phase 1 hydrolysis to salicylic acid. In phase 2 it is congugated with either glycine or glucoronic acid forming a range of ionised metabolytes that can then be excreted in the urine.

Phase 1 metabolism involves chemical reactions such as oxidation, reduction, hydrolysis, epoxidation, hydroxylation, epoxidation, dealkylation, deamination (table 1).

There are three probable outcomes of phase 1 metabolism;

- The compound and its metabolites become fully inactive.
- The metabolite(s) are less active than the original drug.
- An inactive drug e.g. enalapril (a prodrug), metabolized into a pharmacologically active metabolite.

If the metabolites of phase I reactions are enough polar, they can be excreted by the body without passing for phase 2.

Phase	Chemical reaction
	Hydroxylation (aliphatic, aromatic or nitrogen)
	Epoxidation (aliphatic, aromatic)
	Dealkylation (O-, N-, or S-)
	Deamination
Phase I	Oxidation (N-, or S-)
	Reduction (nitro, azo, disulfide, keto, aldehyde, olefin)
	Hydrolysis (amide, ester, cabamate, epoxide)
	Glucuronidation
	Sulfation
	Methylation
Phase II	Acetylation
	Amino acid conjugation (glycine, glutamic acid, and taurine)
	Glutathione conjugation

Table 3. Chemical reactions of phase 1 and 2 metabolism.

In phase 2 metabolism, an ionized group is attached to the compound. This involves glucuronidation, sulfation, methylation, acetylation, amino acid or glutathione conjugation (table 3). Products of conjugation reactions have increased molecular weight and make the metabolite more water soluble.

Most phase 2 reactions inactivate completely drugs and their active metabolites. After phase II, the conjugated compounds may be metabolized again.

Many factors can affect liver metabolism; age, gender, ethnicity, intestinal flora, and nutrition. Frequently consumed food can interfere with Cytochrome activity, like grapefruit juice and the herb St John's Wort inhibit Cytochrome P450 activity[26].

Diseases can diminish enzyme activity, like in the elderly, the numbers of hepatocytes and enzyme activity decline. Coadministration of drugs also has a huge impact on the rate of metabolism. The concentration of metabolites in our body is also linked to various diseases, for example, a low concentration of allopregnanolone is observed in alcoholism.[27].

Structural alerts are commonly used to flag compounds with toxicity risk, and usually, they are modified to avoid ADR. Structural alerts are chemical structures that can be activated into reactive metabolites. Approximately 78–83% of compounds that are linked with ADRs, contain at least one structural alert, and about 62–69% of them are reactive metabolites[28]. Structural alerts are commonly used to flag compounds with toxicity risk, and ususally they are modified to avoid ADR. Studies have revealed that toxicities of anticancer compounds and their adverse effects are linked to their chemical structure and molecular weight. Thus, it may result in a number of metabolites interacting with drug off-target networks networks[29].

Formation of reactive metabolites of drugs in conjunction with a decreased ability for detoxification is believed to be the initiating step in many idiosyncratic reactions[21,28]. They can form covalent and noncovalent interactions with cellular macromolecules such as DNA, proteins, and lipids. Covalent interactions can lead to cancer or trigger hypersensitivity reactions. Noncovalent interactions can cause oxidative and other intracellular stress[30].

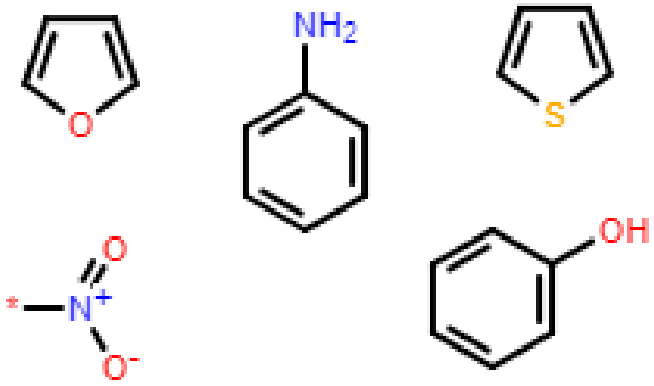

Figure 2: Example of structrual alerts: furan, phenol, thiophene, aromatic amine and aniline

Remove structural alerts like furan, a formyl group, aromatic amines, thiophene, phenol, and aniline sometimes also means lose pharmacological benefits[31]. The dose of the drug and the amount of covalent binding are major factors in the formation of reactive metabolites. Generally, if the doses of the drug do not reach 20mg/day, it's less likely to be associated with idiosyncratic drug reactions[32]. Moreover, structural alerts' toxicity depends on its the metabolic pathway and reactivity of the metabolites[33].

The thiophene structural alert in methapyrilene undergoes bioactivation, while no activation occurs for eprosartan. The differences in biotransformation lead to drastic differences in the safety profiles of the two compounds. While methapyrilene was withdrawn from the market due to hepatotoxicity, eprosartan is safe and commonly prescribed antihypertensive.

Fenfluramine was used to treat obesity, but its reactive metabolite, norfenfluramine affects the serotonin receptor 2B, causing cardiac fibrosis[34]. It was withdrawn from the market in 1997. Norfenfluramine is also a reactive metabolite of Benfluorex, which was withdrawn 12 years later, in 2007 for the same reason, and is associated with the hospitalization of many diabetic patients because of cardiac valvular insufficiency[35].

Strategies to minimize the formation of reactive metabolites are the use of structures and functional groups that are resistant to metabolism or change the site of metabolic activation[32].

One drug or its active metabolite can lead to a serious adverse reaction, which can be difficult to recognize, and the whole picture gets more complex if we add more compounds, heading to a drug-drug interaction.

1.3 Drug drug interactions

A drug-drug interaction (DDI) is when a drug affects the activity of another when both are taken together. This effect can be synergistic, antagonistic or a new effect can emerge. Principal causes of drug interactions and unwanted drug effects are the wrong choice of drug, wrong dosage, errors in taking the drug, health status (e.g. poor renal function). Along with co-administration of drugs, use of dietary supplements, non-prescription drugs, food choice (e.g. coffee, citrus juice) could also alter the effect of the drug, thus leading to adverse drug reactions[36].

DDIs are the most common cause of ADRs in the elderly. Yet, for patients taking two medications, the risk of a drug interaction is 15%. This risk increases to 40% for those using five prescriptions and to a dangerous 80% for patients taking seven or more medications.

We can distinguish three types of DDIs; pharmacodynamic, pharmacokinetic and pharmaceutical interaction (table 4).

In pharmacodynamic interaction the drugs affect each other directly; one drug has an antagonistic, additive, synergistic or indirect pharmacologic effect on another (table 5)[36,37]. For instance, fluoroquinolones taken with macrolides can result in QT prolongation. The combination of ACE inhibitors with potassium-sparing diuretics can increase potassium retention which can lead to life-threatening hyperkalemia.

Interaction	Description	Example
Pharmacodynamic	One drug has an antagonistic, additive, or synergistic effect on another	Fluoroquinolones and erythromycin can result in QT prolongation
Pharmacokinetic	One drug alters the absorption, distribution, metabolism or excretion of the other	Inefficacy of digoxin after coadministration of carbamazepine
Pharmaceutic	Occurence is due to physical or chemical incompatibility	Inactivation of cisplatin by mesna

Table 4. Types of DDIs.

Pharmacokinetic interactions involve the alteration of abortion, distribution, metabolism or excretion of drugs. It alters the drug plasma concentration and involves cytochrome P450 enzymes[38]. For example, increased bioavailability of digoxin when taken with verapamil.

Pharmaceutical incompatibility happens when two drugs are mixed, and one makes a complex with the other. This is a pure chemistry and no pharmacological systems are included. For example the inactivation of the platinum compound cisplatin by the addition of the thiol mesna (sodium 2-mercaptoethanesulfonate). If these compounds are combined, a mesna-platinum adduct forms[37].

Typical additive interactions

Compund 1	Compound 2	Possible side effect
NSAIDs	SSRI, phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
ACE inhibitors	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin syndrome
Tricyclic antidepressants	Low-potency neuroleptics	Increased anticholinergic effects
Quinolones	Macrolides, citalopram	QT-interval prolongation, torsade de pointes

Typical antagonistic interactions

Compund 1	Compound 2	Possible side effect
Acetylsalicylic acid	Ibuprofen	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

Table 5. Examples of typical additive and antagonistic pharmacodynamic interactions (SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug)[37]

Alteration of enzyme and/or transporter activities involved in the absorption, distribution, metabolism, or excretion of a new molecular entity by other concomitant drugs may lead to a change in exposure leading to altered response (safety or efficacy). For example, inhibition of cytochromes P450 and transporters are two of the major mechanisms underlying drug-drug interactions.

Drugs can be categorized as inhibitors (slows down the normal activity level of a metabolic enzyme), inducers (speed up the rate of metabolism), or substrates (a compound that is identified as a metabolic target of a particular enzyme) (figure 3)[39].

Based on this there are six patterns of drug-drug interactions, 1) inhibitor added to a substrate (increase the serum level of the substrate), 2) substrate added to an inhibitor (decrease the serum level of the substrate), 3) inducer added to a substrate (decrease the serum level of the substrate), 4) substrate added to an inducer (ineffective dosing), 5) removal of an inhibitor (reversal of enzyme inhibition), 6) removal of an inducer (reversal on enzyme induction)[40]. For example if a compound A is metabolized by a CYP and compound B inhibits the CYP's activity, the plasma concentration of the compound A will be higher than expected and potentially cause toxicity. CYP inhibition can either be via a reversible or irreversible mechanism. If compound A is metabolized by a CYP and compound B induces or increases the enzyme's activity, then the plasma concentrations of compound A will be lower than expected and may cause compound A to be ineffective[38].

Drug transporters also play an important role in supervising drug concentrations in the blood and in various organs (liver, brain, lung, kidney, small intestine)[40–42].

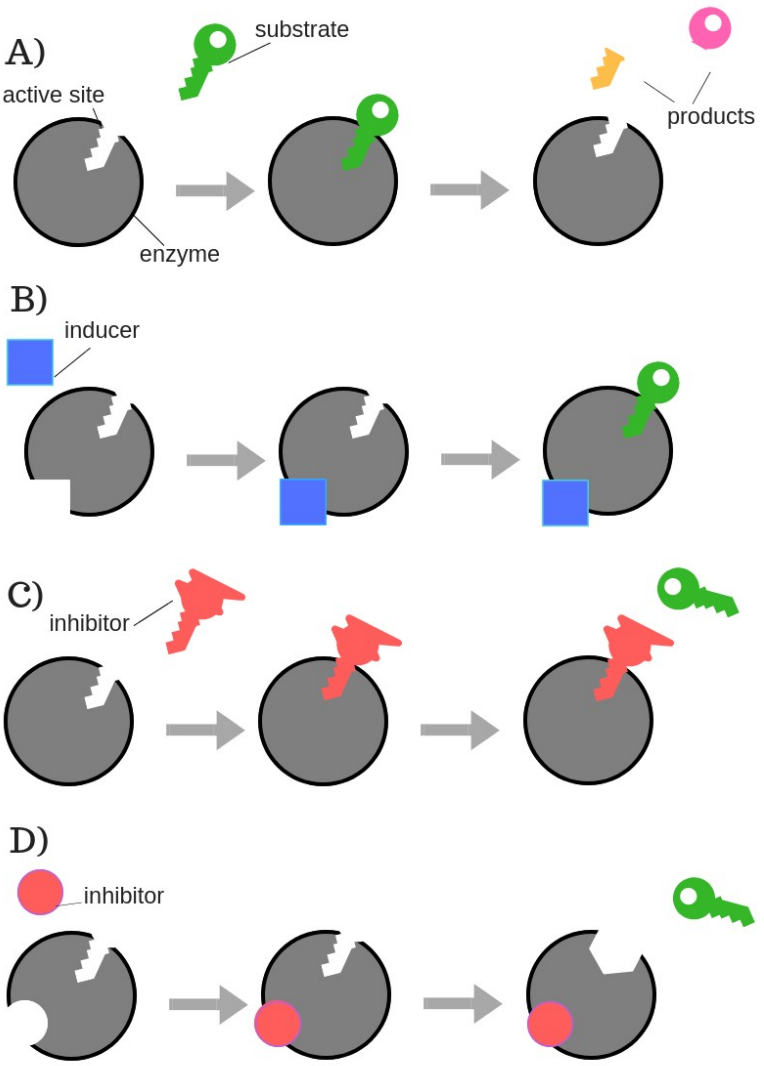

Figure 3. A) Normal reaction, the substrate molecule binds to the enzyme's active side, a reaction occurs, and product molecules are formed. B) Allosteric activation, inducer help the substrate to bind with the active site. C) Competitive inhibition, the inhibitor molecule binds to the active side, preventing the binding of the substrate. D) Allosteric or non-competitive inhibition, the inhibitor prevents the binding of the substrate by changing the shape of the active site.

Transporters comprise the largest family of membrane proteins in the human organism, including members of solute carrier transporter and ATP-binding cassette transporter families. These proteins frequently are in charge of drug absorption, elimination, and can enhance the effectiveness of drugs.

Each drug has its own target profile, one drug one target paradigm was replaced with one drug multiple target i.e polypharmacology. There is the primary target profile, which is the list of targets expected to hit the drug when consumed according to the recommended dose.
The secondary or off target profile is when the drug concentration alters, hitting new, unexpected targets. Many drugs have an incomplete target profile, compared with small amount of experimentally verified drug target interactions, there exist a large number of unknown drug-target interactions.

The inhibition and induction of drug metabolism are generally not altered with aging. Nevertheless, the elderly are more sensitive to drug interactions due to continuous age-related physiologic[41]. For example, age-related changes in body composition (increased fat mass and decreased total body water) may drive to an increased volume of distribution and a prolonged half-life with lipophilic drugs, although water-soluble drugs tend to have a decreased volume of distribution. The most noticeable age-related change is the decrease in renal drug clearance corresponding with the decline in

creatinine clearance. Hepatic blood flow may be decreased too, as well as nutritional status[42]. Changes in pharmacodynamic responses also are very important factors that contribute to drug interaction susceptibility. Even is a dosage is decreased appropriately to account for age-related pharmacokinetic changes and decreased homeostasis may result in greater sensitivity to adverse drug reactions[9].

Therapy with two or more drugs is more the rule than the exception, particularly in aging societies. Drug-drug interactions are frequently undesirable and may lead to increased toxicity and mortality. Accordingly, the evaluation of a new molecular entity's drug-drug interaction potential is an integral part of drug development and regulatory review prior to its market approval[43].

Drug-drug interactions may lead to serious adverse drug reactions. Polypharmacy, which is common in elderly patients, increases the risk substantially[9].

1.4 Polypharmacy in the elderly

Current population ageing in Europe is seen as a challenge for many policy areas, between these, health and long-term care in particular. Europeans are living longer and they want healthier lives. However, ageing entails many problems that simply cannot be solved. The human machinery slows down, often the organs do not work properly as before, the muscles and bones are not strong as they were before, giving rise to chronic diseases, cardiovascular problems, hypertension, diabetes, rheumatoid arthritis, chronic pain, anxiety and insomnia, tremors, falls and consequent fractures, as the most common, between others[44–46].

The average 70-year-old now takes seven or more different prescription medications to cope with the aging condition. The use of multiple medications is often referred to as polypharmacy. Polypharmacy can cause problems such as drug-drug interactions, serious side effects, and non-adherence to treatment if an appropriate drug prescription is not followed. Inappropriate prescribing is currently a hot topic in our aging population. Elder patients see multiple specialists that, either are not well informed of the full medical history and medication that the patient takes, or do not always agree in a consensus[47]. Not to mention patients who self-medicate or take dietary supplements or over the counter drugs, which can cause also problems of drug-drug interactions and adverse effects.

Therefore, we are facing a complex situation. Polypharmacy is necessary for the elderly condition and cannot be prevented. However, it is essential to assess the risks associated to it in order to properly manage it. Hence, the key question is how to better manage the ageing condition in order to give our ageing population well-being and the best possible quality of life.
Consequently, there is currently an increasing interest to generate and start seriously implementing polypharmacy policies in Europe. Moreover, national health agencies are clearly interested in reducing polypharmacy, given the huge sums of money they spend when resulting side effects and hospitalizations, or repeated and avoidable clinical tests.

Generally adults aged over 65 years with chronic diseases, which include heart disease, hypertension, diabetes, arthritis, and cancer, often require multiple medications for optimal management[48]. Patients who take antipsychotics have a higher change to suffer adverse effects of polypharmacy[9]. Self-medication is another contributing factor to polypharmacy. Polypharmacy is more common in women, and its prevalence increases with advancing age[49]. An elderly man between 60-79 takes an average 6 medications, while a woman at the same age 7. Above 80 years both genders take an average 9 medications daily[50,51].

The number of medications a person's uses is by far the strongest risk factor for medication-related problems. As the number of medications rises, adverse drug reactions become more common.

Adherence worsens, drug drug interactions increase [50]. Between 1995 and 2010, the proportion of adults dispensed more than 5 drugs doubled to 20.8%, and the proportion dispensed to more than 10 drugs tripled to 5.8%. Receipt of more than 10 drugs is strongly associated with increased age[52].

There are many negative consequences associated with polypharmacy. The most common consequences of polypharmacy include adverse drug reactions, drug interactions, medication nonadherence, worsen quality of life, cognitive impairment and falls[53]. These may manifest in increased health service utilization and increased risk of geriatric syndromes[54]. As patient age and their health status changes, medications may become ineffective, more harmful, or require dosage changes to prevent adverse drug reactions from occurring. Nonpharmacologic therapy, such as diet and exercise, should be considered whenever possible[55].

We can distinct five classes of polypharmacy: same-class-, multiclass-, adjunctive-, augmentation- and total polypharmacy (table 5). Additionally, there are five factors associated with the rise of polypharmacy: scientific, clinical, economic, political and cultural Kukreja[56].

The number of medications used by older adults is associated with poorer nutritional status. Decrements in physical health were associated with decreasing intake of many fat-soluble and water-soluble vitamins, major minerals, trace minerals and electrolytes. Excessive macronutrient use, specifically relating to the intake of saturated

fats, refined carbohydrates and cholesterol, along with decreased intake of fibre and bioavailable protein sources, was also associated with poor physical health[49].

Type of polypharmacy	Description	Example
Same-Class	use of more than one medication from the same class	use of two selective serotonin reuptake inhibitors in a case of depression
Multi-Class	use of full therapeutic doses of more than one medication from different classes for the same symptom cluster	use of valproate along with an atypical antipsychotic, such as olanzapine, for treatment of mania
Adjunctive	use of one medication to treat the side effects of another medication from a different class	use of trazodone for insomnia caused by bupropion
Augmentation	use of one medication at a lower than normal dose along with another medication from a different class in full therapeutic dose for the same symptom cluster	addition of low dose haloperidol in a patient responding partially to risperidone
Total	total count of medications used in a patient	

Table 5. Types of polypharmacy

Health care providers often utilize various methods to avoid the incidence of polypharmacy. The most common interventions include the utilization of Beers' criteria[57], the “brown bag” approach[58], using mnemonics such as SAIL[59] and TIDE[60], and the “10-step approach”[61].

It is very common in the elderly that unnecessary medications prescribed without indication, without evidence on ongoing therapeutic benefit, used in excessive dose or duration, and in the presence of adverse consequences[51]. More than half of the medication errors is due to wrong prescription, 30% administration errors[50,62]. Studies shown that the use of unnecessary medications in older adults ranges from 40-50%, with medications often continued until death[55,62]. Any insult or adverse event has the potential to irreversibly contribute to patient decline an premature death. It is therefore important to understand how to both identify and reduce unnecessary medications in this vulnerable population[50].

Current European health policies focus on the digitization of healthcare given the increasing digitization of today's society. Information technology in healthcare is the core of the current health policies[63,64]. The greatest difficulty currently encountered is the lack of good interoperable systems to access and share all electronic health records of Europeans citizens. If this can be solved, this will allow health IT data usage and analytics across EU countries borders to the benefit of patients, physicians, and hospitals.

Prevention and educating courses for hospital and primary care workers are fundamental for preventing and handling polypharmacy in the most adequate way[65]. Currently courses are compulsory in parts of Germany and Sweden, and everywhere in Catalonia, Scotland and Northern Ireland.

In Catalonia these courses teach general pharmacy indicators (number of prescriptions per user, average cost of prescription per patient), polypharmacy management specific indicators (% of patients with polypharmacy, index of prescription quality) and pharmacy cost indicators (cost per patient treated with ACEI or ARB, cost per patients treated with cholesterol lowering agents, cost per patient treated with antidepressants)[54].

In Scotland the courses include standard polypharmacy indicators (10 or more British National Formulary (BNF) paragraphs dispensed in a 6 month period with at least one high risk drug) and high risk prescribing indicators (older person >75 years prescribed with antipsychotic drug, older person >65 years currently taking an ACE inhibitor/angiotensin receptor blocker and a diuretic who is prescribed a NSAID -the triple whammy-, older person >75 years prescribed a NSAID without gastroprotection, older person >65 years currently taking either aspirin or clopidogrel who is prescribed a NSAID without gastroprotection, current anticoagulant user prescribed a NSAID without gastroprotection, current anticoagulant user prescribed aspirin or clopidogrel without gastroprotection)[66].

In Sweden the courses teach about drug specific indicators (drugs that should be avoided unless a specific reason exists: long-acting benzodiazepines, drugs with significant anticholinergic properties, tramadol) and diagnosis specific indicators (COPD: irrational use, oral beta-2 receptor agonist, hazardous use, non-selective beta-receptor blocker)[62].

Policy efforts aimed at reducing the impact of morbidity and mortality related to overprescription causing polypharmacy may reduce the supply of prescription drugs and thus reduce the potential for drug diversion that leads to misuse and abuse. According to Twillman et al.[67,68] policy initiatives that focus on the supply of prescription drugs should consider

1. abuse-deterrent opioid formulations,
2. increased medication storage security at home,
3. drug take-back opportunities,
4. improved clinician education,
5. improved effectiveness of prescription drug monitoring programs.

For example, improved clinician education aims to teach clinicians "to prescribe only the number of doses they expect patients to need in acute pain settings and the importance of avoiding excess prescribing." Similarly, PDMP electronic databases provide supplemental information on controlled substance prescriptions and allow for detection of and intervention among individuals attempting to fraudulently obtaining such prescriptions. Although supply-side initiatives are a major focus in prescription drug abuse efforts, the demand side of the equation is equally important.

Policymakers and public health officials must also aim to reduce the demand for prescription drugs to prevent individuals from developing the disease of addiction. Primary drug abuse prevention efforts

that aim to educate patients and their families form the foundation for reducing prescription drug demand. Research efforts must focus on understanding how to improve the effectiveness of primary drug abuse prevention programs. Furthermore, these programs must become more prominent throughout the country to prevent the development of addiction.

As expounded before, drug misuse and abuse are increasing among people in their 60s, together with taking multiple medications concurrently for the treatment or management of several comorbidities. This population is at higher risk for medication misuse than the general population, largely as a result of increased rates of pain, sleep disorders/insomnia, and anxiety. In addition, elderly individuals are typically more sensitive to medications because of their slower metabolism. Therefore, improved health outcomes in this population may depend on successful care coordination and reductions in cases of polypharmacy.

1.5 In silico tools for drug safety

Intervention strategies that aim to curb the overprescription/misprescription drug must

1. improve legislation and enforcement of existing laws,
2. improve medical practice with respect to overprescribing/ misprescribing drugs,
3. educate prescribers regarding the underappreciated risks and benefits of high-dose overprescribed drugs, and
4. include secondary and tertiary prevention measures to improve access to substance abuse services and overdose harm reduction programs[69].

In addition, policy initiatives must not focus solely on the supply side of the overprescription/misprescription drug equation, which could reduce access to treatment among patients who have a legitimate need for medications to control chronic pain. As such, policy initiatives focused on demand must also be considered, with particular attention to populations disproportionately affected by prescription drug misuse and abuse.

A way to implement these measures could be integrated in the form of a "SMART" healthcare service (hospital/primary care center/general practitioner (GP) center/emergency service)[70]. The "SMART" healthcare service would consist on the use of computerization & health information systems to the operational support of the clinical

management plan in order to improve the effectiveness and efficacy of the healthcare system itself.

A health care milieu with a high degree of clinical and economic integration must bring together funding, coordination and the continuum of health services for a given population.
Computerization & health information systems are basic to support/ perform this integration scheme (i.e. computerized clinical history of patients is crucial to

a) have quick access to the information,
b) easier analysis of patient information,
c) perform direct statistics from patient data,
d) easier extraction of conclusions…).

Moreover, various liaison devices can be introduced, such as a matrix structure or information systems, in order to be communicated all the processes / algorithms between them (i.e. communication between patients information, use of resources, interventions, outcomes).
By introducing computerization & health information systems into the clinical practice guidelines, makes it possible to incorporate a concurrent review model with decision-making based on the developed standards and criteria; thus, for example, it allows for the automation of alerts and reminders, and the capture of key outcomes and abnormal data. The computerization & health information systems for analyzing outcome data as a support for medical practice

will provide information on outcomes enabling improvements in coordinated care management at a patient-centered level.

The evaluation of the impact of the aforementioned measures could be done by an observational, prospective multicentric study, evaluating the influence of the measures applied in reducing polypharmacy, patient wellbeing or patient adverse effects, by multivariate regression analysis. If a high association is found between the measures and reducing polypharmacy / adverse effects, the measures would be effective. On the contrary, those related with reducing patient wellbeing, would not be effective.

Current tools for identifying potentially inappropriate prescribing (PIP) in older patients are time-consuming, tedious, impractical and inadequate. As aforementioned, several studies have found that polypharmacy is associated with negative health outcomes, but more research is needed. Regarding European projects, this field has been only tackled recently in the European innovation Partnership Actions: "Polypharmacy Patterns: Unraveling Systematic Associations between Prescribed Medications"[71], the "SIMPATHY project to manage polypharmacy in the elderly by 2030"[72], the "FRIENDD: a study group on DDIs in polypharmacy in the elderly"[73,74], the CRIME project: CRIteria to assess appropriate Medication use among Elderly complex patients[71], the PREDICT EU project: Increasing the PaRticipation of the ElDerly in Clinical Trial[75], the ICARE4U project:[76] Innovating care for people with multiple chronic condi-

tions in Europe, the MICMI project: Methods for Improving Compliance with Medicine Intake[77], EU-ADR[78], eTOX[79], and eTRANSAFE[80].

As aforementioned, there are tools available to help reducing polypharmacy in the elderly. The Screening Tool of Older Person's Prescriptions (STOPP) criteria[65], the STOPP/START of the NHS Cumbria toolkit[81], the Beers Criteria updated 2012[58], the FORTA (Fit FOR The Aged) list[82], the NHS Highland system[83], the Medication Appropriateness Index (MAI) tool[84], the NO TEARS[85] and ARMOR[86] systems, decision algorithms, the French consensus panel[87], McLeod's criteria[88], Lindblad's panel[89], or the PRISCUS list[90]. All of these tools contain a consensus panel with several criteria of body systems or drugs (figure 3).

Additionally, there are currently available several Internet sources helping to tackle and understand better polypharmacy. Pharmacovigilance resources like FAERS[91], Yellowcard[92], European database of suspected ADR reports[93] , OECD Health Statistics[94].

Digitization of healthcare records has literally paved the way for a far more informed, innovative, and personalized care paradigm. Current effort is being put into an open secured access across EU countries borders of the fully digital patient personal electronic health records. This will allow having access to the clinical history of every patient in every hospital in Europe and avoiding inappropriate prescriptions. It is essential though to solve the still existent problem of systems' interoperability, as well as it is essential to

perfectly deal with the cyber security issues. Moreover, a common use of e-health records will avoid unnecessary or repeated expensive clinical tests and will definitely help to avoid inappropriate prescription.

1. Digoxin at a long-term dose > 125µg/day with impaired renal function
2. Loop diuretic for dependent ankle oedema only i.e. no clinical signs of heart failure
3. Loop diuretic as first-line monotherapy for hypertension
4. Thiazide diuretic with a history of gout
5. Non cardioselective Beta-blocker with Chronic Obstructive Pulmonary Disease
6. Beta-blocker in combination with verapamil
7. Use of diltiazem or verapamil with NYHA Class III or IV heart failure
8. Calcium channel blockers with chronic constipation
9. Use of aspirin and warfarin in combination without histamine H_2 receptor antagonist
10. Dipyridamole as monotherapy for cardiovascular secondary prevention
11. Aspirin with a past history of peptic ulcer disease without histamine H_2 receptor antagonist or Proton Pump Inhibitor
12. Aspirin at dose > 150mg day
13. Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event
14. Aspirin to treat dizziness not clearly attributable to cerebrovascular disease
15. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration
16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration
17. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder

Figure 3: STOPP, The following cardiovascular system releated drug prescriptions are potentially inappropriate in persons aged > 65 years of age

Electronic prescribing (e-prescribing) is another important stage in the overall digital technology transformation. There is strong evidence from several health national authorities that digital prescribing saves both time and money, it promotes patient safety with its real-time support and guidance for prescribers. Furthermore, it also definitely helps reducing inappropriate prescription. These policies will help to rational deprescribing. Rational deprescribing is important to better manage polypharmacy. We could reduce

medications to an elder patient, even if the ended medication is less efficacious for the patients' clinical profile, but it is improving the quality of life of the elder patient (less tedious side effects that impede well-being/quality of life).

Hence, the current and future tendency of policies is focused on e-health solutions, mhealth (mobile health) solutions, where mobile health applications are used from monitoring a chronic patient, to attend virtually to doctor visits, to help remembering medication (improving adherence), to control a wearable that monitors specific compounds/metabolites and downloads data that can be send straightforward for the doctor to analyze and take decisions on the lifestyle needed to be carried out (already extensively used with diabetic patients), telehealth, telemedicine, "elderly smart homes", IT advancements to get patients out of the waiting room faster, gathering data such as genomic data and use it through AI health systems, i.e. for cognitive computing health prescriptions (IBM Watson Health system)[95].

In short, current policies are focused on putting the patient at center stage, going from intervention to prevention, from hospital based-care to patient-centered based care (in elderly smart homes, by the use of wearables to gather, share data and monitor patients with, i.e. chronic diseases), and the use of all these personal data gathered towards personalized medicine. Predictive modeling and genomic sequencing are fast becoming components of fully digitized health

organizations in partnership with the patients and communities they serve.

However, is this just the right way to proceed? We could argue about it, taking just a perfect and very timely example, IBM Watson Health platform. Last June 2017 was announced the failing of this IBM platform on prescribing obvious prescriptions or non-sense prescriptions[96]. Until which point can be useful gathering databases and extracting data for AI predictions? A combination from different sources is normally the virtue.

It is worth noting that from the standpoint of wellbeing and health-care improvement it is better to under prescribe to avoid side effects than prescribe without well knowing the effects of combined drugs or even prescribe when the health outcome improvement is not going to be substantial adding a new drug to the patient lists of consumed drugs. Once taken this into account, the adoption of a policy, which takes into account the lines of actions expounded, seems a good solution. Below, some evidence that confirms the effectiveness of the lines of action proposed.

There is a relative risk reduction on medication error and adverse drug events by computerized physician order entry systems (CPOE). There is evidence that electronic prescribing can reduce the risk for medication errors and adverse drug events[97]. Hence, the policy should implement an electronic prescribing system with a log of all the drugs the patients take, listing the prescribing doctor, the date and reason prescribed, and the directions and cautions about

the medication use. In this way any doctor can have information about all the drugs being taken, including those prescribed by other physicians, such as the log called the "Passport to Good Health Care," included in the department's booklet, available free from the National Clearinghouse for Alcohol and Drug Information[98].

Regarding the implementation of psychosocial counseling and treatment for any co-occurring disorders: According to government figures, an estimated 120,000 older people are affected annually by mental impairment or Parkinson's disease-like trembling - induced by drugs. Each year another 32,000, woozy from prescription tranquilizers and sleeping pills, fall and break hips. According to the U.S. Health and Human Services Department, federal officials estimate that some 200,000 elderly are hospitalized each year because of the drugs they take - and this figure, is a gross underestimate[99].
Some older people add to the problem by mis-medicating themselves - confusing schedules or taking too much or too little. Fewer than half of the elderly patients who take prescription drugs follow their physician's orders[100].

Regarding the implementation of mandatory courses for doctors in geriatrics: For one thing, age itself increases the likelihood of bad drug reactions. Drugs tend to be tested on younger people and the dosages set accordingly. The elderly, whose livers and kidneys are less effective at clearing drugs from their systems, can be staggered by quantities that are safe for younger people. Older people also

take a greater number of drugs. The average senior gets more than 15 prescriptions a year.

A study done a few years ago found that fewer than two percent of all medical students were required to take courses in geriatrics. Most physicians had only one class in pharmacology.[100].

Regarding the kind of drugs prescribed when existing poly-pharmacy: The elderly are most likely to be harmed by psychoactive drugs - drugs that affect the mind. They include potent antipsychotics like Haldol or Mellaril, used to treat serious mental illness, and tranquilizing benzodiazepines such as Valium or Halcion. Psychoactive drugs have numerous effects other than the desired ones. They can reduce alertness and coordination, which increases the risk of falling. Older people taking long-acting tranquilizers such as Valium are nearly twice as likely as those not taking the drugs to fall and break a hip - an injury that for an older person can mark the beginning of the end. Hence, for older people, the key question is, 'Do I need this drug in the first place?' and if yes, in which dose?

Regarding the adoption of measures to follow continuously the medical history of the patient, the review with follow up service has been proven to be successful, i.e. the Spanish conSIGUE program[101].

Our life expectancy is nowadays significantly higher than it would have been even some few decades ago. This progress, leading to aging societies, is of influence to the organization of health care and

to the future development. The measures adopted should include research for the development and investigation of appropriate trans institutional information system architectures, of adequate methods for strategic information management, of methods for modeling and evaluating health information systems, the development and investigation of comprehensive electronic patient records, providing appropriate access for health care professionals as well as for patients, including home care and health monitoring facilities[102].

Therefore:

1. Urges public health and public policy education programs to prioritize and implement evidence-based community and provider training programs on mental health, non-pharmacological pain treatment alternatives, substance abuse, and overdose prevention, prescribed drugs that can cause possible or severe adverse effects (Table 1). Gaps in education can be assessed and continuing education provided.

2. Urges public education on non sharing of prescription medications as well as safe storage, use, and disposal of medications. Messaging must come from multiple public health partners and resources, including public radio and television, billboards, and social media.

3. Urges pain prescription providers to become more knowledgeable on identifying and treating pain with alternative mo-

dalities and to coordinate pain management with complementary and integrative care providers.

4. Urge providers to be educated on and require the use of Prescription Drug Monitoring Programs (PDMP) before prescribing pain medications and to increase integration of patients' information into their electronic health records. Prescribers need to be educated on referral and treatment options if concerns are identified on the PDMP assessment.

5. Urges state legislators to prioritize resources for development and continued support of evidence-based polypharmacy treatment programs that include medication-assisted treatment and supportive counseling.

6. Urges state legislation to require individuals to have physical and mental examinations before they are prescribed pain medications.

The classical view of drug action, "one molecule interacts with one target to give one therapeutic effect" has been replaced by the new polypharmacology paradigm "one molecule (or more) interacts with several targets to give several therapeutic effects and certain side effects". These targets are in a complex cellular network.

The emerging discipline of Quantitative systems pharmacology (QSP) aims to understand how drugs modulate cellular networks in

space and time in order to predict drug targets and their role in human pathophysiology. It is worth mentioning that although QSP might be considered to be a new approach, the principle of drug "repurposing" is well-established in the pharmaceutical industry as a way to identify new targets for drug molecules which have failed at the clinical testing stage for their original target.

Hence, both the QSP concept and the enterprise view of polypharmacology can be adapted to the field of polypharmacy. As mentioned above, hospitals are spending large sums of money because of polypharmacy and ADRs, and current tools for identifying PIP in older patients are time-consuming and inadequate. Therefore, QSP can be essential to deal with these problems, with practical application in the promising field of personalized medicine and drug repositioning with reduction of ADRs.

In recent years, several new sources of data have enabled researchers to better identify, predict, and explain polypharmacology and drug safety. Table 6 shows the most representative databases and resources for pharmacology studies. The major sources of scientific articles on biomedical field are Medline[102], Scopus[103] and Google Scholar[104]. Comprehensive drug databases, like Drugbank[105], KEGG[106] and PharmGKB[107] contain detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway), drug metabolite information.

Database	Description
MEDLINE	The world's largest repository of scientific articles in the biomedical domain
SCOPUS	Elsevier’s abstract and citation database
Google Scholar	Indexes the full text or metadata of scholarly literature across an array of publishing formats and disciplines.
Drugbank	Comprehensive drug information database
KEGG	Collection of databases dealing with genomes, biological pathways, diseases, drugs, and chemical substances
PharmGKB	Knowledgebase of human genetic variation on drug response
HMDB	Human Metabolome Database is a comprehensive database of small molecule metabolites found in the human body
Transformer	Transformation and transport of xenobiotics in the human body
CTD	Comparative Toxicogenomics Database illuminates how environmental chemicals affect human health.
FooDB	Database containing chemical composition data on common, unprocessed foods.
ChEMBL	Manually curated chemical database of bioactive molecules with drug-like properties
ChemSpider	Chemical structure database
FAERS	Contains information on adverse event and medication error reports submitted to FDA
SIDER	contains information on marketed medicines and their recorded adverse drug reactions
eTOXsys	Highly relevant proprietary data, donated by pharmaceutical organisations
FDA	Food and Drug Administration is a federal agency of the United States Department of Health and Human Services
JAPIC	Japan Pharmaceutical Information Center is a comprehensive pharaceutical database
Drugs.com	Online pharmaceutical encyclopedia which provides drug information

UMLS	Unified Medical Language System is a compendium of many controlled vocabularies in the biomedical science
ATC	Anatomical Therapeutic Chemical Classification System is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties

Table 6. The most representative databases and rescources for polypharmacology and drug safety.

The Human Metabolome database (HMDB)[103] facilitates human metabolomics research, including the identification and characterization of human metabolites. Likewise the Transformer database[104], which comprehensive information on the transformation and transport of xenobiotics in the human body.

Comparative Toxicogenomics Database (CTD)[105] curates scientific data describing relationships between chemicals/drugs, genes/proteins, diseases, taxa, phenotypes, GO annotations, pathways, and interaction modules. The Food Database (FooDB)[106] is a database containing chemical (micronutrient and macronutrient) composition data on common, unprocessed food.

The most often used chemical structure databases are ChEMBL[107] and ChemSpider[108]. ChEMBL is a manually curated chemical database of bioactive molecules with drug-like properties contains compound bioactivity data against drug targets. ChemSpi-

der contains information on more than 63 million molecules from over 280 data sources.

Principal databases to study drug safety are FAERS[91], SIDER[109] and eTOXsys[110]. FAERS is the FDA Adverse Event Reporting System contains information on adverse event and medication error reports submitted to FDA's Safety Information and Adverse Event Reporting Program (MedWatch). SIDER contains drugs, ADRs and drug–ADR pairs data, as well data set of drug indications, extracted from the package inserts using Natural Language Processing. The eTOXsys delivers access to highly relevant proprietary data, donated by pharmaceutical organisations through the eTOX database.

The Food and Drug Administration (FDA)[2] is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices and cosmetics. Likewise-JAPIC[111], a comprehensive database for pharmaceuticals available in Japan.
The website www.drugs.com[112] is an online pharmaceutical encyclopedia which provides drug information, such as drug interactions, side effects and dosis, for consumers and health care professionals.

A widely used classification system for drugs based on their active ingredients is the Anatomical Therapeutic Chemical (ATC) Classification System. This pharmaceutical coding system divides drugs into different groups according to the organ or system on which they act, their therapeutic intent or nature, and the drug's chemical characteristics. It is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC). The Unified Medical Language System (UMLS) is a compendium of many controlled vocabularies in the biomedical sciences. It provides a mapping structure among these vocabularies and thus allows one to translate among the various terminology systems; it may also be viewed as a comprehensive thesaurus and ontology of biomedical concepts.

With the increasing availability of the above databases, various methods have been applied to predict molecular polypharmacology.

In silico methods are gaining extreme interest to detect drug – target – side effect – coadministration (D-T-SE-CO) relationships. These approches fall into six main group. The first group uses systems biology/pharmacology approaches. The second and third group focuses on similarity methods. The fourth an fifth group contains methods to extract and predict information from databases and text mining. The sixth group uses docking methodologies (table 7).

Methodology	Description
Systems biology/ pharmacology approaches	Uses experimental and computational approaches to have the systems-level understanding of diseases and both the therapeutic and adverse mechanisms of drug actions.
Side-effect similarity	Drugs/Targets are mapped based on phenotypic side-effect similarities.
Similarity ensemble approach (SEA)	Relates proteins based on the set-wise chemical similarity among their ligands. It can be used to rapidly search large compound databases and to build cross-target similarity maps.
Knowledge-based approach	Form the associations and depict as a network between various biomolecules stored in various databases.
Text mining tools	Text mining tools were used to dig the mapping information from literature and public databases
Docking/Inverse docking QSAR	Docking a ligand against several targets

Table 7. A broad classification of polypharmacological methods to study polypharmacy and drug safety.[113]

System biology/pharmacology approaches

Systems biology approaches are being frequently used to identify new off-targets off-targets[114]. Combining pathway and network analyses, pharmacokinetic and pharmacodynamic models, and a knowledge of polymorphisms in the genome will enable the development of predictive models of therapeutic efficacy. For example, a study used tissue protein e symptom relation identification predicted that 10.7% side effect is related to off-target tissue effects. [115]

Side effect similarity

Side effects, or the adverse effects of drugs, contain important clinical phenotypic information that may be useful in predicting novel or unknown targets of a drug[116–119]. It has been suggested that drugs with similar side-effect profiles may share common targets[120]. Side-effect similarity of drugs could also be caused by their target proteins being close in a molecular network, which as such could cause similar downstream effects. A study found that only a minor fraction of side-effect similarities (5.8 %) are caused by drugs targeting proteins close in the network, compared to side-effect similarities caused by overlapping drug targets (64%)[121].

Similarity ensemble approach

The Similarity Ensemble Approach (SEA) considers proteins from a chemocentric point of view, relating them through the chemical similarity of their ligands[122]. Similar molecules have similar biological profiles and bind similar targets. SEA is a promising method, which has been successfully applied in many drug-related studies [120,123,124].

Knowledge-based approach

There are different sources of information used in pharmacovigilance to identify, evaluate, and disseminate medical product safety

evidence including spontaneous reports, published peer-reviewed literature, and product labels. For example, Tatonetti et al. presented an adaptive data-driven approach to study FAERS data, and they built a comprehensive database of drug effects and a database of drug-drug interaction side effects[125]. Another study created a knowledge-based framework for the management and effective use of knowledge on adverse drug event prevention. effects[126]

Text mining tools

Text mining is the computational process of extracting meaningful information from large amounts of unstructured text[127]. Text mining is emerging as a tool to leverage underutilized data sources that can improve pharmacovigilance, including the objective of adverse drug event detection and assessment. For example, a study used internet search logs to identify a very common but undetected DDI[128]. Using text mining tools a group from Spain created a webbased search tool of adverse hepatobiliary reactions[129]

Docking/Inverse docking

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure[130]. In contrast to traditional molecular docking, inverse docking is used for identifying

receptors for a given ligand among a large number of receptors. Inverse docking can be used to discover new targets for existing drugs and natural compounds, explain polypharmacology and the molecular mechanism of a substance, find alternative indications of drugs through drug repositioning, and detecting adverse drug reactions and drug toxicity119-120 toxicity[131]. Computational approaches useful for predicting polypharmacology. Statistical data analysis and bioinformatics, ligand-based, and structure-based approaches can be applied either singularly or in combination, to take advantage of the peculiar features and strengths of each approach.[132]

The concept of polypharmacology involves the interaction of drug molecules with multiple targets, which may interfere with a single or multiple disease pathways. The polypharmacological studies could uncover new off-targets for the existing drugs. The approach could provide us with the explanation for the drug side-effects and disastrous toxicities.

Computational approaches for polypharmacology modeling will witness rapid growth and wide application in drug discovery. High level data curation/integration and methodology development from various drug discovery disciplines would be needed for accurate prediction of polypharmacology prediction and rational design of multi-targeting agents. Various challenges still exist for polypharmacology modeling, and rational design[133]

2. OBJECTIVES

- Construction of a database of drug metabolites (DMdb) by careful extraction, curation, and storage of their chemical structures from public and bibliographic sources

- Development of a new knowledge-based statistical approach to predicting drug metabolites based on the contents of DMdb

- Construction of a database of drug-drug interactions (DDIdb) by careful extraction, curation, and storage of pairs of drug names annotated with the safety issues associated with their co-administration

- Analysis of DDIdb to identify trends among drug classes most susceptible to be involved in drug-drug interactions

- Based on the data and knowledge acquired in the previous objectives, review current worldwide policies on polypharmacy to devise a strategy that could help to reduce the number of co-administered drugs and towards a more cost-effective health system

3. RESULTS

3.1 Dmdb: Drug Metabolite Database

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Abstract

The role of drug metabolites in drug efficacy and safety has gained increasing interest over the past years. Because of that, computational approaches can be of great assistance for the rapid structural determination of drug metabolites. Early identification of the most probable sites of metabolism in NCEs is essential for selecting compounds with favourable pharmacokinetic properties. Accordingly, we have constructed DMdb, a drug metabolite database that contains 6124 metabolites for 1149 drugsand 6124 drug metabolites. On this basis, a new statistical approach for predicting the formation of drug metabolites was developed and its performance compared to other established methodologies.

Introduction

Elderly patients usually take multiple drugs daily to treat one or more illnesses. This polypharmacy naturally leads to an increased number of drug-drug interactions. Many diseases are accompanied by one or more physiological and biochemical changes that affect the absorption, distribution, metabolism and elimination (ADME) of those drugs. Accordingly, gaining a better understanding of drug metabolism is of key importance in polypharmacy.

Aging is not regarded as a disease. However, as we become older, our ability to metabolize drugs decreases. This is thought to be due to several physiological changes that occur in the liver, such as a ~40% decrease in liver volume, a ~40% decrease in liver blood flow, and decline in the expression of CYP enzymes. Liver cirrhosis, hypoxia, infection, inflammation, chronic kidney disease and some genetic disorders are known to have effects on the hepatic and extrahepatic metabolism of drugs[1].

Metabolism is a biochemical process in which compounds generally of lipophilic nature are converted to more hydrophilic entities to enhance their elimination from the body[2]. Most metabolites are pharmacologically less active and less toxic than their corresponding parent drugs. This notwithstanding, it is common that biotransformation reactions may lead to undesirable effects such as rapid drug clearance, formation of pharmacologically active metabolites, drug-

drug interactions via inhibition or induction of drug metabolising enzymes, and/or formation of toxic metabolites. Therefore, the identification of the likely sites of metabolism and determination of the metabolic rate, biotransformation pathways, and pharmacological and toxicological liabilities of drug metabolites have become of paramount importance to pharmaceutical research.

Adverse drug reactions can be classified into type A or type B depending on the source of the adverse effect[3]. Type A reactions are associated with the primary pharmacology of the drug and are responsible for 80% of all major adverse effects. Type B are unrelated to the mechanism of action of the drug and thus they do not occur at normal therapeutic doses in most patients. The generation of reactive metabolites are related with some severe cases of type B adverse reactions such as hepatotoxicity, severe cutaneous reactions, anaphylaxis and blood dyscrasias[4.]

The reactions catalysed by xenobiotic biotransforming enzymes are generally divided into two groups referred to as phase I and phase II[5]. Phase I reactions modify the compounds and involve hydrolysis, reduction, and oxidation. These reactions expose or introduce a functional group and usually result in only a small increase of hydrophilicity. Phase II biotransformation reactions are conjugating elements, which include glucuronidation, sulfonation, acetylation, methylation, conjugation with amino acids. The cofactors for these reactions react with functional groups that are either present on the

xenobiotic or are introduced/exposed during phase I biotransformation. Most phase II biotransformation reactions result in a large increase in xenobiotic hydrophilicity, hence they greatly promote the excretion of foreign chemicals.

Our efforts to compile a database of drug metabolites have involved integrating data from different public sources and carefully curating contents from over 800 articles to come up with a total count of 6124 metabolites for 1149 drugs. Drug-metabolite pairs were then used to developed a statistical knowledge-based approach to predict metabolite structures. Details on the database, the methodological aspects and the main results obtained are provided in the following sections.

Database sources

A priority list of 1394 drugs were selected to search for drug metabolite information. Our goal was to find as many confirmed metabolites of each drug as possible. First of all, we searched all main drug databases. We parsed Drugbank[6], HMDB[7] and ChEMBL[8] for the drugs and their metabolites. In some cases, the drug was linked to a metabolite, but no structure was given, or the given structure was ultimately found to be incorrect. The name and the structure of the parent drug were saved to a text file, alongside with the name (tag) and structure of the drug metabolite and the bibliographical reference.

Once the parsing of the databases was completed, we searched for peer-reviewed articles from the NCBI Pubmed, using keywords as “metabolite”, “metabolism” or the name of the parent drug, for example, "metabolite aspirin" or "metabolism aspirin". The first 20 hits were searched for metabolite structures. If an article had the structure of the drug metabolite, we checked for uniqueness in the other sources and, if new, the metabolite structure was drawn and entered into the database. When annotating records in DMdb, efforts were made to ensure that the database is as complete, correct and updated as possible. A simple protocol was used to obtain the SMILES of the metabolites. We used Chemspider and ChEMBL's drawing tool to draw each structure and then export it to SMILES. An important aspect is that special attention was paid in defining the right stereochemistry in the structures. Once we had the SMILES of the metabolite structure, before entering it in the database, we opened it up with Cactvs and confirmed that the structure was plotted correctly when read directly by the software from the SMILES.

Once the SMILES were confirmed, the process was completed by adding the additional information into a text file with the following five columns: name of parent drug, SMILES of parent drug, name of drug metabolite, SMILES of drug metabolite, and reference to the article from which all data were extracted, for example, Drug Metab Dispos 25 (1997) 133. Finally, some additional information was included: the molecular weight, the InChI key of each structure

using RdKit, and the ChEMBL Id for each metabolite, when available.

Overall, a total of 948 drug metabolites were extracted from HMDB, 1239 from DrugBank, 867 from ChEMBL and the rest was manually identified in journals, the vast majority in Drug Metabolism and Disposition, from which all articles were reviewed since 1997.

Methodological aspects

With DMdb available, we implemented a protocol to extract information from the pairs of drug-metabolite structures stored. First of all, an all atom-by-atom superposition was performed to automatically identify the site of metabolism (SoM) and define the type of chemical transformation produced with details on the parts of the molecules that were added, deleted or modified (change in bond order). Figure 1 provides an example of this step using one of the metabolites of nefazodone.

The next step was to mathematically describe the environment surrounding the SoM. For that we used pharmacological fragments (phrags) up to length 5 around the SoM. The presence of a given set of phrags among a significant percentage of drugs associated to a given chemical transformation (CTphrags) can be interpreted, from a statistical point of view, as the specific structural requirements defining it.

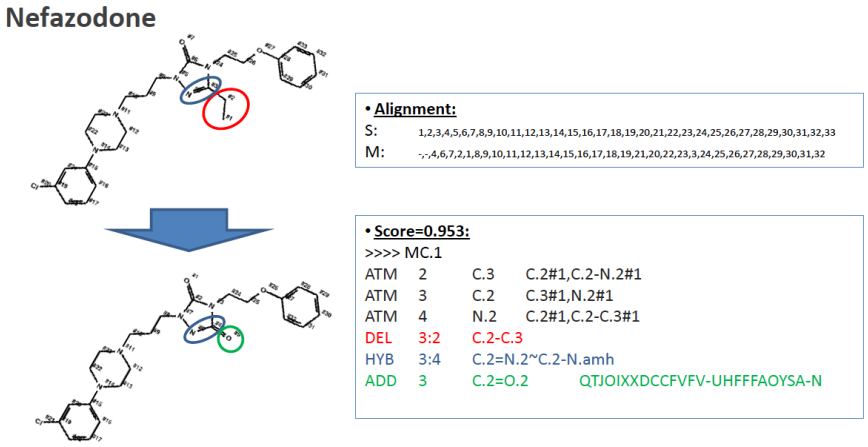

Figure 1. *The all atom-by-atom alignment between nefazodone and one of its metabolites. Portions of the original drug removed (in red), modified (in blue) and added (in green) are marked on the two structures and stored using a purposely designed internal notation.*

1	Amide hydrolysis	25	Diphosphorylation	49	Nitro reduction
2	Aryl-methylation	26	Epoxidation+Hydrolysis	50	N-methylation
3	Azo hydrolisis+Acetylation	27	Epoxidation+Opening	51	N-oxidation
4	Azo hydrolisis	28	Ester hydrolysis	52	N-oxide reduction
5	Carbamate hydrolisis+Acetylation	29	Esterification	53	O-dealkylation
6	Carboxylation	30	Glucuronidation	54	O-methylation
7	C-Methylation	31	Glutathione conjugation	55	Oxidation
8	Cysteine conjugation	32	Glycine conjugation	56	Oxidation+Glucuronidation
9	Dealkylation	33	Hydrogenation	57	Oxidative deamination
10	Dealkylation+Hydroxylation	34	Hydrolysis	58	Oxidative deamination+Oxidation
11	Dealkylation+Oxidation	35	Hydrolysis+Glucuronidation	59	Oxidative deamination+Reduction
12	Deamination	36	Hydrolysis+Oxidation	60	Oxidative decarboxylation
13	Dearylation	37	Hydrolysis+Sulfation	61	Oxidative desulfuration
14	Debromination	38	Hydrolytic deamination	62	Phosphorylation
15	Decarboxylation/Dearylation	39	Hydroxylation	63	Reduction
16	Decarboxylation/Dearylation+Hydroxylation	40	Hydroxylation+Transposition	64	Reduction+Glucuronidation
17	Dechlorination	41	Methoxylation	65	Reduction+Sulfation
18	Dechlorination+Hydroxylation	42	N-acetylation	66	S-methylation
19	Dehydrogenation	43	N-deacetylation	67	S-oxidation
20	Dehydroxylation	44	N-dealkylation+a-Oxidation	68	S-reduction
21	Deiodination	45	N-dealkylation	69	Sulfation
22	Denitration	46	N-dealkylation+Hydroxylation	70	Taurine conjugation
23	Dephosphorylation	47	N-didealkylation	71	Triphosphorylation
24	Dihydroxyacetone cleavage	48	Nitro reduction+Acetylation		

Figure 2. *The all atom-by-atom alignment between nefazodone and one of its metabolites. Portions of the original drug removed (in red), modified (in blue) and added (in green) are marked on the two structures and stored using a purposely designed internal notation.*

Accordingly, each chemical transformation is defined by a unique set of CTphrags. The full list of 71 chemical transformations for which CTphrag models could be derived is provided in Figure 2.

Then, a statistical analysis is performed to assess how often the presence of a given CTphrag in the structure of the drug actually leads to the chemical transformation encoded by the CTphrag. This can be interpreted as the probability that a chemical structure containing that CTphrag would actually undergo that chemical transformation. This is one of the most appreciated aspects of the methodology developed as it assigns every metabolite predicted a confidence score that reflects current metabolite knowledge on drug metabolites, as stored in Dmdb.

Finally, we had to validate the methodology to ensure a proper behavior of the confidence score. For that, we divided the full contents of DMdb into a training set (80% of drug-metabolite pairs) and validation set (20% of drug-metabolite pairs) and repeated the operation 100 times. The results of this validation exercise are illustrated in Figure 3. As can be observed, an optimal balance between recall and precision is achieved in confidence scores between 0.2 and 0.3. Depending on whether the preference to shift the balance to have more recall or more precision expected from the metabolites predicted, the user can use lower or higher confidence scores, respectively.

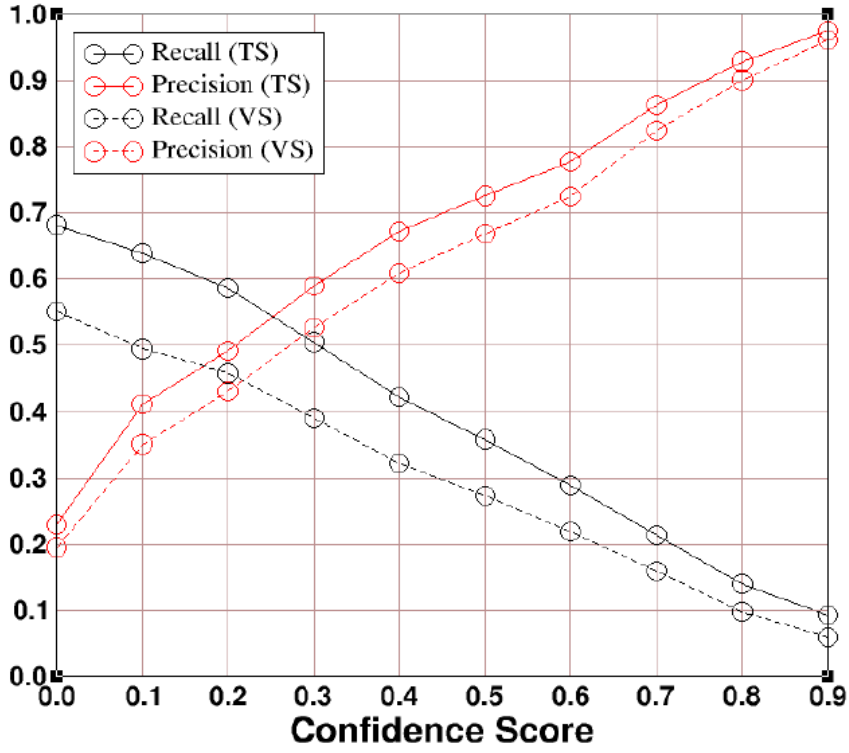

Figure 3. *Levels of recall (in black) and precision (in red) for the training (TS) and validation (VS) sets along the full range of confidence scores.*

Results and Discussion

Analysis of DMdb contents. A total of 829 scientific articles published in 136 journals were used as a reference data to create DMdb. Figure 4 shows the distribution of sources of the metabolite data. It is observed that the main source of drug metabolites is the journal Drug Metabolism and Disposition (in blue), followed by DrugBank (in red), Xenobiotica (in orange), and ChEMBL (in green). These four sources contribute with almost 83% of the contents in DMdb.

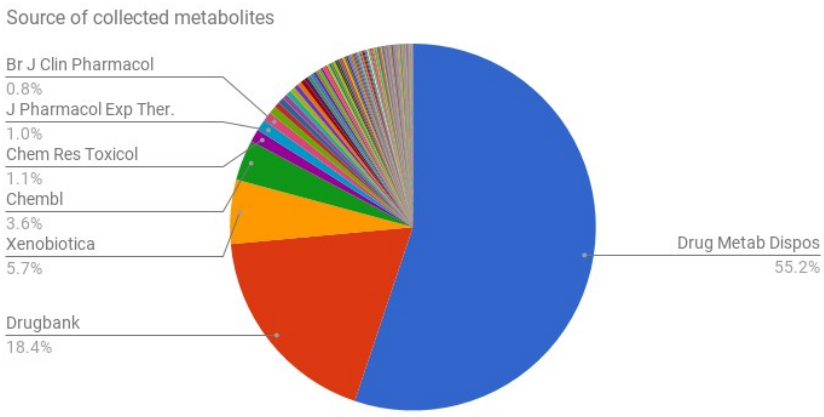

Figure 4. Distribution of sources of drug metabolite data.

The mean number of metabolites per drug in DMdb is 5. Figure 5 shows the distribution of the number of drugs having a certain number of metabolites. Most drugs have between 1 and 2 metabolites whereas only a couple of drugs have more than 20 metabolites.

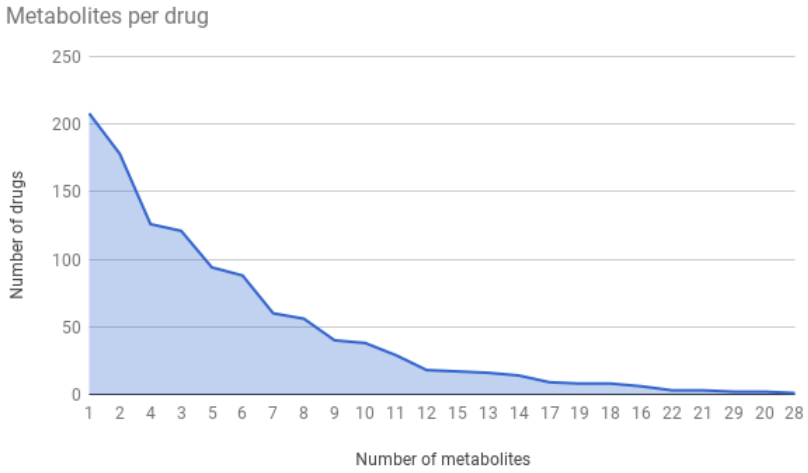

Figure 5. Number of drugs having a certain number of metabolites.

Comparative performance with other methods. At the time of initiating this project, there were very few drug metabolite databases available in the public domain, those available were of limited scope and none of them was actually being exploited to predict drug metabolism. More recently, several computational approaches to predict xenobiotic metabolism have emerged. XenoSite is a tool for predicting the atomic sites at which xenobiotics will undergo metabolic modification by Cytochrome P450 enzymes[9]. SMARTCyp utilizes a set of pre-computed activation energies in combination with topological accessibility descriptors[10]. Metaprint2D derives likelihoods of metabolic transformation for atoms with a defined atomic environment by mining large biotransformation databases[11]. CypScore has a collection of six multiple linear regression (MLR) models to cover the major reaction types of CYPs[12]. RS-WebPredictor is a array of pre-trained support vector machine (SVM) models using topological descriptors and SMARTCyp reactivities for predicting SoMs[13]. FAME is a set of random forest models for predicting phase I and II metabolism in different species trained on drugs, drug-like molecules, endogenous metabolites and natural products[14]. Although these tools seem promising, they remain as prediction data, with a certain precision score, which usually is not higher than 60-70%. All prediction methods are rely on a starter dataset with real data, and we hope our database can help improve their prediction score and improve precision.Some of these tools are highly used but they share a common limitation: they fail to provide a probabilistic

confidence score that allows the user to assess the validity of the predicted metabolite structures.

In addition, some of these methods aim at being comprehensive in the enumeration of metabolite structures, often resulting in hundreds of proposed metabolites that are of limited use to the researcher.
In contrast, our approach generates a limited number of metabolites predicted with an associated probabilistic confidence score. As an example, Figure 6 shows the 7 metabolites predicted for efavirenz, all of them but one having been reported experimentally. Alongside with the predicted metabolite structure, we provide also information on the chemical transformation occurred, the molecular weight difference with respect to the parent drug (to assist in its spectrometric identification), and the confidence score.

Pinto et *al*.[15] performed an analysis of the estrogenic activity of the metabolites for 50 drugs. Some of the drugs had already known metabolites with confirmed estrogenic activity, such as Mestranol or Formonometin. Their main interest was to find metabolites with higher estrogenic activity than the parent drug because xenobiotic chemicals exhibiting estrogenic activity often interact with more than one estrogen receptor subtypes and can produce many biological and adverse health effects in mammals, such as early puberty in females, reduced sperm counts, altered functions of reproductive or-

gans, obesity, altered sex-specific behaviours, and increased rates of some breast, ovarian, testicular, and prostate cancers.

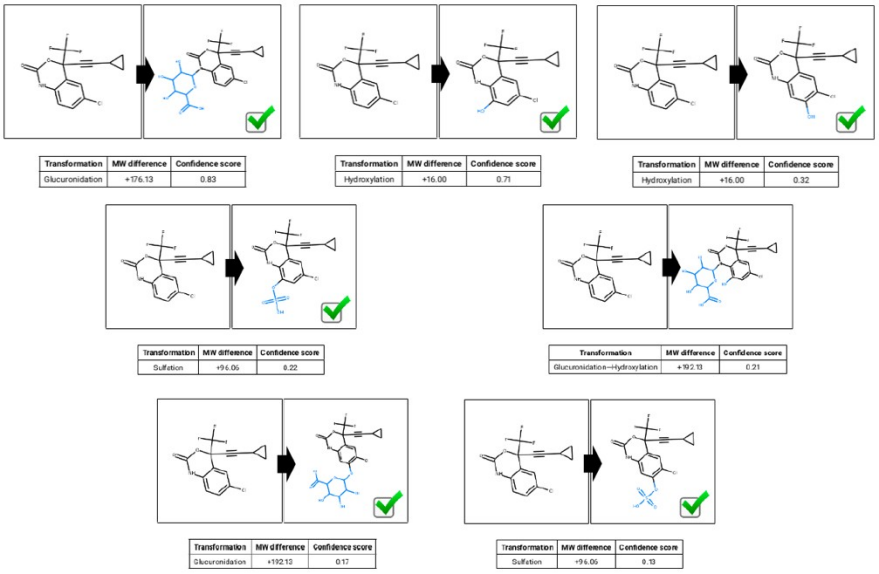

Figure 6. *The list of 7 metabolites predicted for efavirenz. The portion of the metabolite structure that has been added relative to the parent drug is marked in blue.*

Fetal, newborn, and juvenile mammals are reported to be particularly sensitive to chemicals having estrogenic activity, and effects have been observed at very low doses[16]. Using our method based on DMdb, we could predict all 38 parent drug metabolites with estrogenic activity reported in their manuscript in a record time of 1 minute. Besides it also predicted an estrogenic activity for a drug, what they had in their negative set. This is a confirmation what CT-link's prediction method is highly reliable and fast.

Finally, Piechota et al.[17] performed a much more comprehensive validation exercise using three different softwares to predict metabolites, namely, MetaPrint2d, Meteor, and SMART-Cyp, on two different data sets, one composed of a set of 28 homogeneous non-steroidal anti-inflammatory drugs (NSAIDS) and paracetamol (DS1) and the other one containing a diverse set of 30 top-selling drugs (DS2). The results are summarized in Figure 7. As it can be observed, they pushed the boundaries of all methods to predict up to 400 metabolites per drug. Obviously, the larger the number of metabolites generated the higher the recall (recovery of known drug metabolites) but at the expense of heavily penalizing precision.

On average, when they generate 5 metabolites per drug, they achieve recalls around 45% (DS1) and 35% (DS2) with precisions around 25% (for both sets), but when the methods are pushed to generate 20 metabolites per drug, recall levels increase up to 60% (DS1) and 70% (DS2) but precisions decay below 10% (for both sets). In contrast, when we set the confidence score at 0.10, recall and precision values are 47% and 21% for DS1 and 49% and 28% for DS2, and when we move the confidence score bar a bith higher at 0.20, then recall values decrease a bit (42% for DS1 and 49% for DS2) but precision values increase significantly (30% for DS1 and 37% for DS2) at levels unachievable by any other method used in their work.

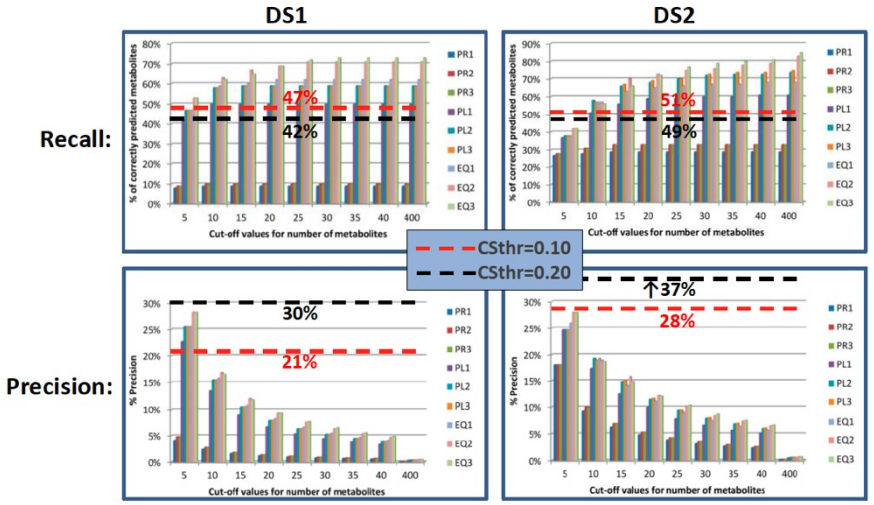

Figure 7. *Comparative performance of recall (top) and precision (bottom) values of our method against MetaPrint2D, Meteor, and SMART-Cyp applied to the DS1 (left) and DS2 (right) drug sets (see text for details). Red and black dashed lines refer to the results obtained with confidence score thresholds (CSthr) of 0.10 and 0.20, respectively.*

Conclusions

A new database of drug metabolites (DMdb) has been constructed. Its contents has been extracted from a diverse range of publicly available sources and every record has been manually curated. The quality of its contents, both in terms of correctness and coverage, is reflected in the quality of the metabolite predictions made by a new purposely designed statistical method. Although much work is still needed to reach high levels of performance when predicting drug metabolites, our method can be regarded as the state-of-the-art in the field and it represents an incremental contribution towards developing safer, more effective, drugs.

Acknowledgements

We acknowledge the contribution from Dr David Vidal in the development of the methodology for predicting drug metabolites. We also acknowledge Dr Scott Boyer for the many discussions and recommendations made to this work.

References

1. R. Sane, M. Sinz. Chaper 1 Introduction of Drug Metabolsim and Overview of Disease Effect on Drug metabolism, Drug Metabolism in Diseases (Elsevier Inc. 2017)

2. Almazroo OA, Miah MK, Venkataramanan R. Drug Metabolism in the Liver. Clin Liver Dis. 2017 Feb;21(1):1-20. doi: 10.1016/j.cld.2016.08.001. Epub 2016 Oct 15. Review. PubMed PMID: 27842765.

3. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7(1):11-22. doi:10.1177/2042098615615472

4. Attia SM. Deleterious effects of reactive metabolites. Oxid Med Cell Longev. 2010 Jul-Aug;3(4):238-53. Doi: 10.4161/oxim.3.4.13246. Review. PubMed PMID:20972370; PubMed Central PMCID: PMC2952084.

5. Crettol S, Petrovic N, Murray M. Pharmacogenetics of phase I and phase II drug metabolism. Curr Pharm Des. 2010;16(2):204-19. Review. PubMed PMID: 19835560.

6. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2008 Jan;36(Database issue):D901-6. Epub 2007 Nov 29. PubMed PMID: 18048412; PubMed Central PMCID: PMC2238889.

7. Wishart DS, Tzur D, Knox C, Eisner R, Guo AC, Young N, Cheng D, Jewell K, Arndt D, Sawhney S, Fung C, Nikolai L, Lewis M, Coutouly MA, Forsythe I, Tang P, Shrivastava S, Jeroncic K, Stothard P, Amegbey G, Block D, Hau DD, Wagner J,Miniaci J, Clements M, Gebremedhin M, Guo N, Zhang Y, Duggan GE, Macinnis GD, Weljie AM, Dowlatabadi R, Bamforth F, Clive D, Greiner R, Li L, Marrie T, Sykes
BD, Vogel HJ, Querengesser L. HMDB: the Human Metabolome Database. Nucleic Acids Res. 2007 Jan;35(Database issue):D521-6. PubMed PMID: 17202168; PubMed Central PMCID: PMC1899095.

8. Gaulton A, Bellis LJ, Bento AP, et al. ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res. 2011;40(Database issue):D1100-7.

9. Matlock MK, Hughes TB, Swamidass SJ. XenoSite server: a web-available site of metabolism prediction tool. Bioinformatics. 2015 Apr 1;31(7):1136-7. doi:10.1093/bioinformatics/btu761. Epub 2014 Nov 18. PubMed PMID: 25411327.

10. Rydberg P, Gloriam DE, Olsen L. The SMARTCyp cytochrome P450 metabolism prediction server. Bioinformatics. 2010 Dec 1;26(23):2988-9. doi: 10.1093/bioinformatics/btq584. Epub 2010 Oct 14. PubMed PMID: 20947523.

11. Carlsson L, Spjuth O, Adams S, Glen RC, Boyer S. Use of historic metabolic biotransformation data as a means of anticipating metabolic sites using MetaPrint2D and Bioclipse. BMC Bioinformatics. 2010 Jul 1;11:362. doi: 10.1186/1471-2105-11-362. PubMed PMID: 20594327; PubMed Central PMCID: PMC2912884.

12. Hennemann M, Friedl A, Lobell M, Keldenich J, Hillisch A, Clark T, Göller AH. CypScore: Quantitative prediction of reactivity toward cytochromes P450 based on semiempirical molecular orbital theory. ChemMedChem. 2009 Apr;4(4):657-69. doi:10.1002/cmdc.200800384. PubMed PMID: 19243088.

13. Zaretzki J, Bergeron C, Huang TW, Rydberg P, Swamidass SJ, Breneman CM.RS-WebPredictor: a server for predicting CYP-mediated sites of metabolism ondrug-like molecules. Bioinformatics. 2013 Feb 15;29(4):497-8. doi:10.1093/bioinformatics/bts705. Epub 2012 Dec 14. PubMed PMID: 23242264; PubMed Central PMCID: PMC3570214.

14. Kirchmair J, Williamson MJ, Afzal AM, Tyzack JD, Choy AP, Howlett A, Rydberg P, Glen RC. FAst MEtabolizer (FAME): A rapid and accurate predictor of sites of metabolism in multiple species by endogenous enzymes. J Chem Inf Model. 2013 Nov 25;53(11):2896-907. doi: 10.1021/ci400503s. Epub 2013 Nov 12. PubMed PMID:24219364.

15. Prediction of Estrogenic Bioactivity of Environmental Chemical Metabolites Caroline L. Pinto, Kamel Mansouri, Richard Judson, and Patience Browne Chemical Research in Toxicology 2016 29 (9), 1410-1427
DOI: 10.1021/acs.chemrestox.6b00079

16. Bittner GD, Denison MS, Yang CZ, Stoner MA, He G. Chemicals having estrogenic activity can be released from some bisphenol A-free, hard and clear, thermoplastic resins. Environ Health. 2014 Dec 4;13:103. doi: 10.1186/1476-069X-13-103. PubMed PMID: 25477047; PubMed Central PMCID: PMC4298073.

17. Piechota P, Cronin MTD, Hewitt M, Madden JC. Pragmatic approaches to using computational methods to predict xenobiòtic metabolism. J. Chem. Inf. Model. 2013, 53(6), 1282-1293.

3.2 Propensity of drug classes to drug interactions

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Abstract

The demographic shift towards an older population is dramatically increasing the public health burden. The average 70-year- old now takes seven different prescription medications. This causes many problems such as drug-drug interactions, serious side effects, and non-adherence to treatment. National health agencies are clearly interested in reducing polypharmacy, given the huge sums of money they spend on the resulting side effects and hospitalizations. In this work, we analyzed the FDA confirmed DDIs and their safety profiles as well as the profiles of the interacting drugs. We categorized the drugs by Anatomical Therapeutic Chemical (ATC) Classification System, to understand the connection between ATC drug classes and safety events and we detected that drug classes on the

ATC 4th level with the highest propensity are targeted at cardio-vascular, nervous system and anti-infective diseases.

Introduction

The average 70-year old now takes seven different prescription medications. The use of multiple medications is often referred to as polypharmacy, but also refers to the administration of more medications than clinically indicated, representing unnecessary drug use. This causes many problems such as drug-drug interactions, serious side effects, and non-adherence to treatment. With increasing, polypharmacy comes rising morbidity and mortality, and public health agencies are being forced to take notice. The Food and Drug Administration (FDA) recently recommended tighter controls on prescriptions. National health agencies are clearly interested in reducing polypharmacy, given the huge sums of money they spend on the resulting adverse reactions and hospitalizations[1]. A small number of studies have shown the potential to reduce polypharmacy, but more research is needed for a molecular-level understanding of drug effects and drug pathways[2].

According to the Food and Drug Administration (FDA), there are over 2 million ADRs reported yearly, of which 100,000 cases result in patient death[3]. Because of this, ADRs have become the 4th leading cause of death in the US and are associated with a financial cost of 136 million dollars per year[1]. Hence, taking one drug can cause side effects but taking a combination of several drugs can lead

to unexpected life-threatening adverse events. In this respect, it is worth stressing that ADRs increase exponentially with 4 or more drugs taken in combination, which puts the elderly population particularly exposed to this extreme danger, since a 65-year old patient is recognized to take, on average, 5 different drugs for a diverse range of health conditions[4].

Identifying drug-drug interactions is a major challenge in drug development.

There are many methods available, but until now, none of them can predict if two drugs will interact with each other or not. Every method has its limitations, with the newer methods, like the data-driven approach by Tatonetti NP *et al*.[5], producing decent predictions of not only if the drugs will interact, but also what will be the expected side effects.

Ligand-based DDI predictions are QSAR and similarity search based, depending on the number of known ligands for target protein of interest[6].

There are also receptor-based DDI predictions, using docking methods[7]. which main limitation is that they cannot be applied to targets lacking 3D structures. The literature based text mining predictions suffer from the problem of redundancy in the compound/gene names in the literature[8]. In the recent years network-based approaches have become the hot topic in DDI prediction studies[9].

Relying on the usage of bipartite graphs, just like the phenotype-based approaches[10]. They are considered as the most reliable methods so far. The latest idea is about making drug interaction predictions based on side effect similarity[11]. If two drugs share a side effect, there is a high possibility that they share a target as well.
The problem for studying DDIs, is that there is not enough precise information available for DDIs nor for drugs, and using this data to predict new effects cannot be complete and truly reliable. Another weak point of all the approaches trying to predict interactions, is the difficulty to put them into practice.

Methods

We manually curated an in-house database of currently known DDIs, targets, safety terms, and participating drugs. Drug-drug interaction data and their possible adverse effect were extracted from online databases Drugbank[13] and drugs.com[14]. The DDIs in drugs.com are divided into three groups, based on their therapeutic effect (minor, moderate and major). We decided to extract just the major interactions to stay within manageable numbers and to detect the most significant drug combinations.

The drug safety profile was downloaded from Comparative Toxicogenomic Database[17], Drugmatrix[18], PharmGKB[19], and drug labels. Chemical structures were extracted from public repositories such as DrugBank, PubChem[15] and ChEMBL[16]. We downloaded drug target information from the Therapeutic Target Database, UniProt and

Drugbank. In total, our raw database contained 57.494 DDIs, 1034 safety terms, and 1033 drugs, (figure 1).

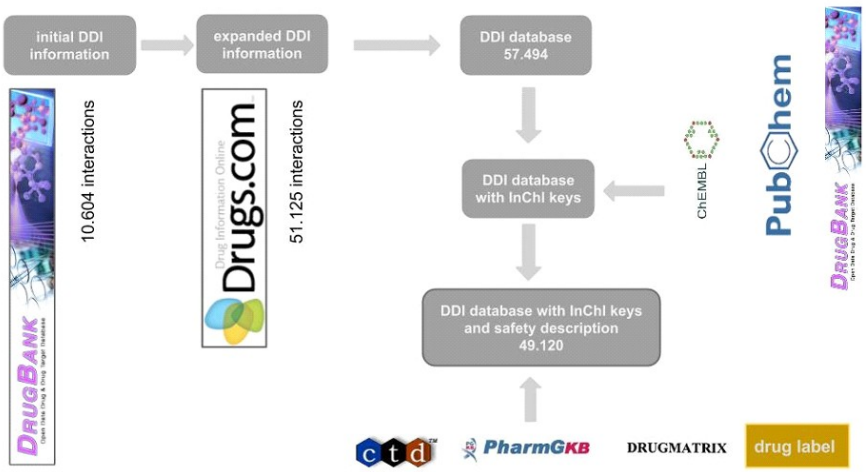

Figure 1. Flowchart of protocol to integrate and curate the contents from different sources

The IUPAC International Chemical Identifiers (InChI), precisely InChI keys were used for an identification key for each compound. Then, drugs were categorized by the Anatomical Therapeutic Chemical (ATC) Classification System[12] which has five levels. The drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance.

We parsed the safety description and we removed the ones with unclear description. Then, the safety terms had been linked to the Unified Medical Language System (UMLS). For every safety

record, we collected synonyms to make sure the program detects every illness listed, even if the illness is described by its acronym.

ATC code	Descriprion
A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	metformin (5th level, chemical substance)

Table 1. Example of ATC classification system

Consistently, safety terms described the same side effect with a distinct name (renal toxicity and nephrotoxicity) but not classified as synonyms in UMLS. It was very time-consuming to manually collapse those terms. Nevertheless, it was a crucial step to get a better view of the analysis. It is worth to mention, that even though "elderly" are not considered as an illness, it was present in 27% of the DDI safety description.

We filtered our database, and we removed DDI pairs with no clear safety description. Thus, we ended up with 49.120 DDIs with safety description. In case of 24.079 DDIs, both participating drug with safety profile, and 27.676 with target profile for both compounds.

In the database we had 23.879 DDIs, where both participating

compounds had safety and target profile information. Next, we checked how many of them shared at least one target, and how many of them shared at least one cytochrome target. We found out, that 13.29 DDIs shared at least one target, and 8.343 had at least one cytochrome target in common.
As expected, the most common cytochrome targets are CYP3A4, CYP2D6, CYP2C9, CYP1A9, and CYP2C8. While the most common GPCR targets are Multidrug resistance protein 1, Sodium-dependent noradrenaline transporter, Potassium voltage-gated channel subfamily H member 2, Sodium-dependent serotonin transporter, Sodium-dependent dopamine transporter, and Serum albumin.

The ability of drugs to act as inducers, inhibitors, or substrates is predictive of whether concurrent administration of these compounds with a known substrate might lead to altered drug disposition, efficacy or toxicity. Hence, we also wanted to see the drug-target relation, whether the target acts as an inhibitor, an inducer, a substrate or it is inconclusive. Figure 2 shows the distribution of CYP targets, and their role. We see that the main combination is substrate and inconclusive, as well as substrate and inhibitor.

Drug targets are also associated with certain safety terms. Based on the frequency of the safety term in DDIs and drugs, as well the target significance, we reviewed what safety terms are linked to DDI, drug, and target.

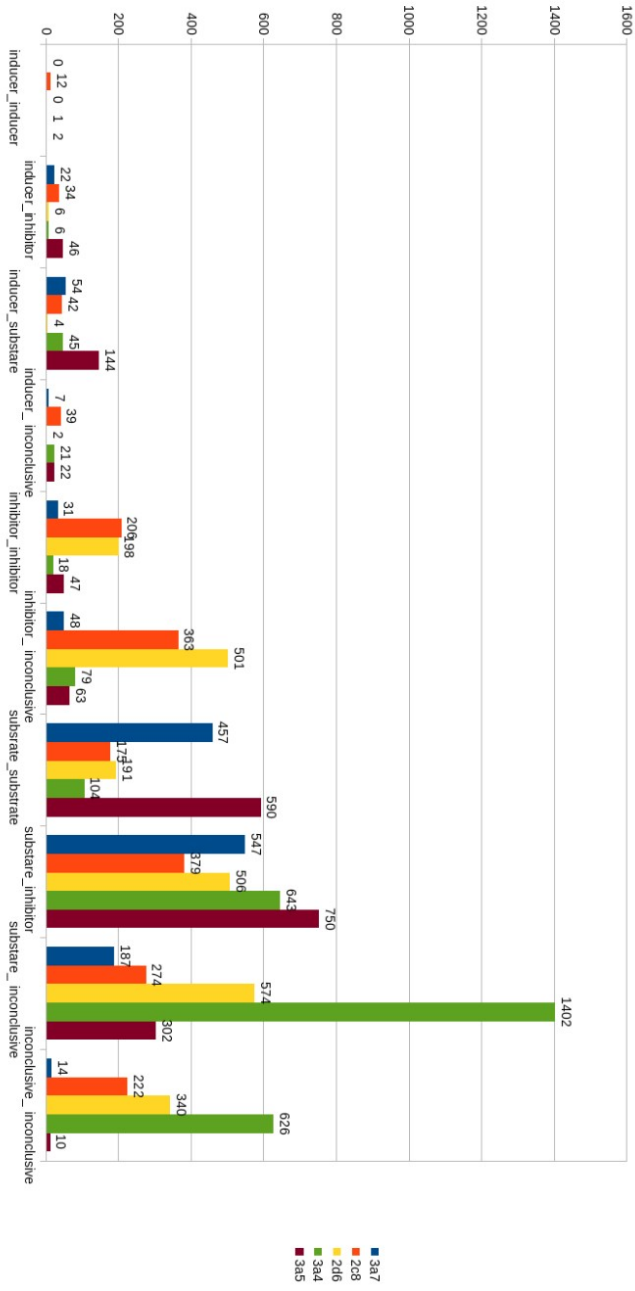

Figure 2. Distribution of the role of CYP targets in DDIs

For the CYP3A4 the top five safety terms are dizziness, depression, nervousness, respiratory depression, and lightheadedness; for CYP2D6 is dizziness, tachycardia, lightheadedness, depression, and nervousness, for CYP2C9, is dizziness, depression, nervousness, agitated and pain, for CYP1A2, is dizziness, increased heart rate, lightheadedness, nervousness, and arrhythmia, for CYP2C19 is depression, nervousness, dizziness, respiratory depression, and increased heart rate, for CYP2C8 is dizziness, palpitation, arrhythmia, pain, and nausea.

For multidrug resistance protein 1 is dizziness, lightheadedness, arrhythmia, increased heart rate and torsades de pointes, for sodium-dependent noradrenaline transporter is agitated, increased heart rate, confusion, increased body temperature, and depression, for potassium voltage-gated channel subfamily H member 2 is arrhythmia, tachycardia, depression, torsades de pointes and nervousness, for sodium-dependent serotonin transporter is increased heart rate, agitated, increased body temperature, mydriasis, and depression, for sodium-dependent dopamine transporter is agitated, increased heart rate, confusion, increased body temperature, and mydriasis, for serum albumin is inflammation, dizziness, urinary tract disorder, gastrointestinal disorder, and nausea.

We checked how many times a safety term is present in the DDIs descriptions. Using the compounds present in DDIs with at least one safety description, we created a confusion matrix (Table 1). In this matrix, we analyzed how many DDIs and their interacting

drugs are reported to have the same side-effect. We also counted the DDIs not reported with a safety term. In order to complete the matrix, we did the same analysis for the single drugs. To find the safety events that are significantly present in DDIs, we applied chi-square analysis over this matrix.

Drug and safety event (A)	Drug with no safety event (C)
DDI and safety event (B)	DDI with no safety event (D)

Table 1. Confusion matrix of appearance of safety events in DDIs and single drugs

Using cell "B" of the matrix of table 1, we created three subgroups:

1) both of the drugs in the DDI are linked to the safety event,

2) one of the drugs is annotated to this safety term,

3) none of them are.

For every drug and safety term pair we completed this analysis. With this data, we created a second confusion matrix (table 2). We also applied chi-square analysis over this matrix.

DDIs involving drugs and linked to safety term	DDIs not involving drugs and linked to safety
DDIs involving drugs and not linked to safety	DDIs not involving drugs and not linked to safety

Table 2. Confusion matrix of appearance of safety events in DDIs

Safety terms, that are annotated to DDI, but neither of the interacting drug, which suggest that those effects are a result of the drug combination (Appendix B).

Until this point we used InChI keys in the analysis, but from this point we switched to ATC codes. Removing the last level of the ATC code, we clustered the drugs into drug-classes. As we did previously, for every ATC code and safety term pair we did the same analysis. We formed a new matrix based on the previous matrix's cells (table 3) and a chi-square analysis was also applied over this matrix.

DDIs involving drugs in ATC level and linked to safety term	DDIs not involving drugs in ATC level and linked to safety
DDIS involving drugs in ATC level and not linked to safety	DDIS not involving drugs in ATC level and not linked to safety

Table 3. Confusion matrix of appearance of safety events in ATC drug classes

Results

In 49.120 studied interactions, we have found 859 different safety events for the DDIs with the most frequent being dizziness, hypotension, hypertension, pain, and depression(table 4). In the top 25 safety terms, we see various life-threatening events, such as tachyarrhythmia, arrhythmias, irregular heartbeat, torsade de pointes,

ventricular arrhythmia, hallucinations, and respiratory distress syndrome. What is worrisome, is to find death and sudden death in the top of the list.

	Safety term	Frequency %
1	Dizziness	62,76%
2	Hypotension	37,99%
3	Hypertension	37,35%
4	Pain	28,03%
5	Depression	27,91%
6	Tachyarrhythmia	27,75%
7	Nervous	27,48%
8	Syncope	26,25%
9	Tendinopathy	25,06%
10	Arrhythmias	17,70%
11	Hyperthermia	17,66%
12	Irregular heartbeat	17,03%
13	Hypoventilation	16,71%
14	Torsade de pointes	13,62%
15	Confusion	13,15%
16	Death	12,56%
17	Ventricular arrhythmia	12,30%
18	Seizures	11,35%
19	Fever	10,76%
20	Weakness	10,27%
21	Nausea	10,03%
22	Hypokalemia	9,95%
23	Hallucinations	9,78%
24	Sudden death	9,68%
25	Respiratory distress syndrome	9,60%

Table 4: list of safety issues most often linked to DDIs

Those DDIs were made of 865 single drugs, and we obtained safety profiles for 808 of them. We determined that the ten most common

safety terms for single drugs are nausea, dizziness, headache, rash, vomiting, diarrhea, weakness, pain hypotension, and itching. We can certainly see, that safety terms of single drugs are not as that serious as the possible safety effects of the combination of drugs.

The top presented drugs in DDIs are acetaminophen, caffeine, acetylsalicylic acid, trimipramine, clomipramine, clozapine, hydrochlorothiazide, imipramine, perphenazine, and thioridazine (table 5). Hydrochlorothiazide is a cardiovascular drug, while the rest has a therapeutic effect on the nervous system. Acetaminophen is present in 458 DDIs (0.98%), caffeine in 440 DDIs (0.90%) and acetylsalicylic acid in 439 DDIs (0.88%). The frequency of the most present drugs is in table 5.

Rank	**Drug name**	**Frequency**
1	Acetaminophen	0,98
2	Caffeine	0,90
3	Acetylsalicylic acid	0,88
4	Trimipramine	0,87
5	Clomipramine	0,86
6	Clozapine	0,86
7	Hydrochlorothiazide	0,84
8	Imipramine	0,82
9	Perphenazine	0,81
10	Thioridazine	0,81

Table 5: list of drugs with high propensity to DDIs

After the collation of the ATC codes to 4th level, we got 36.336 DDIs, with 342 unique fourth level ATC codes. The top drug classes with a high propensity to DDIs are non-selective monoamine reuptake inhibitors, beta-blocking agents, plain, selective, hydantoin

derivatives, protein kinase inhibitors, beta-blocking agents, non-selective, benzodiazepine derivatives, fluoroquinolones, thiazides, plain, platelet aggregation inhibitors excl. heparin, and other antidepressants (table 6).

ATC category name	ATC code	Frequency
Non-selective monoamine reuptake inhibitors	N06AA	9,72
Beta-blocking agents, plain, selective	C07AB	5,69
Hydantoin derivatives	N03AB	5,48
Protein kinase inhibitors	L01XE	5,36
Beta-blocking agents, non-selective	C07AA	4,97
Benzodiazepine derivatives	N05BA	4,75
Fluoroquinolones	J01MA	4,74
Thiazides, plain	C03AA	4,71
Platelet aggregation inhibitors excl. heparin	B01AC	3,83
Other antidepressants	N06AX	3,54

Table 6: list of drug classes with high propensity

Safety terms, that are annotated to DDI, but neither of the interacting drug, which suggests that those effects are a result of the drug combination (Appendix B.1). Most commonly occurring safety terms for ATC 4th level are tachyarrhythmia, depression, hypoglycemia, dizziness and tendinopathy (Appendix B.2).

There are thirteen ATC groups (A:Alimentary tract and metabolism, B:Blood and blood forming organs, C:Cardiovascular system, D:Dermatologicals, G:Genito-urinary system and sex hormones, H:Systemic hormonal preparations, excluding sex hormones and insulins, J:Antiinfectives for systemic use, L:Antineoplastic and immunomodulating agents, M:Musculo-skeletal system, N:Nervous

system, P:Antiparasitic products, insecticides and repellents, R:Respiratory system, S:Sensory organs, V:Various)

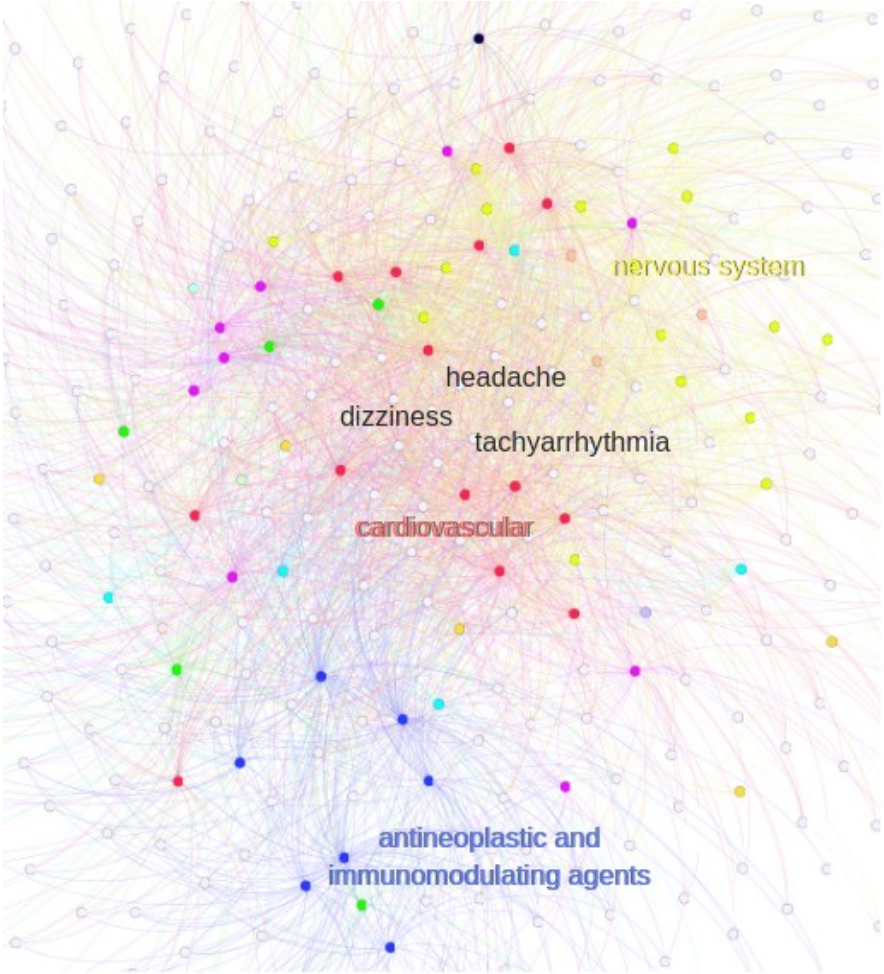

Figure 3. Interaction network between drug classes and safety events.

We created a graph to display the result of the chi-square analysis based on the confusion matrix of the appearance of safety events in the ATC drug classes (figure 3). L (dark blue), C (red) and N (yellow) drug classes show a strong signal while the top side effects take place in the middle of the graph. S (pink), J (green), M (cyan)

and A (orange) drug classes do not show a strong connection between the group members and safety terms.

Next, we displayed the drug pairs of 4th level ATC group (figure 4). There is a strong cross-signaling in drug class C, drug class J, and drug class N. A class has two fourth level drug pairs; sulfonamides, urea derivatives, and H2-receptor antagonists. Interestingly inside the group, they do not show significant interaction. B interacts with most of the other drug classes. C has many drug pairs in common and they are also connected with most of the other drug groups, especially with the ones related to N. J is highly connected with group C. The group L has two subgroups that are showing connections with other drug classes; “other antineoplastic agents” and “other immunosuppressants”.

In M, the subgroups “other centrally acting agents” and “coxibs” show a high diversity of drug groups, which can be found among most of the other drug classes. Most of the drugs that show a high propensity to DDIs are related to N. Subgroups “other antidepressants”, “non-selective monoamine reuptake inhibitors” and “other antipsychotics” are linked to various drug groups, especially with the compounds related to drug class C. Drug class R also shows a high diversity of shared drug pairs with other drug classes. S has four subgroups that are linked to significant drug pairs. Those drug classes are antibiotics, anti-inflammatory agents, non-steroids, beta-blocking agents and anti-infectives. Beta-blocking agents have significant connections with group C and N.

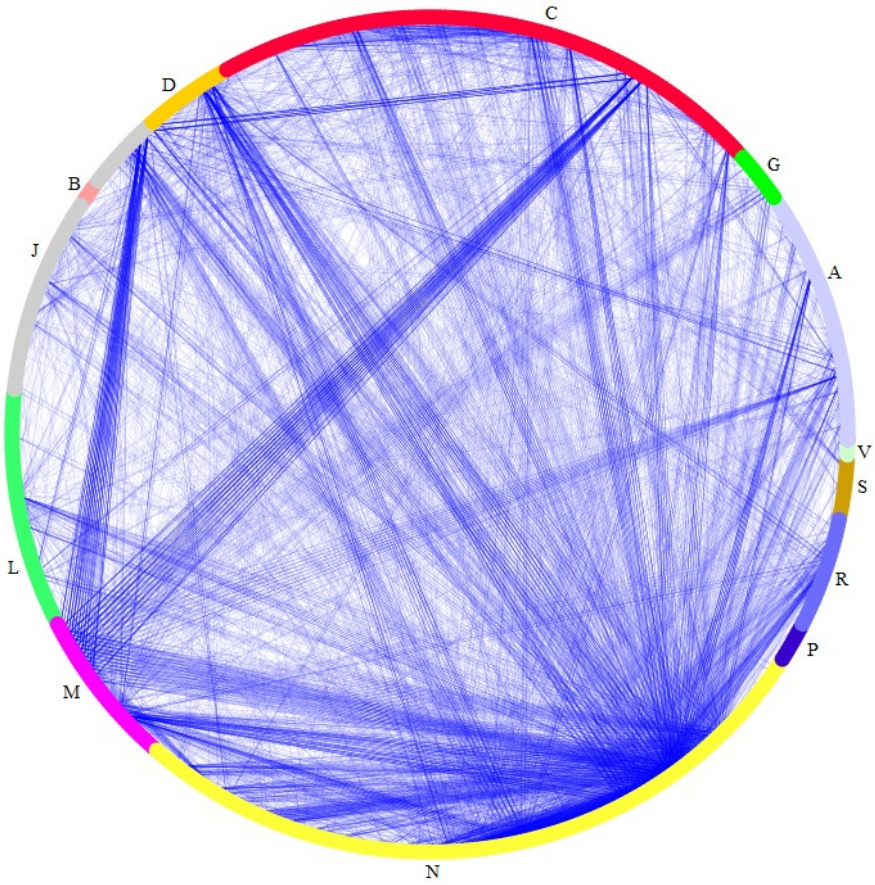

Figure 4. Shares safety terms between ATC 4th level drug classes.

The highest number of shared safety terms present in ATC 4th level drug classes belong to non-selective monoamine reuptake inhibitors, other antidepressants, thiazides, plain, dihydropyridine derivatives and other psychotics (appendix b.3).

Discussion

The top five side effects of DDIs and single drugs are related to the general not-feeling-well side-effects. This may mean that, as present

in most of the single drugs, these side-effects are probably the effect of the drug and not a new side-effect of the DDI. However, if we examine the other significant side-effects of single drugs, we can see they are not life-threatening. In the contrary, many side-effects of the DDIs can be serious, even lethal, such as “torsade de pointes”, respiratory depression or even death/sudden death itself. “Torsade de pointes” it is also a very well known side effect for drugs, but according to the analysis, it is the 14th most common side-effect among DDIs and 191th in single drugs.

The highest propensity to DDIs includes over the counter drugs, such as paracetamol and caffeine. Also, many of them are being used to treat mental illnesses, which explains the high number of safety terms related to the nervous system. The fact, that in 259 cases the side effect is not linked, or not annotated to either of the drug presents in the interaction (appendix b.1), can mean two things.: either the description of the DDIs is poor, maybe due to a lack of pharmacovigilance data; or those side effects are caused by the co-administration of two drugs while taking either of them alone would not result in this safety term.

Heat tolerance is, for instance, linked to 2675 DDIs and none of the interacting drugs have been annotated to this effect. Blood pressure medicines and decongestants may cause a decrease in the blood flow to your skin, also inhibiting sweat production. Decongestants can also cause increased muscle activity, which can raise the body’s temperature. Stereotypy is also present in a high number of DDIs,

which is not typically linked to the effect of a drug. In figure 3 we can observe a really strong connection between cardiovascular, nervous system and antineoplastic and immunomodulating agents, indicating that those groups have many common significant safety terms.

The co-administration of these drugs causes more frequent side effects than other drug classes. Also if both of the interacting drugs belong to the same drug class, it is a high possibility of an adverse reaction (appendix b.1). Appendix b.2 shows the drug class “other antidepressants” is highly present among the top drug-classes sharing a side effect. while most of the drug-classes belong to the nervous system and cardiovascular system. There are also many studies confirming a significant connection between cardiovascular and nervous system interactions (20, 21).

Conclusions

Drug-classes do have similar side-effects, especially “cardiovascular system”, “nervous system”, “sensory organs” and “antineoplastic and immunomodulating agents”, thus taking drugs from these drug-classes could facilitate the prediction of a possible DDI. On the other hand analyzing new effects of DDIs, which are not linked to either drug could lead us one step closer to develop a successful prediction method.

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We would like to acknowledge for the members of the “Systems Pharmacology group”.

References

1. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995 Jul 5;274(1):29-34. PubMed PMID: 7791255.

2. Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. Pharmacotherapy. 2004Sep;24(9):1099-104. PubMed PMID: 15460169.

3. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997 Jan 22-29;277(4):301-6. PubMed PMID: 9002492.

4. Cadieux RJ. Drug interactions in the elderly. How multiple drug use increases risk exponentially. Postgrad Med. 1989 Dec;86(8):179-86. Review. PubMed PMID:2685792.

5. Tatonetti NP, Ye PP, Daneshjou R, Altman RB. Data-driven prediction of drug effects and interactions. Sci Transl Med. 2012 Mar 14;4(125):125ra31. doi:10.1126/scitranslmed.3003377. PubMed PMID: 22422992; PubMed Central PMCID:PMC3382018.

6. Ekins S, Williams AJ, Xu JJ. A predictive ligand-based Bayesian model for human drug-induced liver injury. Drug Metab Dispos.

2010 Dec;38(12):2302-8. doi:10.1124/dmd.110.035113. Epub 2010 Sep 15. PubMed PMID: 20843939.

7. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des. 2011 Jun;7(2):146-57. Review. PubMed PMID: 21534921; PubMed Central PMCID: PMC3151162.

8. Duke JD, Han X, Wang Z, Subhadarshini A, Karnik SD, Li X, Hall SD, Jin Y, Callaghan JT, Overhage MJ, Flockhart DA, Strother RM, Quinney SK, Li L. Literature based drug interaction prediction with clinical assessment using electronic medical records: novel myopathy associated drug interactions. PloS Comput Biol. 2012;8(8):e1002614. doi: 10.1371/journal.pcbi.1002614. Epub 2012 Aug 9. PubMed PMID: 22912565; PubMed Central PMCID: PMC3415435.

9. Kim S, Jin D, Lee H. Predicting drug-target interactions using drug-drug interactions. PLoS One. 2013 Nov 21;8(11):e80129. Doi: 10.1371/journal.pone.0080129. eCollection 2013. PubMed PMID: 24278248; PubMed Central PMCID: PMC3836969.

10. Cheng F, Liu C, Jiang J, Lu W, Li W, Liu G, Zhou W, Huang J, Tang Y. Prediction of drug-target interactions and drug repositioning via network-based inference. PLoS Comput Biol. 2012;8(5):e1002503. Doi: 10.1371/journal.pcbi.1002503. Epub 2012 May 10. PubMed PMID: 22589709; PubMed Central PMCID: PMC3349722.

11. Campillos M, Kuhn M, Gavin AC, Jensen LJ, Bork P. Drug target identification using side-effect similarity. Science. 2008 Jul 11;321(5886):263-6. doi: 10.1126/science.1158140. PubMed PMID: 18621671.

12. WHO Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs, 2013. Oslo 2012.

13. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, Pon A, Banco K, Mak C, Neveu V, Djoumbou Y, Eisner R, Guo AC, Wishart DS. Nucleic Acids Res. 2011 Jan;39(Database issue):D1035-41. PMID: 21059682

14. Drugs.com [Internet database]. Zyrtec Information from Drugs.-com; c2000-10

15. Bolton E, Wang Y, Thiessen PA, Bryant SH. PubChem: Integrated Platform of Small Molecules and Biological Activities. Chapter 12 IN Annual Reports in Computational Chemistry, Volume 4, American Chemical Society, Washington, DC, 2008 Apr.
16. ChEMBL: a large-scale bioactivity database for drug discovery"" Nucleic Acids Research. Volume 40. Issue D1. Pages D1100-D1107. 2011.

17. Davis AP, Murphy CG, Johnson R, Lay JM, Lennon-Hopkins K, Saraceni-Richards C, Sciaky D, King BL, Rosenstein MC, Wiegers TC, Mattingly CJ. The Comparative Toxicogenomics Database: update 2013. Nucleic Acids Res. 2013 Jan 1;41(D1):D1104-14.

18. Ganter, B., Tugendreich, S., Pearson, C. I., Ayanoglu, E., Baumhueter, S., Bostian, K. A., Brady, L., Browne, L. J., Calvin, J. T., Day, G. J., Breckenridge, N., Dunlea, S., Eynon, B. P., Furness, L. M., Ferng, J., Fielden, M. R., Fujimoto, S. Y., Gong, L., Hu, C., Idury, R., Judo, M. S., Kolaja, K. L., Lee, M. D., McSorley, C., Minor, J. M., Nair, R. V., Natsoulis, G., Nguyen, P., Nicholson, S. M., Pham, H., Roter, A. H., Sun, D., Tan, S., Thode, S., Tolley, A. M., Vladimirova, A., Yang, J., Zhou, Z. and Jarnagin, K. (2005). Development of a large-scale chemogenomics database to improve drug candidate selection and to understand mechanisms of chemical toxicity and action. J Biotechnol 119, 219-44

19. M. Whirl-Carrillo, E.M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein. "Pharmacogenomics Knowledge for Personalized Medicine" Clinical Pharmacology & Therapeutics (2012) 92(4): 414-417.

20. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med. 2000 Dec 21;343(25):1833-8. PubMed PMID: 11117974.

21. Hanlon JT, Schmader KE, Koronkowski MJ, Weinberger M, Landsman PB, Samsa GP, Lewis IK. Adverse drug events in high risk older outpatients. J Am Geriatr Soc. 1997 Aug;45(8):945-8. PubMed PMID: 9256846.

3.3 Reducing inappropriate prescription medicine consumption in the elderly

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Abstract

Introduction: The demographic shift towards an older population is dramatically increasing the public health burden. The average 70-year- old now takes seven different prescription medications. The use of multiple medications is often referred to as polypharmacy. This causes many problems such as drug-drug interactions, serious side effects, and non-adherence to treatment. National health agencies are clearly interested in reducing polypharmacy, given the

huge sums of money they spend on the resulting side effects and hospitalizations.

Areas covered: We present the risks, determinants and complexity of polypharmacy, and the current existing approaches and possible solutions to tackle and reduce polypharmacy in the elderly. We describe the medicine utilization pattern in people aged 65 years and older, especially focusing on inappropriate prescriptions, and we estimate the health and economic benefits of the prevalence of excessive polypharmacy. We report on the potential of a novel approach to reduce polypharmacy by using systems pharmacology and in silico chemo-informatic methods, and its potential impact into the current digitization of society.

Expert opinion: Eliminate all taken drugs by the elderly is not yet possible, but reducing the number of medications taken can greatly improve the quality of life of the patients. Current existing approaches to tackle polypharmacy follow an experimental test and adjust methodology, which makes them very tedious and costly. Hence, the great number of challenges associated with exploiting systems pharmacology, and in silico chemo- and bio-informatic methods combined with data mining, to tackle polypharmacy in the elderly should be seen as a great source of opportunities for the future, for experimental and computational scientists alike.

Keywords: ACOVE-3, adverse effects, adverse drug reactions, BEERS, chemo-informatics, comorbidity, data mining, drug combinations, drug-drug interactions, drug-related targets' molecular function and associated biological pathways, elderly, de-prescribing, inappropriate prescription, in silico tools, mathematical and systems-based computational models, network pharmacology, non-adherence, pathways-gene associations, pharmacovigilance, polypharmacy, proteins-drug side effects, public health burden, START, STOPP, systems pharmacology.

Article highlights box:

• An aging population is an imminent economic and social burden. The objective is to improve the health of senior citizens while also reducing the burden of health-care costs.

• Polypharmacy is the use of multiple medications. With increasing polypharmacy comes rising morbidity and mortality, and public health agencies are being forced to take notice.

• The medicine utilization pattern in people aged 65 years and older is an average of 7 drugs, where the most commonly used drugs are paracetamol, senna, lactulose, sangobion, aspirin, isosorbide dinitrate, potassium chloride, amlodipine, famotidine and enalapril. These drugs may lead to potential serious adverse effects.

• The main determinants of polypharmacy and inappropriate prescribing are age, gender, number of medications taken (prescription and OTC) reason for admission to hospital (acute disease, exacerbation of a chronic disease), nutrition, lifestyle, emotional well-being, dwelling, number of general practitioner (GP) or emergency room (ER) visits during the previous month.

• In order to reduce the inappropriate prescribing in the elderly, the key questions are, 'Do I need this drug in the first place?', ‘Will the benefit of taking the drug be greater than the risk of possible side effects?’, and if yes, in which dose?

• Current existing approaches to tackle polypharmacy follow an experimental test and adjust methodology, which makes them very tedious and costly. Doctors do their best to avoid inappropriate prescribing, but they do not always have all the information from all the specialists that see the patients, and hence it is difficult to arrive to a consensus between doctors, and they don’t normally use prevention strategies.

• Systems pharmacology, chemo-and –bio- informatics approaches combined with data mining have a great potential as a novel way to tackle polypharmacy.

1. **Polypharmacy in the society**

An aging population is an imminent economic and social burden. According to the United Nations, Department of Economic and Social Affairs[1], Germany and Spain are the European countries, after Japan, S. Korea and China, which its growing number of older people is a major problem. Germany's and Spain's old-age dependency ratio (number of people age 65 and older per 100 working age people (age 15-64) may rise 55 percentage points to 60 and 52 percentage points to 67, respectively, within four decades.

This older growing population live longer but have comorbidities and multiple chronic diseases, which reduces their quality of life. Today, the average 70-year-old takes seven different prescription medications[2.] With more people currently dying from prescription drug overdoses than from motor vehicle crashes, public health agencies are being forced to sit up and take notice[3]. Polypharmacy and inappropriate prescription continues to increase and is known to be an important risk factor for morbidity and mortality[4]. Nearly one in 25 older people are at risk of serious health problems, such as QT prolongation, twisting of the points, arrhythmias, bleeding and muscle weakness because they take unwise combinations of drugs, which often include over-the-counter (OTC) medications[5]. The use of prescription drugs and OTC medications and dietary supplements has increased during the past decade[1,6]. Serious drug-drug interactions (DDIs) can occur between prescription and non-prescription drugs as well as dietary supplements. For example, taking warfarin (a prescription blood thinner) together with simvastatin (a prescrip-

tion cholesterol-lowering drug) increases the risk of bleeding and rhabdomyolysis (a breakdown of muscle tissue). Taking lisinopril (a prescription anti-hypertension drug) with potassium (a food supplement) produces a higher risk of abnormally high blood levels of potassium. Taking both niacin (a non-prescription cholesterol-lowering medication) and garlic (a dietary supplement) may lead to rhabdomyolysis[5].

Polypharmacy is a complex situation, and managing it is also complex. Around 3000 existing prescription drugs, 300 dietary supplements, and 600 herbal products[7] are currently available. It is extremely difficult for physicians to take into account polypharmacy problems for patients for whom little history is known and who often cannot recount the medicines and supplements that they are already taking[8]. Naturally, doctors do their best to avoid adverse drug interactions. Nonetheless, for patients taking two medications, the risk of a DDI is 15%. This risk rises to 40% for those taking five medications and to an alarming 80% for patients taking seven or more[9]. The risk of a toxic medication interaction is very real, considering that more than one half of non-institutionalized adults older than 65 years take five or more different medications, and 12% use 10 or more[10]. Indeed, in hospitalized patients, adverse drug interactions are estimated to be the fourth leading cause of death[6]. According to the Agency for Healthcare Research and Quality, more than 770,000 people are injured or die each year in hospitals from

adverse drug reactions (ADRs) and other adverse drug events (ADEs), which may cost up to $5.6 million per hospital[11].

Unfortunately, while national governments and health insurance companies are equally interested in reducing polypharmacy, there remains a gap in the literature regarding the polypharmacy and its developmental course [9-12].

Many studies have found that simultaneous drug treatments for different conditions are associated with negative health outcomes, but more research is needed to further delineate the consequences associated with unnecessary drug use in elderly patients. De-prescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes[13]. Currently, it is very difficult to de-prescribe drugs rationally to achieve a desired effect in a clinical setting. However, evidence is emerging in support of a structured approach to de-prescribing. For example, doctors may follow a series of steps to manage polypharmacy in practice comprising:

(a) a patient assessment,

(b) identification of inappropriate drugs from an accurate list of medications using software tools[14,15,16,17,18,19,20,21,22] or decision algorithms[23,24,25],

(c) assess each drug for specific risks versus benefits (consecutive take one drug at a time and discontinue it over weeks to months),

(d) agree to stop/reduce dose and withdraw slowly,

(e) communicate with prescriber,
(f) monitor, review and adjust regularly.

However, beyond this structured and practical approach, there are very few rigorously designed intervention studies that have been shown to reduce unnecessary polypharmacy[24, 25]. Moreover, the current approach is very tedious, costly and not mandatory. Doctors do not always have enough time to investigate every drug in the patient's medication list, suggest changes, and monitor the process. On the other hand, most patients undertaking this experimental approach get tired before a proper statement of polypharmacy reduction can be made and they normally see multiple specialists that do not always agree in a consensus (i.e., specific practical studies in Spain carried out by San José et al. [26, 27]).

The aims of this work are

1) analyze and collect all recently published studies related to polypharmacy and inappropriate prescribing in the elderly.
2) Identify the most important risks, determinants and consequences of inappropriate prescribing, focusing on economic, social and health impact.
3) Present current approaches to identify and reduce DDIs.
4) We present MINI-MED, a project to combine all this information in order to reduce inappropriate prescribing in the elderly.

2. **Aspects To Take Into Account To Manage Polypharmacy**

National governments and health insurance companies are highly interested in reducing polypharmacy to reduce its economic impact (i.e. hospitals are spending large sums of money because of polypharmacy and ADRs[11]).

The consumption of pharmaceuticals per capita in the EU has increased by around 50% since 2000, as well as the numbers of doctors and nurses per capita (EU annual average growth rate of around 3.1%)[28.] Furthermore, there are 96 million people over the age of 65 in the 28 EU member states (EU28)[31]. If every retired person in the EU could avoid taking just one prescription medicine and if we assume a cost of 100 euro per year for a generic medicine, the total saving would be in the order of 9.6 billion euros per year. Moreover, since the average health expenditure per capita in EU28 is currently around 2,800 euros[28], this estimate is probably highly conservative. If we could reduce the excess consumption of prescription medicines by one third or even one half, this would mean an average cost reduction per person per year of around 1400 euros. Given that EU countries allocate on average 10% of their GDP to health, from which almost three-quarters is publicly financed[28], and that several EU countries have been forced to cut their health spending since the economic crisis of 2009 (EU annual average growth rate of 3.1% in 2000-2009 compared to 0.7% between 2009-2012). The public spending on long-term care as a share of GDP is also projected to grow over the coming decades due to population aging, which means that achieving this aim could have an enormous impact on

old peoples' health, and it could dramatically reduce the cost to the state-funded prescription medicines in Europe and around the world.

One of the inherent of aging is body and mind changes. There are conditions that are directly linked to aging, such as chronic pain, cardiovascular and heart diseases, weaker immune system, osteoarthritis, osteoporosis, dementia or delirium. Also, social and emotional life changes with age, social networks narrow, and the experience of negative emotions affects physiological functioning and ultimately physical health[29]. Reducing the number of taken medications also has an important health benefit on the patients. Taking fewer drugs means less risk of potential DDIs, ADRs and side effects, which can greatly improve the patient's quality of life. The most common ADRs caused by DDIs are depression, tachycardia, nervousness, dizziness and fainting. Reducing the possibility of suffering from any of these conditions, and only having to take a drug or two, enhance the mood of the patient. The elderly gains social and emotional well-being, and feels it can be an active and useful member of the society once again[29]. Elderly who have strong and positive social networks are 60% less likely to show signs of dementia[30]. Women are more vulnerable to emotional changes related to aging, especially to low levels of emotional support. Elderly women who received low levels of emotional support are twice as likely to die, that women with high levels of emotional support[29]. There are many aspects influencing the well-being of the elderly,

such as family, economic situation, mental and physical health, and reducing inappropriate prescribing can help to the elderly to have as well a better quality of life and well-being.

The consequences of reducing even just one prescription drug per person can have a huge impact , not only on the quality of life and well being of the elderly, who wants to live longer and healthier, but also strongly on the health economics aspect.

3. **Current Tools To Identify And Reduce Polypharmacy**

Current tools for identifying potentially inappropriate prescribing (PIP) in older patients[14, 15, 16, 17, 18, 19, 20, 21, 22 ,23, 32, 33, 34] are time-consuming, tedious, impractical and inadequate. As aforementioned, several studies have found that polypharmacy is associated with negative health outcomes, but more research is needed[23, 25, 35,36, 37,38, 14,39, 40,41,42,43,26, 27, 44, 45, 46, 47, 48, 49, 50, 51,51,52,26,27]. Regarding European projects, this field has been only tackled recently in the European innovation Partnership Actions[53]: "Polypharmacy Patterns: Unraveling Systematic Associations between Prescribed Medications"[52], the "SIMPATHY project to manage polypharmacy in the elderly by 2030"[54,55], the "FRIENDD: a study group on DDIs in polypharmacy in the elderly"[56], the CRIME project: CRIteria to assess appropriate Medication use among Elderly complex patients[7], the PREDICT EU project: Increasing the PaRticipation of the ElDerly in Clinical Trial [57], the ICARE4U project: Innovating care for people with multiple chronic conditions in Europe[58], or the MICMI project: Methods for Improving Compliance with Medicine Intake[59].

As aforementioned, there are tools available to help reducing polypharmacy in the elderly. The Screening Tool of Older Person's Prescriptions (STOPP)[14] criteria, the STOPP/START of the NHS Cumbria toolkit[15], the Beers Criteria updated 2012[16,17], the FORTA (Fit FOR The Aged) list[18], the NHS Highland system[19], the MAI tool[20], the NO TEARS[21] and ARMOR systems[22], decision algorithms 2[3,24,25], the French consensos panel[60], McLeod's criteria[61], Lindblad's panel[62], or Potentially inappropriate medications in the elderly: the PRISCUS list[63].

Additionally, there are currently available several Internet sources helping to tackle and understand better polypharmacy. Pharmacovigilance resources like FAERS[64], Yellowcard[65], European database of suspected ADR reports[66], OECD Health Statistics[67]. Patients' forums such as Ehealthme[68], Smart Patients[69], Patients like me[70], or Healthkeep[71]. DDI checking tools such as drugs.com[72] and drugbank database[73].

Although there are many ongoing projects, useful tools, and Internet sources to tackle, identify and help to reduce polypharmacy in the elderly, these tools are not currently applied by most of the doctors and hospitals (except when a research group carries out a study in polypharmacy). Even when these tools are applied, GPs, specialists and health centers are not aware off or do not have access to all the medications the patient takes, or if they do, they do not usually have enough time to apply these experimental tools.

4. **Determinants Linked To Polypharmacy**

a) Studies analysing current tools to reduce polypharmacy and determinants linked to it

The BELFRAIL study is a prospective, observational, population-based cohort study of 500+ patients aged 80 years and older in Belgium[40] gems, egb studies. All of these studies deal with inappropriate prescribing in elderly people, gender differences, prevalence, most frequently used medicines, most common drug combinations and adverse effects, and associated factors to polypharmacy (such as economic cost).

There was not much literature regarding this issue until the last couple of years. However, recently some experimental studies have been carried out to try to delineate the consequences associated with unnecessary drug use in elderly patients. Mainly in Australia [23, 25, 35], Singapore[36], UK[37], Ireland[38,14], Austria[39], Belgium[40], Croatia[41], Germany[42], Italy[43], and Spain[26, 27, 44, 45, 46, 47, 48, 49, 50, 51]. Concerning the existing literature, scarce studies have been carried out regarding the determinants of polypharmacy in healthcare: three studies in Spain[74,75,76], one in Belgium[77], one in Germany[78], one in Sweden[79] and one in China[80]. All of them with quite recent data, J. Díez-Manglano et al. use data coming from internal medicine and acute geriatrics (n = 457)[74]. E. Frutos Bernal et al. use a subsample data of the National Health Survey 2006, for adults over 65 (n = 458)[75]. D.

Walckiers et al. use data from the Belgian Health Interview Survey carried out in 2008 for population of 65 years and older (n= 2835). C. Jäger et al. use data from general practitioners participating in the HzV care contract of one German health insurance in one federal state in Germany, for patients over 64 years old, with prescriptions for more than four different drugs in at least one quarter of the year and diagnosis of at least three chronic conditions (n= 3400) [78]. B. Hovstadius et al. use data from the the Swedish prescribed drug register of dispensed prescription drugs in the entire Swedish population[79], L. Dong et al. use data from 20 125 prescriptions from June 2005 to August 2005 collected from 680 primary health clinics in villages from 40 countries in 10 provinces of Western China (n = 20125)[80]. Other related studies are those from Mukhtar et al.[81], Ching Ho et al.[82], Krause et al.[83], Zamorano et al.[84], Mateos et al.[85], Gamma et al.[86], Domínguez et al.[87], Hervás and García de Jalón[33].

A. San-José et al. (Spanish Ministry "PUMEA" project[26,27]) carried out a thorough observational, prospective and multicentric study in elderly patients admitted to seven Spanish hospitals for a year, involving 336 patients[48] and 672 patients[49]. They performed a multivariate logistic regression analysis with dependent variable: inappropriate prescribing indicators and independent variables a) sociodemographic variables b) multimorbidity variables[49], c) geriatric conditions and d) number of prescription medicines in the preceding month before hospitalization. The data of San-José tries to relate by multivariate regression analysis the risk factors associated with po-

tentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO). Their data relate: a) PIMs and PPOs with the age, b) Risk factors associated with PIM, PPO and inappropriate prescribing (IP), c)Risk factors associated with STOPP, START and ACOVE-3 criteria, d) Beers, STOP, START criteria with medications (drugs' family) inappropriate prescribed (See Tab. 2,3).
Studies from Paul Gallagher[38], M. Noale[43], E. Delgado-Silveira[88] or S Chuen Li[36] deal with the similar issue. All of them study, using multiple logistic regression models, the determinants (sociodemographic, geriatric, multimorbidic) associated with the non-existence, mild, moderate or high existence of polypharmacy (normally highly related with inappropriate prescribing). They investigate the most commonly prescribed drugs, significant potential DDIs, the drugs more frequently involved in drug adverse reactions, the most frequently encountered PIPs according to Beers', STOPP and START criteria, and the prevalence rates of developing Drug Related Problems (DRPs) and ADRs for the various patient subgroups.

The baseline characteristics of patients normally taken into account for studying the determinants of polypharmacy are: age group (65-74, 75-84, 85 or older), gender (female, male), reason for admission to hospital (acute disease, exacerbation of a chronic disease), origin (emergency room, others), dwelling (community, nursing home, others), living with (couple/family, single, others), number of general practitioner visits during the previous month of admission to hospital (none, one, two or more), Brathel index (basal, on admis-

sion, at discharge), Reisberg index (1-2, 3-5, 6-7), positive confusion assessment method (CAM) at admission to hospital (providing qualitative measure of “delirium present” or “delirium absent”), failures in Pheiffer test, Charlston index, multimorbidity and discharged to (home, nursing home, died, others)[49].

Regarding the PIMs and the PPOs, in patients aged 85 years and over compared with those aged 75 to 84 years, the main PIMs are: 1) short to intermediate-acting benzodiazepines and tricyclic antidepressants for syncope and falls, 2) ferrous sulfate at dose 32.5 mg/dl and amiodarone for other adverse effects, 3) long-term and long-acting benzodiazepines for central nervous system and psychotropic symptoms, 4) benzodiazepines which adversely affect those prone to falls, 5) aspirin at dose >150 mg day, 6) aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event for the cardiovascular system, 7) calcium channel blocker for chronic constipation, 8) long term NSAID for relief or mild moderate joint pain in osteoarthritis for musculoskeletal system[47, 48].

On the other hand, the main PPOs are 1) ACE inhibitor with chronic heart failure or chronic heart failure, 2) warfarin in the presence of chronic atrial fibrillation and statin therapy with history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is >5 years for cardiovascular system, 3) calcium and vitamin D supplement in patients with known osteoporosis for musculoskeletal system, 4) antiplatelet therapy in diabetes mellitus if one or more coexisting major cardiovascular risk factors are pre-

sent for the endocrine system, 5) ACE inhibitor or ARB in elderly with known history of HF, left ventricular hypertrophy, IHD, chronic kidney disease, or cardiovascular event for hypertension, 6) anticoagulations with chronic artial fibrillation and medium to high risk for stroke and atrial fibrillation, 7) beta-blocker with hypertension and IHD for hypertension, 8) bisphorsphonates, raloxifene, calcitonin, hormone replacement therapy or teripapatide with osteoporosis in females for osteoporosis, 9) acetaminophen when elderly treated for osteoarthritis, 10) rapid-acting bronchodilator for chronic obstructive pulmonary disease[47, 48].

Following the aforementioned PIMs and PPO, Table 1 shows the most commonly encountered PIMs and PPO according to the respective instruments. Beer-listed PIM conditions, STOPP-listed PIM systems, START-listed PPO systems and ACOVE-3-listed PPO conditions[49].

Regarding the inappropriate prescriptions, in general, the most frequently encountered PIPs according to Beers', criteria are 1) short-intermediate acting BZDZ or TCAs with syncope or falls, 2) calcium channel blockers, anticholinergics or TCAs with constipation, 3) long-term BDZ with depression, amiodarone, barbiturates, anticholinergics, muscle relaxants or CNS stimulants with cognitive impairment, 4) long-acting BDZ, long-term stimulant laxatives, fluoxetine, anticholinergics or antihistamines with bladder ou-

tflow obstruction, 5) aspirin, NSAIDs, dipyridamole, ticlopidine or clopidogrel with blood clotting disorders or anticoagulation.

Beers-listed PIM		
Condition	Drug	%
Independent of diagnoses or conditions	Long-acting benzodiazepines	11.8
Syncope or falls	Short-to intermediate-acting benzodiazepines and tricyclic antidepressants	9.9
Depression	Long-term benzodiazepine use. Sympatholytic agents	8.1
Blood clotting disorders or receiving anticoagulant therapy	Aspirin, NSAIDs, dipyridamole, ticlopidine and clopidogrel	6.6
Chronic constipation	Calcium channel blockers, anticholinergics, and triclyclics antidepressants	6.4
STOPP-listed PIM		
System	Drug	%
Drugs that adversely affect those who are prone to falls	Benzodiazepines	15.0
Central nervous system	Long-term, long-acting benzodiazepines	11.5
Musculoeskeletal system	Long-term NSAID for relief of mild–moderate joint pain in osteoarthritis	8.5
Duplicate drug classes	Any regular duplicate drug class prescription	8.3
Cardiovascular system	Aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event	7.6
START-listed PPO		
System	Drug	%
Cardiovascular system	ACE inhibitor with chronic heart failure.	13.4
Cardiovascular system	Warfarin in the presence of chronic atrial fibrillation	11.2
Cardiovascular system	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is >5 years.	8.2
Musculoeskeletal system	Calcium and vitamin D supplement in patients with known osteoporosis (radiological evidence or previous fragility fracture or acquired dorsal kyphosis).	7.6
Respiratory System	Regular inhaled beta-2 agonist or anticholinergic agent for mild to moderate asthma or COPD.	6.1
ACOVE3-listed PPO		
Condition	Drug	%
Hypertension (HTN)	Angiotensin-converting enzyme (ACE) inhibitor for comorbid vascular disease. IF a VE (vulnerable elderly) with HTN has a history of heart failure (HF), left ventricular hypertrophy, IHD (Isquemic Heart Disease), chronic kidney disease, or cardiovascular accident, THEN he or she should be treated with an ACE inhibitor or angiotensin-receptor blockers (ARB).	10.8
Stroke and atrial fibrillation	Anticoagulate atrial fibrillation. IF a VE has chronic atrial fibrillation and is at medium to high risk of stroke, *then* anticoagulation should be offered.	9.0
Chronic obstructive pulmonary disease (COPD)	Rapid-acting bronchodilator IF a VE has COPD (GOLD stage > I), *then* he or she should be prescribed a rapid-acting bronchodilator.	8.9
Osteoporosis	Calcium and vitamin D for osteoporosis IF a VE has osteoporosis, *then* he or she should be prescribed calcium and vitamin D supplements.	8.5
Osteoarthritis (OA)	First-line pharmacological therapy IF a VE is started on pharmacological therapy to treat OA, *then* acetaminophen should be tried first.	8.5

Table 1. The most commonly encountered PIMs and PPO according to the respective instruments[49].

The most common PIPs according to STOPP‘ criteria are 1) BDZs in those prone to falls, 2) any regular duplicate drug class prescription, 3) PPIS for peptic ulcer disease at full therapeutic dosage for >8 weeks, 4) neuroleptic drugs in those prone to falls, 5) aspirin without coronary, cerebral or peripheral symptoms, 6) long-term aspirin >150mg/day, 7) calcium channel blocker with chronic constipation, 8) long-term, long acting benzodiazepines, long-term neuroleptics with Parkinsonism, 9) long-term neuroleptics as hypnotics. The PIPs according to START’ criteria are 1) calcium/vitamin D

with known osteoporosis, 2) statin with known coronary, cerebral or peripheral vascular disease, 3) statin with diabetes mellitus and >1 major cardiovascular risk factor, 4) ACE inhibitor with chronic heart failure, 5) aspirin or clopidogrel with known atherosclerotic coronary, cerebral or vascular disease, 6) antidepressant drug with moderate-severe depressive symptoms lasting >3 months, 7) metformin with type 2 diabetes mellitus+metabolic syndrome, 8) regular inhaled beta-2 agonist or anticholinergic agent for mild-moderate asthma or COPD, 9) fiber supplement with chronic symptomatic diverticular disease with constipation, 10) anticoagulant with chronic atrial fibrillation[38].

Regarding the independent risk factors associated to inappropriate prescribing (IP), PIMs and PPOs. Table 2 shows these associated independent risk factors with the correspondent multivariate logistic regression analysis and the independent risk factors associated with Beers, STOPP, START and ACOVE-3 criteria, with its corresponding multivariate logistic regression analysis according to the work of San Jose et al.[49].

According to the results of the multivariate regression analysis in San-José et al. PUMEA project , the associated factors to PIM and PPO are number of medicines (10 or more) for the Beers criteria, number of medicines (5-9, 10 or more), severe dependence in ADL and multimorbidity for the STOPP criteria, non-community dwe-

lling and multimorbidity for the START criteria and STOPP-listed PIM for ACOVE-3 criteria for 85 years old and over[48].

A)

Risk factor	Global IP (n: 597)	No global IP (n: 75)	OR	95% CI
Gender				
• Female	58.71	36.19	2.36	1.31–4.25
• Male	41.3	63.81	1	
Number of medicines				
• 10 or more	59.12	32.86	11.34	4.96–25.94
• 5–9	36.43	37.48	6.00	2.63–13.67
• 0–4	4.45	29.66	1	
Risk factor	**Global PIM (n: 488)**	**No global PIM (184)**	**OR**	**95% CI**
Gender				
• Female	59.94	44.05	1.72	1.12–2.63
• Male	40.06	55.95	1	
Number of medicines				
• 10 or more	62.13	37.38	14.16	6.44–31.12
• 5–9	35.47	39.77	7.36	3.34–16.22
• 0–4	2.4	22.85	1	
Global PPO				
• Yes	72.66	51.14	2.26	1.44–3.56
• No	27.34	48.86	1	
Barthel Index basal				
• Total dependence	12.98	3.39	5.42	1.96–14.98
• Severe dependence	8.62	11.11	0.75	0.30–1.83
• Moderate dependence	19.36	22.01	0.84	0.40–1.74
• Mild dependence	47.91	46.20	1.28	0.67–2.46
• Independence	11.12	17.29	1	
Risk factor	**Global PPO (483)**	**No global PPO (189)**	**OR**	**95% CI**
Multimorbidity[a]				
• Yes	67.18	51.18	1.93	1.25–2.97
• No	32.82	48.82	1	
Global PIM				
• Yes	80.79	62.34	2.79	1.81–4.28
• No	19.21	37.66	1	
Barthel Index basal				
• Total dependence	8.98	13.81	0.29	0.12–0.68
• Severe dependence	9.06	9.64	0.52	0.21–1.24
• Moderate dependence	22.65	14.65	0.95	0.43–2.07
• Mild dependence	46.43	49.63	0.67	0.35–1.28
• Independence	12.88	12.27	1	
Dwelling				
• Others	14.96	8.55	2.20	1.14–4.25
• Community	85.04	91.45	1	

Global IP was considered when a patient was prescribed with at least one Beers, STOPP, START and/or ACOVE criterion.
Global PIM was considered when at least one Beers and/or STOPP criterion was prescribed, and global PPO, when at least one START and/or ACOVE-3 criterion was prescribed.
[a] (≥2 clinical categories in the Polypathological Patient scale)

B)

Risk factor	Beers (n: 317)	No Beers (n: 355)	OR	95% CI
Gender				
• Female	61.8	49.8	1.57	1.07–2.3
• Male	38.2	50.2	1	
Age				
75–84 years	68.28	59.35	1.53	1.07–2.2
85 and over	31.72	40.65	1	
Number of medicines				
• 10 or more	66.42	44.88	8.19	3.01–22.28
• 5–9	31.98	41.34	4.71	1.71–12.99
• 0–4	1.6	13.79	1	
Risk factor	**STOPP (n: 414)**	**No STOPP (n: 258)**	**OR**	**95% CI**
Multimorbidity[a]				
• Yes	63.54	59.38	0.57	0.36–0.92
• No	36.46	40.62	1	
Number of medicines				
• 10 or more	64.17	42.71	8.21	3.47–19.44
• 5–9	33.45	41.49	4.13	1.74–9.78
• 0–4	2.38	15.79	1	
Barthel Index basal				
• Total dependence	13.07	6.58	3.79	1.5–9.54
• Severe dependence	8.22	10.89	1.1	0.46–2.63
• Moderate dependence	19.35	21.1	1.33	0.62–2.84
• Mild dependence	49.06	44.98	1.68	0.86–3.3
• Independence	10.3	16.45	1	
ACOVE3 criteria				
• Yes	65.63	41.94	2.68	1.77–4.06
• No	34.37	58.06	1	
Risk factor	**START (n: 374)**	**No START (298)**	**OR**	**95% CI**
Multimorbidity				
• Yes	70.53	52.88	1.76	1.14–2.7
• No	29.47	47.12	1	
Global PIM				
• Yes	56.01	37.38	1.6	1.02–2.51
• No	43.99	62.62	1	
Dwelling				
• Others	16.77	8.75	1.82	1.02–3.24
• Community	83.23	91.25	1	
Risk factor	**ACOVE3 (n: 418)**	**No ACOVE3 (n: 254)**	**OR**	**95% CI**
STOPP criteria				
• Yes	71.29	48.44	2.3	1.51–3.49
• No	28.71	51.56	1	

[a] (≥2 clinical categories in the Polypathological Patient Scale)

Table 2. A) Independent risk factors associated to inappropriate prescribing (IP), potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO). Multivariate logistic regression analysis. B) Independent risk factors associated with Beers, STOPP, START and ACOVE-3 criteria. Multivariate logistic regression analysis[49].

Other associated factors to polypharmacy are shown in Table 3: sex, living area, diabetes duration, body mass index, hypoglycemic events, diabetes complications, short portable mental status questionnaire, cumulative illness rating scale comorbidity index, and mini nutritional assessment[43].

	OR	95 % CI	*p* value
Sex, females	**1.56**	**1.18–2.07**	**0.0019**
Living area			**0.0016**
Northern Regions versus Southern Regions and Islands of Italy	**1.76**	**1.26–2.45**	
Central Regions of Italy versus Southern Regions and Islands of Italy	1.15	0.76–1.74	
Diabetes duration ≥5 years	**1.93**	**1.38–2.70**	**0.0001**
Body mass index ≥30 kg/m^2	**1.53**	**1.15–2.04**	**0.0039**
Hypoglycemic events in the last 3 months	1.52	0.93–2.50	0.0958
Diabetes complications, coronary	**4.67**	**3.01–7.25**	**<0.0001**
Diabetes complications, cerebrovascular	1.56	0.96–2.52	0.0731
Diabetes complications, peripheral neuropathy	**2.18**	**1.44–3.30**	**0.0002**
Diabetes complications, nephropathy	**2.66**	**1.66–4.27**	**<0.0001**
Short Portable Mental Status Questionnaire score <4 (errors)	**1.38**	**1.02–1.87**	**0.0386**
Cumulative Illness Rating Scale Comorbidity Index ≥2	**1.90**	**1.41–2.54**	**<0.0001**
Mini Nutritional Assessment ≤23.5 (malnourished or at risk versus well-nourished)	**2.26**	**1.54–3.33**	**<0.0001**

P values <0.05 are indicated in bold

Table 3. Characteristics associated with polypharmacy, multiple logistic regression model: METABOLIC Study[43].

b) Other determinants linked to polypharmacy in the elderly

Although drug prescribing is often beneficial to patients, elderly patients are particularly exposed to the side effects of medications and their consequences. Metabolic and hormonal changes, nutritional status changes, food-nutrient, and food-nutrient - drug interactions are also determinants linked to polypharmacy. Advancing age is characterized by impairment in the function of the many regulatory processes that provide functional integration between cells and organs [89]. Because of this we get more vulnerable to drugs. There are important issues on absorption (deglutition disorders, reduction of gastric acid), distribution (decrease of lean body mass, smaller volume of distribution), metabolism (progressive reduction in liver volume and liver blood flow) and elimination (reduced renal function) of drugs[89,90]. As a result, water-soluble drugs become more concentrated and fat-soluble drugs have longer half-lives because of

the slow release of the drug from the fatty tissues[91]. Other problem is, that due to several reasons that lead to inadequate diets, many elderly are malnourished. Malnutrition in aging, associated with impairment in food and drug metabolism, leads to many complications such as adverse reactions, drug-drug and drug-nutrient interactions[92]. There is statistically significant inverse correlation between increasing number of medications and intake of fiber. This might be because they have difficulty of chewing (missing teeth) or swallowing (decreased saliva production)[93]. On the other hand, intake of cholesterol, glucose and sodium are positively associated with increasing medication use. A trend is also observed for increased phosphorus intake and increased number of medications used. Decrements in physical health are associated with decreasing intake of many fat-soluble and water-soluble vitamins, major minerals, trace minerals and electrolytes. Excessive macronutrients, specifically relating to the intake of saturated fats, refined carbohydrates and cholesterol, along with decreased intake of fiber and bioavailable protein sources, is also associated with poor physical health[94].

Medicines taken incorrectly with food, or the wrong kind of food can alter drug bioavailability, which may lead to a serious ADR. Fruit juices, caffeine and herbal teas are the most common cause of food-drug interaction, as they are very likely to share the same target as the drug. Drugs likely to interact with food are warfarin, monoaminine oxidases, antihypertensive drugs, antibiotics, analgesics and antipyretics, bronchiodilators, antihistamines, antitubercu-

lar drugs, antidiabetics, thyroxine and antitumor drugs[95]. These drugs are highly consumed by the elderly[5,96].

Prescription drug use increases with age. Three-quarters of those aged 50 to 64 use prescription drugs, compared to 91 percent of those age 80 and older. The average number of prescriptions filled also increases with age, from 13 prescriptions filled annually for adults aged between 50 to 64, increases to 22 annual prescriptions for elderly of 80 and older[97]. Many studies confirm that females take an average of 2-3 additional drugs than males, and they also have higher chance to suffer from an ADR or DDI[98,99]. However, for patients older than 80 years old, or being hospitalized, there is no significant difference between female and male drug consumption [97]. Depression is twice as common in women than men likely related to the hormonal profile and gender differences in serotonin levels and activities[99]. Women have 1.5 to 1.7 fold-increased risk to develop ADRs compared with men. This can be attributed to gender differences in immunological and hormonal physiology[100].

With regard to the most common prescribed drugs, for the elderly aged between 75-84 they are: paracetamol, senna, lactulose, sangobion, aspirin, isosorbide dinitrate, potassium chloride, amlodipine, famotidine and enalapril[36]. On the other hand, omeprazole, paracetamol, furosemide, acethylsalicylic acid, lorezapam, enalapril, amlodipine, metformin, nitroglycerin nitrate, simvastatin, ipratropium bromide, acenocoumarol and hydrochlorothiazide are the most com-

mon prescribed drugs for the 85 years old and older, as shown in Table 4[48].

85 years old and over		75 to 84 years old	
Medicine	**%**	**Medicine**	**%**
omeprazole	61.4	omeprazole	61.2
paracetamol	51.5	paracetamol	45.2
furosemide	47.0	furosemide	43.7
acethylsalicylic acid	38.1	acethylsalicylic acid	29.7
lorazepam	21.5	acenocoumarol	26.0
enalapril	20.8	enalapril	21.9
amlodipine*	18.8	simvastatin	21.7
metformin	18.6	metformin	21.7
nitroglycerin nitrate	17.4	ipratropium bromide	19.1
simvastatin	16.4	hydrochlorothiazide	16.9
ipratropium bromide	16.3	metamizole	16.8
acenocoumarol	16.2	lorazepam	15.3
hydrochlorothiazide	15.8	nitroglycerin nitrate	14.8

*Amlodipine 13.26% in those aged 75 to 84.

Table 4. The most frequently prescribed medicines according to age groups[48].

The most prescribed drugs with identified cases of ADRs are: 1) coffee ground vomits, bleeding GIT, epigastric pain with vomiting and gastric ulcer for aspirin, 2) declining renal function, chronic cough with wheezing and postural hypotension for enalapril, 3) hyponatremia and thrombocytopenia for carbazepine, 4) giddiness for phenytoin, 5) tremors for valproate, 6) hypoatremia, increased INR, increased liver function tests for fluvoxamine, 7) hyponatremia for fluoxetine, 8) dehydration and increased liver function tests for fru-

semide, 9) postrural hypotension for amlodipine, 10) generalized rash and decreased hemoglobin for ticlopidine, 11) itch for paracetamol, 12) antiphopholipid syndrome for procainamide, 13) generalized rash for ethambutol, 14) extrapyramidal side effects for sulpiride, 15) asthma exacerbation for propranolol, 16) rigors and facial flushing for streptokinase, and finally 16) increased liver function tests for simvastatin and glipizide[36]. The common prescribed drugs with significant potential DDIs are: 1) atenolol with nifedipine causing severe hypotension and heart failure occasionally, 2) phenytoin with folic acid decreasing the plasma level of phenytoin, 3) simvastatin with erythromycin increasing the risk of myopathy, 4) simvastatin with warfarin which may lower enhanced threshold, and 5) theophylline with calcium channel blocker which possibly enhance theophylline effect[36]. The most problematic drugs for the elderly are antiaggregants, statins, ACE inhibitors, PPIs, diuretics, betablockers, metformin, acenocoumarol, calcium/cholecalciferol, benzodiazepines, risperidone, haloperidol, clomethiazole and antidepressants, as shown in Table 5[88].

As it has been shown, polypharmacy in elderly has many determinants that doctors should handle with care. Patients often receive additional medications to treat side effects, especially the elderly. Indications for medication should be taken individually, in order to develop a realistic risk–benefit ratio, taking into consideration factors such as quality of life and life expectancy.

Drug	Total (%)	Hospitalized (%)	Institutionalized (%)
Antiaggregants (ASA, clopidogrel)	10.3	10.9	7.1
Statins (Atorvastatin, simvastatin)	8.7	9.8	2.6
ACE Inhibitors (Enalapril, Ramipril)	6.7	7.4	2.6
PPIs (Omeprazol, Pantoprazol)	5.7	4	10.9
Diuretics (furosemide, spironolactone)	3.9	4.3	1.9
Betablockers (carvedilol, bisoprolol)	3.4	3.8	-
Metformin	3.3	3.6	-
Acenocoumarol	2.9	3.1	1.9
Calcium /cholecalciferol	2.4	2.5	1.9
Benzodiazepines (Lorazepam, alprazolam)	1.4	1.2	4.5
Risperidone, haloperidol, clomethiazole)	1.3	1.2	4.5
Antidepressants (clomipramine, trazodone, escitalopram)		-	7.1

ASA: acetylsalicylic acid; ACE inhibitors: Angiotensin Converting Enzyme Inhibitors; PPIs: Proton Pump Inhibitors.

Table 5. Drugs more frequently involved in Drug Reaction Problems[88].

Most of the adverse drug reactions are preventable. If the patient receives many medications for a long period of time, doctors should revise them, as some of them may have become unnecessary. In the next section we present a novel way to tackling polypharmacy in the elderly, by using an in silico tool combining existing chemoinformatic and systems pharmacology approaches.

5. **A Novel Way To Tackling Polypharmacy In The Elderly**

More research is needed to examine the extent of simultaneous poly-drug use as well as the factors and consequences associated with multiple drug use. For many applications including drug discovery, drug re-purposing, and the definition of pharmacogenomic modulators, we need a molecular-level understanding of drug effects, but this is often either missing or incomplete. There are significant gaps in our understanding of the pathways by which drugs act. This incomplete knowledge limits our ability to use rational me-

chanistic molecular information to re-purpose drugs, to understand their interactions with other drugs, and to predict both positive clinical outcomes (COs), i.e. the desired therapeutic effects of drugs (often referred to as “indications”) and negative clinical outcomes, usually known as drug side effects (SEs).

In this regard, systems pharmacology, chemo-and –bio- informatics approaches combined with data mining have a great potential as a novel way to tackle polypharmacy.

For example, the MINI-MED project awarded by the Spanish Ministry of Economy and Industry / Carlos III Health Institute associated with the 2016 call for the Strategic Health Action 2013 - 2016 (Ref: CP16 / 00088) aims to exploit multiple chemical and biological databases to build drug-target-SE-CO networks. By analyzing these diverse databases containing structural features of compounds, their bioactivity profiles, their relationships to the phenotypic effects observed, gene–SE and gene-disease associations, related molecular functions, and target-related pathways, the project aims to properly (a) predict the SEs associated with a given target, (b) re-purpose drugs for two or more medical conditions, (c) reduce SEs, (d) predict DDIs, and (e) generate biologically meaningful hypotheses for reducing drugs in simultaneous prescription medications.

By using in silico methods in combination with the large amount of bioactivity and bioinformatics information available in databases, MINI-MED advances the understanding of drug-target-SE-CO relationships and opens the way to rational drug de-prescribing.

a) Systems pharmacology to predict drug-drug, drug-target interactions and adverse effects

The classical view of drug action, “one molecule interacts with one target to give one therapeutic effect” has been replaced by the new polypharmacology paradigm “one molecule (or more) interacts with several targets to give several therapeutic effects and certain side effects”. These targets are in a complex cellular network. The emerging discipline of quantitative systems pharmacology (QSP) aims to understand how drugs modulate cellular networks in space and time in order to predict drug targets and their role in human pathophysiology (Figure 1). It is worth mentioning that although QSP might be considered to be a new approach, the principle of drug “re- purposing” is well established in the pharmaceutical industry as a way to identify new targets for drug molecules that have failed at the clinical testing stage for their original target.

However, it has never been applied to polypharmacy. This is, i.e. the main novelty of the aforementioned MINI-MED project. Hence, both the QSP concept and the enterprise view of polypharmacology (i.e. dealing with drug-target-SE-CO cellular networks) can be adapted to the field of polypharmacy.

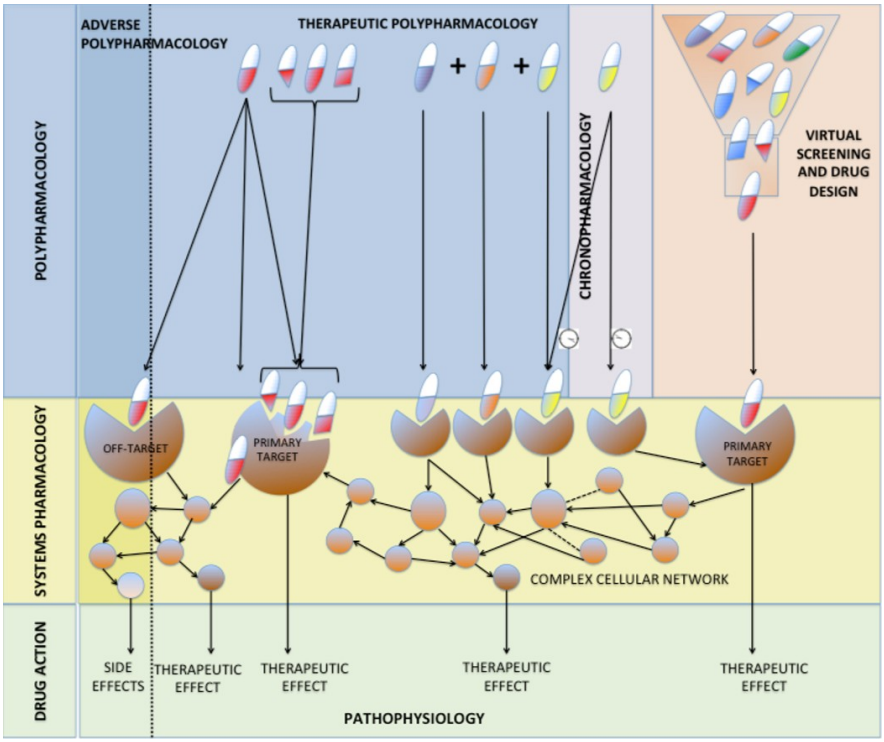

Figure 1. The big picture: QSP. This Figure was reproduced from Pérez-Nueno VI. Expert Opin. Drug Discov. (2015) 10(12)[138].

As mentioned above, hospitals are spending large sums of money because of polypharmacy and ADRs, and current tools for identifying PIP in older patients[14-23,32,33,34] are time-consuming and inadequate. Therefore, QSP can be essential to deal with these problems, with practical application in the promising field of personalized medicine and drug repositioning with reduction of SEs.

There are numerous databases containing information about DDIs. The DrugBank database[73], Drugs.com[72], the Food and Drug Admi-

nistration is a federal agency[64], the JAPIC database[101,102], the KEGG DRUG database[103], the Comparative Toxicogenomics Database (CTD)[104], the Anatomical Therapeutic Chemical (ATC) Classification System[105], the World Health Organization (WHO)[106], or Transformer[108].

Regarding data mining, text mining and statistical analysis of pharmacovigilance resources for predicting DDIs, Cheng et al. created a heterogeneous network- assisted inference framework to assist with the prediction of DDIs[109]. They calculated drug–drug pair similarities using four features: phenotypic, therapeutic and genomic similarity. David et al. created an update of the CTD database in collaboration with Pfizer[110]. Revising almost 100.000 scientific articles manually, they updated the database with toxicogenomic interactions, chemical–disease, chemical–gene, gene–disease and phenotype interactions. Boyce et al. used natural language processing to identify pharmacokinetic DDIs described in drug labels[111]. Their machine-learning algorithm can identify and classify pharmacokinetic DDIs. Thirty institutes work together in the eTOX project[112]. It aims to develop a drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data, innovative in silico strategies and novel software tools to better predict the toxicological profiles of small molecules in early stages of the drug development pipeline. Zazo et al. organized a DDI extraction challenge in 2011 and 2013, where participants from 14 groups compared their best text mining methods[113]. They created a DDI corpus where all the data of the challenge was inclu-

ded, and can be used for academic research. Abacha et al. took it to the next level and applied the corpus used in text mining for pharmacovigilance and created a machine learning methodology[114]. Takarabe et al. created a network based characterization of adverse drug-drug reactions, based on ATC classification from the Japanese JAPIC and KEGG DRUG database[115]. Percha et al. published an automated text mining solution for identifying gene-drug relationships and aggregating them to predict novel DDIs[116]. Ayvaz et al. created a complete dataset of DDIs[117]. To do so they combined all the publicly available sources of DDIs using a common data model after conducting a comprehensive and broad search.

Regarding the prediction of potentially dangerous DDIs by means of Internet based searches and the analysis of drugs, targets, metabolism, and safety profiles, White et al. discovered an unknown DDIs of paroxetine and pravastatin from a Google search analysis [118]. Google users searched paroxetine and pravastatin as drugs they were taking together, as well as the symptoms they were experimenting, such as thirst, fatigue, or blurred vision. Those are typical symptoms of hyperglycemia. Takarabe et al. defined pharmacological similarity for all possible drugs using the FDA Adverse Event Reporting System and developed a method to predict unknown drug-target interactions (DTIs) on a large scale[119]. They made a prediction for off-targets of 1874 drugs with known targets and potential target profiles of 2519 drugs without known targets. Tatonetti et al. created an adaptive data-driven approach that reduces

confounding factors[120]. They created two resources of adverse drug effects and DDIs, a comprehensive database of drug effects OFFSIDES, and a database of DDIs side effects TWOSIDES. Using these two datasets, they made and confirmed the prediction that selective serotonin reuptake inhibitors and thiazides are associated with specifically increased incidence of prolonged QT intervals.

Each drug has its target profile. The primary target profile is the list of targets expected to hit the drug when consumed in a recommended dose. The secondary or the off target profile is when the drug concentration alters, so it can hit new, unexpected target(s). Many drugs have an incomplete target profile, given that exists a large number of unknown DTIs compared with the small amount of experimentally verified DTIs. The study and understanding of the complete target profile of drugs can prevent unexpected side-effects, DDIs and the reduction of healthcare costs. Regarding network pharmacology and chemoinformatic approaches for predicting DDIs, Cobanoglu et al. used a probabilistic matrix factorization for a quantitative analysis of known DTIs[121]. They created a mechanism for predicting hidden DTIs with 88% confidence. Alaimo et al. presented a network based interference network method, called Domain Tuned-Hybrid, which extends drug target prediction by domain -based knowledge including drug and target similarity[122]. Laarhoven et al. created a machine learning method that uses the drug-target network as the only source of information[123]. They introduced interaction profiles of drugs in a network, which are binary vectors specifying the presence or absence of interaction with every

target in the network. They made predictions for DTIs with a Gaussian Interaction Profile, with a precision recall profile of 92.7. Chen et al. studied four important classes of DTI networks, including enzymes, ion channels, GPCRs and nuclear receptors[124]. They used a semi-supervised learning network, based on similarity values.

Secondary pharmacology is an essential component of drug discovery and is used extensively in the pharmaceutical industry for achieving optimal specificity on new drugs via early hazard identification and off-target mitigation[125]. The importance of this discipline has been achieved by target-drug-ADR associations and integration of secondary pharmacology data with pharmacokinetic parameters. Whitebread et al wrote the first review about an essential tool, an in vitro safety pharmacology profiling in 2005[126]. They collected a selection of cardiovascular targets that when hit by certain compounds possible ADRs can be expected. Urban et al. analyzed the modeling safety aspects of drugs with an integrated molecular network approach[127]. In silico methods are more frequently used to test compounds. They have a great utility in the design of new molecules devoid of off-target effects and guide chemists to synthesize those structures which carry less or no hazard towards unwanted ADRs. Urban et al. also created a Drug-Target-ADR network[128]. In their network they predicted and confirmed more than half of the predicted off-targets and side effects. Simon et al. introduced a polypharmacology-based approach which is able to relate complex drug – protein interaction profiles with effect profiles[129].

Their prediction method, the Drug Profile Matching is a robust and highly accurate approach that calculates the effect profile of drugs solely on a basis of their complex binding properties. A year later, Peragovics et al. improved the Drug profile matching method using it for target fishing as well[130]. Kepiro et al. presented an opto-pharmacological tool, molecular tattooing, which enables in vivo subcellular localization of drug effects[104]. They apply two-photon microscopy for covalent enrichment of photoreactive drugs on specific targets, confining drug effect solely to the irritated area[131].

b) MINI-MED methodology

MINI-MED investigates which drugs can be reduced in common combinations of prescription medications taken by the elderly, either because a SE of one drug produces the desired effect of another one already being taken, or because a new drug can be used for two or more medical conditions. By developing formal mathematical and systems-based computational models, MINI-MED aims to predict therapeutic and adverse drug SEs and evaluate the biological relevance of combinations of drugs according to pathway and molecular function enrichment analyses. The project has a direct application in the field of personalized medicine, which the emerging discipline of quantitative and systems pharmacology encourages.

Some of the strategies to reduce adverse effects are:

- Eliminate unnecessary drugs (PIM)
- Use drugs for diseases that had not been taken into account (besides the disease treated), or drugs than can be used for two diseases (PPO)

Hence, the data of San-José et al., which refers to the kind of drug and inappropriate prescription, is a reference work very interesting for this purpose.

Figures 2 and 3 show two example cases of using drug-target-SE-CO networks to decrease the number of drugs in simultaneous prescription medications. This in silico supplement to conventional polypharmacy approaches will be extremely beneficial to speed up the process and to enlighten the path to reducing polypharmacy. Example 1 reduces 11 medications to 6. Example 2 reduces 13 medications to 7. Commonly prescribed dosage for drugs is shown just for illustrative purposes. A medical validation step has not yet been performed in the aforementioned examples.

There are also real example studies describing successful reduction of inappropriate prescription[132]. A case study in 2015 describes a 85-year-old female, who took 7 drugs for a long time (amlodipine, valsartan, hydrochlorothiazide, lysine acetylsalicylate, sinvastatine, and trimetazidine). In June 2013, she presented thoracic pain and received propranolol, tramadol, and paracetamol. One week later, she developed a diffuse skin lesion. After that, drugs considered unnecess-

ary were discontinued (Sinvastatine, trimetazidine, antihistamic and iron) and corticosteroid was administered orally.

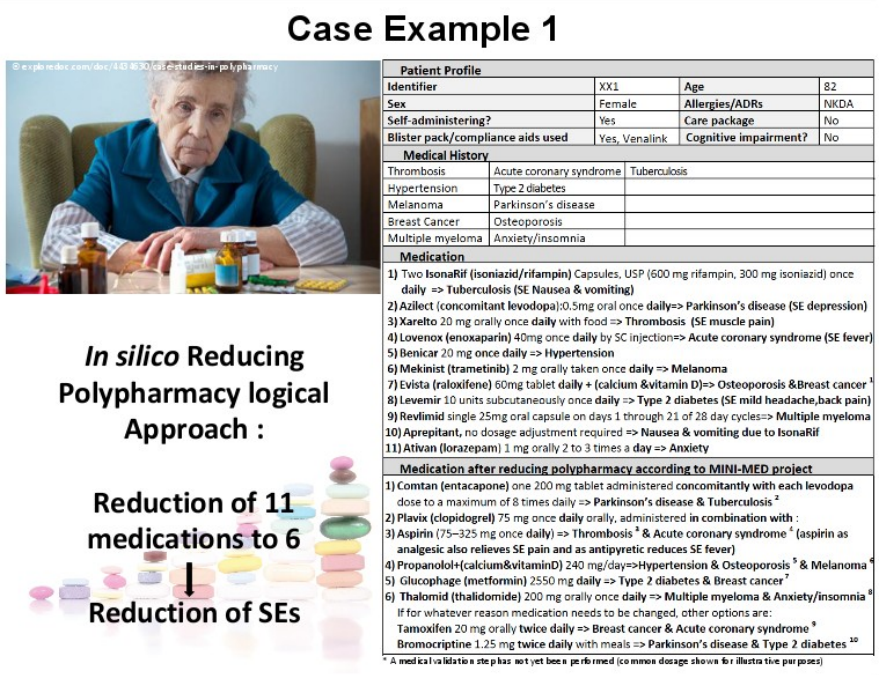

Figure 2. Reducing polypharmacy Case Example 1. Example 1 reduces 11 medications to 6. Commonly prescribed dosage for drugs is shown just for illustrative purposes. A medical validation step has not yet been performed.

About 10 months later, the patient received only 20 mg of corticosteroid and she has not presented any vesiculobullous disease since. When analyzing simultaneous prescription medications, MINI-MED first looks at the prescribed drugs and the disease/COs according to the clinical profile of the patient. After, these disease/COs are mapped with their corresponding targets, and the SEs associated to these targets are found using calculated scores. Having created the drug-target-SE-CO network relationships, both from available experimental data and -when missing experimental data-

from predicted data by systems pharmacology using i.e. CTlink[133] or GES[134,135] and GESSE[136] approaches, MINI-MED checks for drugs in the clinical profile that can be repositioned.

***In silico* Reducing Polypharmacy logical Approach :**

Reduction of 13 medications to 7

Reduction of SEs

Patient Profile			
Identifier	XX2	**Age**	79
Sex	Male	**Allergies/ADRs**	NKDA
Self-administering?	No	**Care package**	Carer all day
Blister pack/compliance aids used	No	**Cognitive impairment?**	Yes

Medical History		
Schizophrenia	Rheumatoid arthritis	Migraine
Plaque psoriasis	High cholesterol & triglycerides	Benign Essential Tremor
Hepatic fibrosis	Urinary incontinence	
Epilepsy	Depression	
Hypertension	Colorectal cancer	

Medication

1) Enablex 7.5mg/**day => Urinary incontinence (SE stomach discomfort, sour, indigestion)**
2) Celexa (citalopram) 40 mg orally once a **day => Depression**
3) Xeloda 1250 mg/m2 orally **twice daily => Colorectal cancer (SE stomach pain or upset)**
4) Humira injection 40 mg administered every other week => **Rheumatoid & Psoriatic arthritis**
5) Bystolic 2-week intervals up to 40 mg **=> Hypertension**
6) Kalydeco 150 mg tablet taken orally **daily => Hepatic fibrosis**
7) Lipitor 20 mg once **daily => High cholesterol**
8) Keppra 500 mg every **12h => Epilepsy**
9) Stelara injection 45 mg during 4 weeks, followed by 45 mg every 12 weeks**=> Plaque psoriasis (some people using Stelara have developed skin cancer)**
10) Abilify 15 mg/**day** orally **=> Schizophrenia**
11) Omeprazol 20 mg orally once a day before a meal **=> Stomach discomfort**
12) Relpax (eletriptan) single dose 40 mg **=> Migraine**
13) Zonegran (zonisamide) 100 mg **daily => Benign Essential Tremor**

Medication after reducing polypharmacy according to MINI-MED project

1) Cymbalta (duloxetine) 30 mg orally twice a **day => Depression & Urinary Incontinence** [1]
2) Anafranil (clomipramine) 3 mg/kg **daily => Antidepressant & Colorectal cancer** [2]
3) Prolixin (fluphenazine) 10 mg **daily => Schizophrenia & Rheumatoid arthritis** [3] **(SE Tremors)**
4) Valsartan 160 mg orally once a **day => Hypertension & Hepatic fibrosis** [4]
5) Altoprev (lovastatin) 20 mg/**day** at bedtime => **Lowering high cholesterol & Epilepsy** [5]
6) Trexall (methotrexate) 10 to 25 mg/**week** orally **=> Cancer (skin between them) & Plaque psoriasis** [6] **& Rheumatoid arthritis** [7]
7) Propanolol 240 mg/**day => Essential Tremor** [8] **& Hypertension & Melanoma** [9] **& Migraine** [10]
In case of pain, fever and/or migraine, take **Aspirin** 3 grams/**day** in divided doses (now that stomach discomfort is not a SE, because we avoid the drugs producing this SE, and aspirin is known to be bad for stomach ulcers). It will be beneficial for several diseases of the clinical profile **=> Rheumatoid arthritis** [11] **& Migraine** [12] **& Colorectal cancer** [13]

Figure 3. Reducing polypharmacy Case Example 2. Example 2 reduces 13 medications to 7. Commonly prescribed dosage for drugs is shown just for illustrative purposes. A medical validation step has not yet been performed.

If one drug is found to bind both the therapeutic target for which is prescribed and an off-target, this drug is kept and the drug given in the prescription for the off-target is eliminated. New drugs that are not present in the clinical profile but which can be used for two or more diseases/COs are also checked. If a new drug is found to bind two or more therapeutic targets or off-targets, then this drug is introduced in the clinical profile, and those drugs initially prescribed for

these targets are eliminated. Figure 4 shows schematically this strategy to reduce polypharmacy.

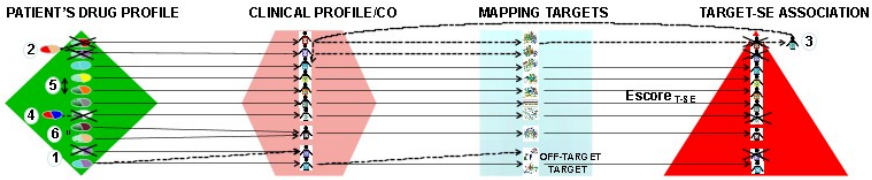

Figure 4. Scheme of the MINI-MED strategy to reduce polypharmacy. In this scheme it is assumed that drug-target-SE-CO network has a one-to-one relation for simplification purposes. (1) From the list of medications, one drug for two of the COs present in the patient's clinical profile is re-purposed (e.g. Evista for osteoporosis & breast cancer in Example 1). Given that the drug that is eliminated could produce a SE, a SE could be reduced, and only keep the SE for the drug that is used. (2) A new drug that can be used for two COs is used, hence binding two targets, and probably also reducing SEs because two drugs are reduced to one (e.g. cymbalta for depression & urinary incontinence in Example 2 is used instead of enablex, that was for urinary incontinence, and celexa, that was for depression, thus avoiding the SE stomach discomfort). (3) This new drug can be used for two COs since it is a new drug for the patient, it could have a different SE, but since one drug was successfully reduced, the patient will still have fewer SEs than before. Ideally, the introduced SE would be a desired therapeutic effect in the clinical profile (e.g. prolixin for schizophrenia & rheumatoid arthritis in Example 2 has the new SE essential tremor, which is a CO of the clinical profile).

In this scheme it is assumed that drug-target-SE-CO network has a one-to-one relation for simplification purposes. However, as before, each drug can have several SEs, can be used for several COs, or can bind several targets. Figure 5 shows a specific example of the MINI-MED strategy to reduce polypharmacy. Following the strategy to reduce polypharmacy, schematized in Figure 4, in the example shown in Figure 5 the patient is prescribed zonegran for tremor and propanolol for hypertension, propranolol can be repurposed for tremor and avoid zonegran and its SEs.

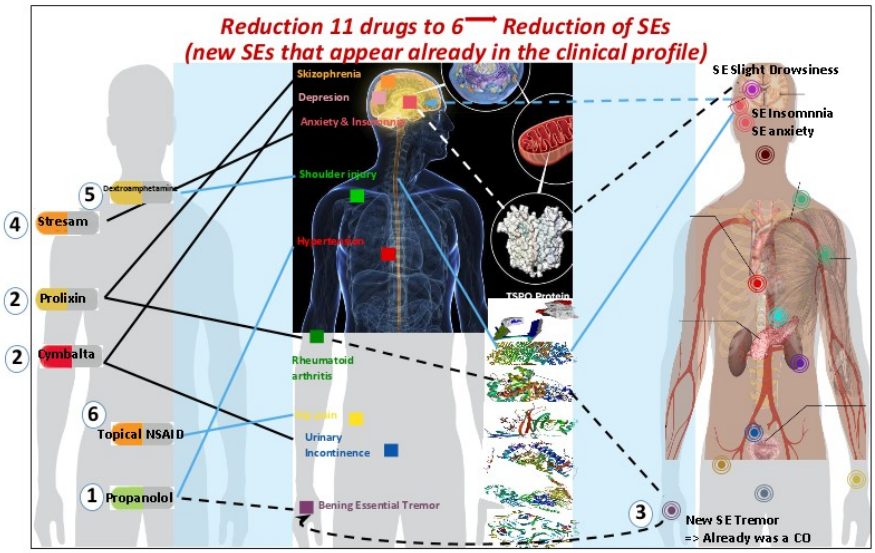

Figure 5. Example of the MINI-MED strategy to reduce polypharmacy. Scheme of a 80 year old man with a drugs profile of 11 drugs to treat the following clinical profile: skizofrenia, depression, a shoulder injury, hypertension, stomach disconfort, rheumatoid arthritis, hip pain, urinary incontinence, and tremor. By using systems pharmacology approaches, the patient's profile and clinical outcomes (CO) can be matched with the corresponding mapping targets and target-SE assocations. By analysing the drugs-CO-targets-SE networks it is possible to reduce non-essential medications and check for drug-drug, drug-disease, drug-target interactions in order to avoid serious side effects.

The patient is prescribed enabex for urinary incontinence and lexapro for depression, and omeprazol for stomach discomfort, a new drug (cymbalta) can be found for both CO, hence avoiding enablex and its strong stomach discomfort SEs, not needing the omeprazol.

The patient is prescribed abilify for skizofrenia and humira for rheumatoid arthritis, a new drug (prolixin) can be found for both CO. The SE of this new prolixin drug is tremore, which is already treated y propanolol in the clinical profile

The patient is prescribed dextroamphetamine for a shoulder injury, which SE is insomnia and anxiety, so he is prescribed diazepam.

Diazepam is a sedative (increases sedation), while dextroamphetamine is a CNS stimulator (decreases sedation). One drug offsets the effects of the other; this DDI can lead to serious adverse effects such as serotonin syndrome, leading to seizures and high blood pressure.

For this reason, the strategy number 5 is avoiding the DDIs leading to serious adverse effects, for instance using strategy number 4, changing dizaepam, which is a sedative, by stresam, which is a CNS stimulant, such as dextroamphetamine, hence avoiding the bad DDIs.

Moreover diazepam is a non-selective benzodiazepine binding GABAA receptor, and as it is well known for benzodiazepines, with high drowsiness; tired feeling; muscle weakness; or loss of coordination SEs between others, However, stresam binds the mitochondrial translocator protein (18 kDa) (TSPO). TSPO, which in its turn modulates GABAA receptors, thereby exerting anxiolytic effects. The fact of binding the TSPO protein first, and no directly GABAA receptor as benzodiazeines, avoids the benzodiazepines addictive-based SEs ad has less SEs, such as slight drowsiness, appearing in the early days of admission and usually disappearing on their own in the course of treatment.

Finally, the patient is prescribed two non-steroidal anti-inflammatory drugs (NSAIDs.) for his hip pain. Following strategy number 6, one of the drugs can be suppressed, hence avoiding drug duplication for the same CO. If the pain is not strong, it is recommendable to stop the oral doses which, although more potent, causes higher SEs

such as stomach discomfort or hypertension (which in this case there are already treated in the clinical profile, except if we remove omeprazol as aforementioned).
In summary, it could be possible to reduce 11 drugs to 6, with the consequent reduction of SEs such as stomach discomfort and drowsiness, and the new SEs that would appear (tremor, hypertension, insomnia) they would be already treated on the clinical profile.

Overall, the MINI-MED example of a systems pharmacology approach combined with chemo–bio- informatics and data mining to reduce polypharmacy may be summarized as a five-step protocol:
Step 1: ASSES the patient's medications, especially certain groups of medications that have a potential for adverse outcomes, in order to use drug repositioning to avoid side effects (e.g. beta blockers, antidepressants, antipsychotics, other psychotropics, pain medications, other medications listed in the Beers criteria, vitamins and supplements).
Step 2: CHECK for drug-drug, drug-disease, drug-target interactions in order to avoid side effects by building drug-target-SE-CO networks and analyzing them using chemoinformatics and mining approaches.
Step 3: REDUCE non-essential medications. Eliminate medications that lack evidence for their usage. Eliminate medications for COs that can be achieved by drug re-purposing, while decreasing SEs. Try to reduce those drugs whose risks out-weigh their benefits and which have high potential for a negative impact on primary body

functions (appetite, weight, pain, mood, vision, hearing, bladder, bowel, skin, swallowing, activity level).

Step 4: EVALUATE the reduced list of medications according to several rounds of prospective computational and medical validation to increase trust in the networks and SE/CO prediction. Adjust medications with the help of doctors' assessment.

Step 5: REFINE results (chemoinformatics + data mining + strong biostatistics + network analysis) to make them fit the computational and medical validation using several rounds of testing and refinement.

6. **Conclusion**

The use of multiple medications is often referred to as polypharmacy, but also refers to the administration of more medications than clinically indicated, representing unnecessary drug use.

With increasing polypharmacy comes rising morbidity and mortality, and public health agencies are being forced to take notice. The FDA recently recommended tighter controls on prescriptions. Here we show that the medicine utilization pattern in people aged 65 years and older is an average of 7 drugs, where the most common used drugs are paracetamol, senna, lactulose, sangobion, aspirin, isosorbide dinitrate, potassium chloride, amlodipine, famotidine and enalapril, which can cause potential serious adverse effects. We

show that the main determinants of polypharmacy and inappropriate prescribing are age, gender, number of medications taken (prescription and OTC), reason for admission to hospital (acute disease, exacerbation of a chronic disease), nutrition, lifestyle, emotional well-being, dwelling,number of general practitioner (GP) or emergency room (ER) visits during the previous month.

A small number of studies have shown the potential to reduce polypharmacy, but more research is needed for a molecular-level understanding of drug effects and drug pathways. Here we show the potential of a novel approach to reduce polypharmacy by using systems pharmacology and in silico chemo-informatic methods. Chemoinformatic approaches start from the molecular structures of drugs, and biostatistics and data mining analyze the available drug-target-SE-CO relationships. These approaches deal with huge volumes of chemical and biological data, which is processed, stored, and queried efficiently, for drug re-positioning simultaneously reducing SEs. By defining drug-target-SE-CO networks for the most common drugs and their related targets, these approaches could reduce poly-drug use in the most common simultaneous prescription medications (the most common examples of polypharmacy), which is vital to advance in this challenging and important area.

Hence, systems pharmacology, chemo-and –bio- informatics approaches combined with data mining have the potential to transform current strategies for reducing polypharmacy. The polypharmacy

predictions that could be retrieved by these approaches, could even be complemented, and may be improved, by exploring the effect of patients' age and gender response to drugs by means of pharmacogenomics.

7. **Expert Opinion**

Unfortunately, while national governments and health insurance companies are equally interested in reducing polypharmacy, there remains a gap in the literature regarding the polypharmacy and its developmental course. Current existing approaches to tackle polypharmacy follow an experimental test and adjust methodology, which makes them very tedious and costly. Most patients using them get tired before a proper statement of polypharmacy reduction can be made and they normally see multiple specialists that do not always agree in a consensus.

Systems pharmacology, chemo-and –bio- informatics approaches combined with data mining have a great potential as a novel way to tackle polypharmacy. For example, the MINI-MED project aims to build the first in silico reducing polypharmacy logical approach by combining bioactivity and bioinformatics data (collected through several repositories and practical approaches) with computational systems pharmacology approaches (developed and refined with this data). This will provide insights into the drug pharmacology, drug safety and differentiation of patient drug response towards persona-

lized medicine, hence opening the way to rational drug de-prescribing.

By developing and using these in silico approaches it will be possible to make statements such as the following: If compound 1 is active on target A and compound 1 has SEs n1, n2, ..., nx, then target A has n1,n2,...,nx associated SEs; so it will be possible to answer "which are the side effects associated to a given target"? The objective is that these in silico approaches propose alternative treatments with fewer SEs for certain COs by re-positioning existing drugs, and recommend ways to reduce the profile of simultaneous prescription drugs taken by the elderly in a way which will still treat a given patient's profile of diseases but with fewer SEs. Possible limitations of these approaches are the assumption that the phenotypic effects of drugs are protein-mediated and that these drugs reach only protein targets (i.e. ignoring all kinds of RNA). Drug concentration effects should be also explored, given that reducing a drug's concentration can be an important practical polypharmacy consideration. Tissue location, the presence of active metabolites and additional information related to CO and SE needs to be used for complex cases (i.e.. by creating tissue specific functional relationship networks utilizing knowledge of tissue-specific gene expression patterns manually associating each SE with a specific tissue/organ). Regarding the risks of these approaches, a percentage of false-positive drug-target or drug-SE associations are predicted for this reason a thorough computational validation step, by in vitro and/or cellular assays, is needed to confirm the predictions. However, these false-

positives can be also taken as new known information of real negative results.

Understanding the “magic triangle” of drugs, targets, and their SEs has become a “holy grail” of the pharmaceutical industry. Understanding the triangle of drugs- targets-SEs, and being able to make predictions, i.e. by developing new computational approaches for the emerging discipline of quantitative and systems pharmacology (QSP), will allow the biological relevance of combinations of drugs to be evaluated in terms of related pathways, molecular functions and disease-gene relationships, making a significant contribution towards understanding the effects of poly-drug use. All pharmaceutical companies desperately want to know in advance that working with target X could cause side effects n1, n2, ..., nx. Once a tool for linking systems pharmacology with drug action has been developed, it seems straightforward to apply it to the increasingly important problem of reducing polypharmacy. The ability to do this is highly relevant to the rational treatment of complex conditions requiring simultaneous prescription medications and to provide a deeper understanding of the adverse SEs that may be caused by multiple drug combinations.

There is currently more and more experimental available data to exploit to tackle specific targets, as well as algorithms, to predict off-targets for drugs and to annotate them with pathway-related molecular functions and disease-related genes. Hence, there is a need to ex-

ploit the large amount of data in the field of active aging and polypharmacy.

As far as we know, nobody has applied systems pharmacology tools to the field of polypharmacy, which urgently needs from an in silico help to improve the current very tedious and costly experimental approaches. Furthermore, computers are more powerful than ever before, there is more data than ever before, and hence it is much easier to perform larger-scale studies/calculations than ever before. All these data we are currently capable to manage and process can be very useful to complement, help to understand, and make quickly advance the research of experimental experts (biologists, chemists, genetics...). We believe that the future in science comes from joining more and more several branches of science in an interdisciplinary way to help understand the complicated scientific problems with a wide perspective, as QSP promotes. Therefore, it is very important to promote the interdisciplinary work, i.e on the border between biology, chemistry, pharmacology and computer science, fundamental for advancing in the future in health research, between other fields. In this respect, for example, the Food and Drug Administration launched precisionFDA (https://precision.fda.gov/), a cloud-based research and development portal designed to allow researchers to analyze genome data and run comparisons against reference material, such as sample data widely accepted. It is a crowdsourced platform to provide a digital environment for members of the genomics community to work together. Hence, allowing more

data available for developing pharmacogenomic approaches, following President Obama's Precision Medicine Initiative [137].

Hence, the great number of challenges associated with exploiting systems pharmacology, and in silico chemo- and bio-informatic methods combined with data mining, to tackle polypharmacy in the elderly should be seen as a great source of opportunities for the future, for experimental and computational scientists alike.

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Declaration of interest

None.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1.World Population Prospects: 2012 Revision, June 2013 http://esa.un.org/unpd/wpp/index.htm

2. A.W. Schoenenberger, A.E. Stuck. Inappropriate drug use among older persons: is it time for action? Age Ageing 2014 (43) 737-739.

3. New York Times October 24, 2013. http://www.nytimes.com/2013/10/25/business/fda-seeks-tighter-control-on-prescriptions-for-class-of-painkillers.html?nl=todaysheadlines

4. G. Onder, et al. Polypharmacy in Nursing Home in Europe: Results From the SHELTER Study. J Gerontol A Biol Sci Med Sci. 2012 (67A) 698-704.

5. D.M. Qato, et al. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med. 2016 (176) 473-482.

6. Y. Bao, et al.Inappropriate medication in a national sample of US elderly patients receiving home health care. J Gen Intern Med. 2012 (27) 304-310.

7. G. Onder, et al. Recommendations to prescribe in complex older adults: results of the CRIteria to Assess Appropriate Medication Use Among Elderly Complex Patients (CRIME) Project. Drugs Aging 2014 (31) 33-45.

8. C. Cahir,et al.Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients.Br J Clin Pharmacol 2014 (77) 201-10.

9. Hedna K, Hakkarainen KM, Gyllensten H, Jönsson AK, Petzold M, Hägg S. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. Eur J Clin Pharmacol. 2015 Dec;71(12):1525-33. Doi: 10.1007/s00228-015-1950-8. Epub 2015 Sep 26. PubMed PMID: 26407684; PubMed Central PMCID: PMC4643104.

•• High interest paper on inappropriate prescribing and adverse effect in the elderly.

10. M. Tosato, et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. Age Ageing 2014 (43) 767-773.

11. S.J. Lynn. Adverse Drug Reactions in the Elderly: Can we stem the tide? Am Nurs Today. 2012 (7) 1-8.

12. Deprescribing in Clinical Practice : Reducing Polypharmacy in Older Patients. Medscape. Nov 26, 2013.

13. W. Thompson, B. Farrell. Deprescribing : What Is It and What Does the Evidence Tell Us ? Can J Hosp Pharm. 2013 (66) 201-202.

14. P. Gallagher, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008 (46) 72.
15.D. O'Mahony, et al. STOPP/START criteria for potentially inappropriate prescribing in older people:version 2. Age and Ageing 2014 (0) 1-6.
•• High interest paper on preventing inappropriate prescribing.

16. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 (60) 616.

17. http://www.americangeriatrics.org/files/documents/beers/Beers-CriteriaPublicTranslation.pdf (accessed October 2015).

18. A.M. Kuhn-Thiel, et al. FORTA authors/expert panel members. Consensus validation of the FORTA (Fit fOR The Aged) List : a cli-

nical tool for increasing the appropriateness of pharmacotherapy in the elderly. Drugs Aging 2014 (31) 131.

19. http://www.nhshighland.scot.nhs.uk/publications/documents/guidelines/polypharmacy%20guidance%20for%20prescribing%20in%20frail%20adults.pdf

20. J. Hanlon, et al. Medication Appropriateness Index- MAI. J Clin Epidemiol 1992 (45) 1045-1051.

21. http://www.wales.nhs.uk/sites3/documents/814/Prescribing-ForFrailAdults-ABHBpracticalGuidance%5Bmay2013%5D.pdf (October 2015).

22. M.D. Raza Haque. ARMOR : A Tool to Evaluate Polypharmacy in Elderly Persons. Annals of Long Term Care 2009 (17) 1-5.

23. I.A. Scott, et al. Minimizing inappropriate medications in older populations : a 10-step conceptual framework. Am J Med. 2012 (125) 529-537.

24. D. Garfinkel, D. Mangin. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults : addressing polypharmacy. Arch Intern Med 2010 (170) 1648-1654.

25. I.A. Scott, et al. Deciding when to stop : towards evidence-based deprescribing of drugs in older populations. Evid Based Med 2013 (18) 121-124.

26. A. San José. Prescripción Potencialmente Inapropiada en Pacientes de Edad Avanzada. Proyecto PUMEA. Servicio de Medicina Interna. Hospital Universitario Vall d'Hebron.https://www.fesemi.org/sites/default/files/documentos/ponencias/vii-reunion-pppyea/6.pdf
•• High interest paper on inappropriate prescribing in the elderly.

27. A. San José. Ordenando la polifarmacia en las personas de edad avanzada y/o con alta multimorbilidad. XII Jornada d'actualització terapèutica 2012. Servicio de Medicina Interna. Hospital Universitario Vall d'Hebron. http://projectes.camfic.cat/CAMFiC/Seccions/Formacio/Docs/11_12/03_SANJOSE.pdf
•• High interest paper on polypharmacy in the elderly.

28. OECD Health Statistics 2016; Eurostat Statistics Database; WHO Global Health Expenditure Database. Health at a Glance: Europe 2016, OECD. http://www.oecd.org/els/health-systems/Health-at-a-Glance-Europe-2016-CHARTSET.pdf

29. Charles ST, Carstensen LL. Social and emotional aging. Annu Rev Psychol.2010;61:383-409. Doi: 10.1146/annurev.psych.093008.100448. Review. PubMed PMID:19575618; PubMed Central PMCID: PMC3950961

30. Singh-Manoux A, Richards M, Marmot M. Leisure activities and cognitive function in middle age: evidence from the Whitehall II study. J Epidemiol Community Health. 2003 Nov;57(11):907-13. PubMed PMID: 14600119; PubMed CentralPMCID: PMC1732329.

31. Eurostat Statistics Explained. Population structure and ageing. http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing

32. B. Hill-Taylor, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther. 2013 (38) 360-72.

33. Hervás A, García de Jalón E. Situación cognitiva como condicionante de fragilidad en el anciano. Perspectiva desde un centro de salud. An Sist Sanit Navar. 2005;28:35–47.

34. M. Wehling, et al. VALFORTA: a randomised trial to validate the FORTA (Fit fOR The Aged) classification. Drugs Aging 2016 (45) 262-267.

35. Kouladjian L., Hilmer S.N., Chen T.F., Le Couteur D. G., Gnjidic D. Assessing the harms of polypharmacy requires careful interpretation and consistent definitions. Letter to the Editors. Br J Clin Pharmacol , 78 »3, 670-671

36. Koh Y., Bte Moideen Kutty F., Chuen Li S. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. Therapeutics and Clinical Risk Management 2005:1(1) 39–48.
• Interest paper on polypharmacy in the elderly.

37. Gallacher KI., Batty GD., McLean G., Mercer SW., Guthrie B., May CR., Langhorne P., Mair FS. Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. BMC Medicine 2014, 12:151, 1-9.

38. P. Gallagher et al.Prevalence of potentially inappropriate prescribing in acutely ill population of older patients admitted to 6 European hospitals.Eur J Clin Pharmacol 2011 (67)1175-88.
•• High interest paper on inappropriate prescribing in the elderly.

39. Schuler J, Dückelmann C, Beindl W, Prinz E, Michalski T, Pichler M. Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. Wien Klin Wochenschr. 2008;120(23-24):733-41. doi: 10.1007/s00508-008-1089-z. PubMed PMID: 19122984.

40. Vaes B, Pasquet A, Wallemacq P, Rezzoug N, Mekouar H, Olivier PA, Legrand D, Matheï C, Van Pottelbergh G, Degryse J. The BELFRAIL (BFC80+) study: a population-based prospective cohort study of the very elderly in Belgium. BMC Geriatr. 2010 Jun

17;10:39. doi: 10.1186/1471-2318-10-39. PubMed PMID: 20565795; PubMed Central PMCID: PMC2906485.

41. Popović B, Quadranti NR, Matanović SM, Lisica ID, Ljubotina A, Duliba DP, Vlahović-Palčevski V. Potentially inappropriate prescribing in elderly outpatients in Croatia. Eur J Clin Pharmacol. 2014 Jun;70(6):737-44. Doi: 10.1007/s00228-014-1667-0. Epub 2014 Mar 21. PubMed PMID: 24647976.

42. Sönnichsen A., Trampisch U.S., Rieckert A., Piccoliori G., Vögele A., Flamm M., Johansson T., Esmail A., Reeves D., Löffler C., Höck J., Klaassen-Mielke R., Trampisch HJ., Kunnamo I. Polypharmacy in chronic diseases–Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS):study protocol for a randomized controlled trial. Sönnichsen et al. Trials (2016) 17:57

43. Noale M., Veronese N., Perin P.C., Pilotto A., Tiengo A., Crepaldi G., Maggi S.. Polypharmacy in elderly patients with type 2 diabetes receiving oral antidiabetic treatment. Acta Diabetol (2016) 53:323–330.
• Interest paper on polypharmacy in the elderly.

44. Jodar-Sanchez, F. et al. Cost-Utility Analysis of a Medication Review with Follow-Up Service for Older Adults with Polypharmacy in Community Pharmacies in Spain : The conSIGUE Program. Pharmacoeconomics. 2015 Jun ;33(6) :599-610.

45. A. Vilà, A. San José, C. Roure, Ll.Armadans, M. Vilardell. Estudio multicéntrico prospectivo de reacciones adversas a medicamentos en pacientes ancianos hospitalizados. Med Clin (Barc)2003; 120: 613-8

46. Formiga, F. ; Agusti, A. ; San José, A. Polypharmacy in elderly people with diabetes admitted to hospital. Acta Diabetol (2016) 53:857–858.

• Interesting paper on polypharmacy in the elderly.

47. Formiga et al. Inappropriate prescribing in elderly people with diabetes admitted to hospital. Diabet. Med. 33, 655–662 (2016)

48. San-José et al. Inappropriate prescribing to the oldest old patients admitted to hospital: prevalence, most frequently used medicines, and associated factors. BMC Geriatrics (2015) 15 :42.
•• High interest paper on causes and factors in hospitalization of the elderly.

49. San-José et al. Inappropriate prescribing to older patients admitted to hospital: A comparison of different tools of misprescribing and underprescribing. European Journal of Internal Medicine 25 (2014) 710–716.
•• High interest paper on causes and factors in hospitalization of the elderly.
50. San-José et al. An inter-rater reliability study of the prescribing indicated medications quality indicators of the Assessing Care Of Vulnerable Elders (ACOVE) 3 criteria as a potentially inappropriate prescribing tool. Archives of Gerontology and Geriatrics 58 (2014) 460–464.
• Interesting paper on tools to prevent inappropriate prescribing in the elderly.

51. Calderón-Larrañaga A. , Gimeno-Feliu L.A., González-Rubio F., Poblador-Plou B., Lairla-San José M., Abad-Díez J.M., Poncel-Falcó A., Prados-Torres A. Polypharmacy Patterns: Unravelling Systematic Associations between Prescribed Medications. Plos One, December 2013, Volume 8, Issue 12, e84967.

52. https://ec.europa.eu/eip/ageing/library/polypharmacy-patterns-unravelling-systematic-associationsbetween-prescribed-medications-0

53. https://ec.europa.eu/eip/ageing/home_en

54. https://ec.europa.eu/eip/ageing/news/simpathy-project-tackle-polypharmacy-elderly

55. http://www.simpathy.eu
•European Project dealing with polypharmacy in the Elderly.

56. https://ec.europa.eu/eip/ageing/comitmments-tracker/a1/friendd-study-group-drug-interactionspolypharmacy-elderly

57. Crome P, Cherubini A, Oristrell J. The PREDICT (increasing the participation of the elderly in clinical trials) study: the charter and beyond. Expert Rev Clin Pharmacol. 2014 Jul;7(4):457-68. Doi: 10.1586/17512433.2014.922864. Review. PubMed PMID: 24939469.

58. http://www.icare4eu.org/

59. https://www.sites.google.com/site/micmiproject/

60. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol. 2007 Aug;63(8):725-31. Epub 2007 Jun 7. PubMed PMID: 17554532.

61. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997 Feb 1;156(3):385-91. PubMed PMID: 9033421; PubMed Central PMCID: PMC1226961.

62. Lindblad CI, Hanlon JT, Gross CR, Sloane RJ, Pieper CF, Hajjar ER, Ruby CM, Schmader KE. Clinically important drug-disease interactions and their prevalence in older adults. Clin Ther. 2006 Aug;28(8):1133-43. PubMed PMID: 16982290.

63. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010 Aug;107(31-32):543-51. Doi: 10.3238/arztebl.2010.0543. Epub 2010 Aug 9. PubMed PMID: 20827352; PubMed Central PMCID: PMC2933536.

64. https://open.fda.gov/data/faers/

65. https://yellowcard.mhra.gov.uk/

66. http://www.adrreports.eu/

67. http://www.oecd.org/els/health-systems/health-data.htm

68. http://www.ehealthme.com/

69. https://www.smartpatients.com/

70. https://www.patientslikeme.com/

71. http://www.healthkeep.com/

72. https://www.drugs.com/

73. https://www.drugbank.ca/

74. J. Díez-Manglano et al. Excessive polypharmacy and survival in polypathological patients. Eur J Clin Pharmacol 2015 (71) 733–739.

75. E. Frutos Bernal et al. Factores asociados a la polifarmacia en población anciana no institucionalizada. Análisis de la submuestra de la Encuesta Nacional de Salud 2006 para personas mayores de Castilla y León. Rev Esp Geriatr Gerontol. 2011 (46) 303–306.

76. A. Calderón-Larrañaga et al. Non-adherence to antihypertensive medication: The role of mental and physical comorbidity. International Journal of Cardiology 2016 (207) 310–316

77. D.Walckiers et al.Factors associated with excessive polypharmacy in older people.Archives of Public Health 2015(73)50-62.
• Interesting paper on polypharmacy factors in the elderly.

78. C. Jäger et al. A tailored implementation intervention to implement recommendations addressing polypharmacy in multimorbid patients: study protocol of a cluster randomized controlled trial. Trials 2013 (14) 420-428.
• Interesting paper on polypharmacy in the elderly.

79. B. Hovstadius et al. Dispensed drugs and multiple medications in the Swedish population: an individual based register study. BMC Clinical Pharmacology 2009 (9) 11-21.

80. L. Dong et al. Polypharmacy and its correlates in village health clinics across 10 provinces of Western China. J Epidemiol Community Health 2010 (64) 549-553.

81. O. Mukhtar et al. Intentional Non-Adherence to Medications by Older Adults. Drugs Aging 2014 (31) 149–157.

82. S. Ching Ho et al. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders 2016 (193) 1–10.

83. J. Krause et al. Identifying determinants of care for tailoring implementation in chronic diseases: an evaluation of different methods. Implementation Science 2014 (9) 102-112.

84. J.D. Pedrera Zamorano et al. Estudio de salud de las personas mayors en Extremadura: consumo de fármacos y patologías crónicas más frecuentes. Rev Esp Salud Pública. 1999 (73) 677–86.

85. C.R. Arjona Mateos et al. Enfermedades crónicas y consumo de fármacos en mayores de 65 años. Med Gen. 2002 (47) 684-95.

86. E. Valderrama Gamma et al. Consumo de medicamentos en los ancianos: resultados de un estudio poblacional. Rev Esp Salud Pública. 1998 (72) 209-19.

87. R. Castelo Domínguez et al. Prevalencia de polifarmacia en mayores de 80 años. FAP. 2006 (4) 69-73.

88. Delgado-Silveira, E. et al. The impact of Pharmacy Intervention on the treatment of elderly multi-pathological patients. Farm Hosp. 2015;39(4):192-202.
• Interesting paper on polypharmacy in the elderly.

89. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004 Jan;57(1):6-14. Review. PubMed PMID: 14678335; PubMed Central PMCID: PMC1884408.

90. Shepler SA, Grogan TA, Pater KS. Keep your older patients out of medication trouble. Nursing. 2006 Sep;36(9):44-7. PubMed PMID: 16951619.

91. Terrell KM, Heard K, Miller DK. Prescribing to older ED patients. Am J EmergMed. 2006 Jul;24(4):468-78. Review. PubMed PMID: 16787807.

92. Akamine D, Filho MK, Peres CM. Drug-nutrient interactions in elderly people.Curr Opin Clin Nutr Metab Care. 2007 May;10(3):304-10. Review. PubMed PMID:17414499

93. Brownie S. Why are elderly individuals at risk of nutritional deficiency? Int J Nurs Pract. 2006 Apr;12(2):110-8. Review. PubMed PMID: 16529597.

94. Heuberger R. Polypharmacy and food-drug interactions among older persons: a review. J Nutr Gerontol Geriatr. 2012;31(4):325-403. doi: 10.1080/21551197.2012.729902. Review. PubMed PMID: 23157216
• Interest paper on nutritional status in the elderly.

95. Bushra R, Aslam N, Khan AY. Food-drug interactions. Oman Med J. 2011 Mar;26(2):77-83. doi: 10.5001/omj.2011.21. PubMed PMID: 22043389; PubMed Central PMCID: PMC3191675

96. Tsuyoshi Chiba, Yoko Sato, Sachina Suzuki, and Keizo Umegaki. Concomitant Use of Dietary Supplements and Medicines in Patients due to Miscommunication with Physicians in Japan Nutrients. 2015 Apr; 7(4): 2947–2960. doi: 10.3390/nu7042947 PMCID: PMC4425182

97. Prescription Drugs, Health Policy Institute, Georgetown Univeristy 5/09/2002 https://hpi.georgetown.edu/agingsociety/pubhtml/rxdrugs/rxdrugs.html

98. Venturini CD, Engroff P, Ely LS, Zago LF, Schroeter G, Gomes I, De Carli GA, Morrone FB. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. Clinics (Sao Paulo). 2011;66(11):1867-72. PubMed PMID: 22086515; PubMed Central PMCID: PMC3203957.

99. Santalucia P, Franchi C, Djade CD, Tettamanti M, Pasina L, Corrao S, Salerno F, Marengoni A, Marcucci M, Nobili A, Mannucci PM; REPOSI Investigators. Gender difference in drug use in hospitalized elderly patients. Eur J Intern Med. 2015 Sep;26(7):483-90. doi: 10.1016/j.ejim.2015.07.006. Epub 2015 Jul 22. PubMed PMID: 26209883.

100. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Therapeutic Advances in Drug Safety. 2016;7(1):11-22. doi:10.1177/204209861561547
• Interest paper on preventing adverse reaction in the elderly.

101. http://www.japic.or.jp/

102. https://www.pharmagkb.org/

103. http://www.genome.jp/kegg/drug/

104. Davis AP, Grondin CJ, Johnson RJ, Sciaky D, King BL, McMorran R, Wiegers J, Wiegers TC, Mattingly CJ. The Comparative Toxicogenomics Database: update 2017. Nucleic Acids Res. 2016 Sep 19

105. http://www.whocc.no/atc_ddd_index/

106. http://www.who.int/en/

107. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R. SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. doi: 10.1093/nar/gkp970. PubMed PMID: 19934256; PubMed Central PMCID: PMC2808967

108. Michael F. Hoffmann, Sarah C. Preissner, Janette Nickel, Mathias Dunkel, Robert Preissner and Saskia Preissner. The Transformer database: biotransformation of xenobiotics. Nucleic Acids Res. 2014 Jan 1;42(1):D1113-7. Doi: 10.1093/nar/gkt1246. Epub 2013 Dec 10.

109. Cheng F, Zhao Z. Machine learning-based prediction of drug–drug interactions by integrating drug phenotypic, therapeutic, chemical, and genomic properties. Journal of the American Medical Informatics Association : JAMIA. 2014;21(e2):e278-e286. doi:10.1136/amiajnl-2013-002512.

110. Davis AP, Wiegers TC, Roberts PM, et al. A CTD–Pfizer collaboration: manual curation of 88 000 scientific articles text mined for drug–disease and drug–phenotype interactions. Database: The Journal of Biological Databases and Curation. 2013;2013:bat080. doi:10.1093/database/bat080.
• Interesting paper on text mining approches to study drug interactions.

111. Boyce, Richard, Gregory Gardner, and Henk Harkema. "Using natural language processing to identify pharmacokinetic drug-drug interactions described in drug package inserts." Proceedings of the 2012 Workshop on Biomedical Natural Language Processing. Association for Computational Linguistics, 2012.

112. http://www.etoxproject.eu/

113. Herrero-Zazo M, Segura-Bedmar I, Martínez P, Declerck T. The DDI corpus: an annotated corpus with pharmacological substances and drug-drug interactions. J Biomed Inform. 2013 Oct;46(5):914-20. doi: 10.1016/j.jbi.2013.07.011. PubMed PMID: 23906817.

114. Ben Abacha A, Chowdhury MF, Karanasiou A, Mrabet Y, Lavelli A, Zweigenbaum P. Text mining for pharmacovigilance: Using

machine learning for drug name recognition and drug-drug interaction extraction and classification. J Biomed Inform. 2015 Dec;58:122-32. doi: 10.1016/j.jbi.2015.09.015. PubMed PMID: 26432353.

115. Takarabe M, Shigemizu D, Kotera M, Goto S, Kanehisa M. Network-based analysis and characterization of adverse drug-drug interactions. J Chem Inf Model. 2011 Nov 28;51(11):2977-85. doi: 10.1021/ci200367w. PubMed PMID: 21942936.

116. Percha B, Garten Y, Altman RB. Discovery and explanation of drug-drug interactions via text mining. Pac Symp Biocomput. 2012:410-21. PubMed PMID: 22174296; PubMed Central PMCID: PMC3345566.

117. Ayvaz S, Horn J, Hassanzadeh O, Zhu Q, Stan J, Tatonetti NP, Vilar S, Brochhausen M, Samwald M, Rastegar-Mojarad M, Dumontier M, Boyce RD. Toward a complete dataset of drug-drug interaction information from publicly available sources. J Biomed Inform. 2015 Jun;55:206-17. doi: 10.1016/j.jbi.2015.04.006. PubMed PMID: 25917055; PubMed Central PMCID: PMC4464899.

118. White RW, Tatonetti NP, Shah NH, Altman RB, Horvitz E. Web-scale pharmacovigilance: listening to signals from the crowd. J Am Med Inform Assoc. 2013 May 1;20(3):404-8. doi: 10.1136/amiajnl-2012-001482. PubMed PMID: 23467469; PubMed Central PMCID: PMC3628066.
• Interesting paper on pharmacovigilance via Google searches..

119. Takarabe M, Kotera M, Nishimura Y, Goto S, Yamanishi Y. Drug target prediction using adverse event report systems: a pharmacogenomic approach. Bioinformatics. 2012 Sep 15;28(18):i611-i618. doi: 10.1093/bioinformatics/bts413. PubMed PMID: 22962489; PubMed Central PMCID: PMC3436840.

120. Tatonetti NP, Ye PP, Daneshjou R, Altman RB. Data-driven prediction of drug effects and interactions. Sci Transl Med. 2012 Mar 14;4(125):125ra31. Doi: 10.1126/scitranslmed.3003377. PubMed PMID: 22422992; PubMed Central PMCID: PMC3382018.
• Interesting paper on drug interaction and side effect prediction.

121. Cobanoglu MC, Liu C, Hu F, Oltvai ZN, Bahar I. Predicting drug-target interactions using probabilistic matrix factorization. J Chem Inf Model. 2013 Dec 23;53(12):3399-409. doi: 10.1021/ci400219z. PubMed PMID: 24289468; PubMed Central PMCID: PMC3871285.

122. Alaimo S, Pulvirenti A, Giugno R, Ferro A. Drug-target interaction prediction through domain-tuned network-based inference. Bioinformatics. 2013 Aug 15;29(16):2004-8. doi: 10.1093/bioinformatics/btt307. PubMed PMID: 23720490; PubMed Central PMCID: PMC3722516.

123. van Laarhoven T, Nabuurs SB, Marchiori E. Gaussian interaction profile kernels for predicting drug-target interaction. Bioinformatics. 2011 Nov 1;27(21):3036-43. doi: 10.1093/bioinformatics/btr500. PubMed PMID: 21893517.

124. Chen H, Zhang Z. A semi-supervised method for drug-target interaction prediction with consistency in networks. PLoS One. 2013 May 7;8(5):e62975. Doi: 10.1371/journal.pone.0062975. PubMed PMID: 23667553; PubMed Central PMCID: PMC3646965.

125. Whitebread, Steven, et al. "Secondary pharmacology: screening and interpretation of off-target activities–focus on translation." Drug discovery today (2016).
•• High interest paper on secondary pharmacology.

126. Hamon, Jacques, and Steven Whitebread. "In vitro safety pharmacology profiling: An important tool to decrease attrition."

Hit and Lead Profiling: Identification and Optimization of Drug-like Molecules, Volume 43 (2009): 273-295.

127. Urban, Laszlo, et al. "Translation of off-target effects: prediction of ADRs by integrated experimental and computational approach." Toxicology Research 3.6 (2014): 433-444.

128. Lounkine E, Keiser MJ, Whitebread S, Mikhailov D, Hamon J, Jenkins JL, Lavan P, Weber E, Doak AK, Côté S, Shoichet BK, Urban L. Large-scale prediction and testing of drug activity on side-effect targets. Nature. 2012 Jun 10;486(7403):361-7. doi: 10.1038/nature11159. PubMed PMID: 22722194; PubMed Central PMCID: PMC3383642.

129. Simon Z, Peragovics A, Vigh-Smeller M, Csukly G, Tombor L, Yang Z, Zahoránszky-Kohalmi G, Végner L, Jelinek B, Hári P, Hetényi C, Bitter I, Czobor P, Málnási-Csizmadia A. Drug effect prediction by polypharmacology-based interaction profiling. J Chem Inf Model. 2012 Jan 23;52(1):134-45. doi: 10.1021/ci2002022. PubMed PMID: 22098080.

130. Peragovics Á, Simon Z, Tombor L, Jelinek B, Hári P, Czobor P, Málnási-Csizmadia A. Virtual affinity fingerprints for target fishing: a new application of Drug Profile Matching. J Chem Inf Model. 2013 Jan 28;53(1):103-13. doi: 10.1021/ci3004489. PubMed PMID: 23215025.

131. Képiró M, Várkuti BH, Rauscher AA, Kellermayer MS, Varga M, Málnási-Csizmadia A. Molecular tattoo: subcellular confinement of drug effects. Chem Biol. 2015 Apr 23;22(4):548-58. doi: 10.1016/j.chembiol.2015.03.013. PubMed PMID: 25892202.

132. Rhita Bennis Nechba, Moncif El M'barki Kadiri, Mounia Bennani-Ziatni, Amine Ali Zeggwagh, Abdelhalim Mesfioui, Difficulty in managing polypharmacy in the elderly: Case report and review of the literature, In Journal of Clinical Gerontology and Geriatrics,

Volume 6, Issue 1, 2015, Pages 30-33, ISSN 2210-8335, https://doi.org/10.1016/j.jcgg.2014.06.002.

133. http://www.chemotargets.com/
•• CTlink, a software for predicting the target and safety profile of small molecules. CT-link is Chemotargets' state-of-the-art platform-independent software for large-scale off-target pharmacology and predictive safety of small molecule pharmaceuticals, cosmeceuticals, agrochemicals, and environmental pollutants.

134. Pérez-Nueno VI, Karaboga AS, Souchet M, Ritchie DW. GES Polypharmacology Fingerprints: A Novel Approach for Drug Repositioning. J. Chem. Inf. Model. 2014 (54) 720-34. doi:10.1021/ci4006723
•• The GES computational polypharmacology fingerprint was the first target fingerprint to encode drug promiscuity information. It is based on the Gaussian ensemble screening (GES) approach to predict relationships between drug classes.

135. Pérez-Nueno VI, Venkatraman V, Mavridis L, Ritchie DW. Detecting drug promiscuity using Gaussian ensemble screening. J Chem Inf Model. 2012 Aug 27;52(8):1948-61. doi: 10.1021/ci3000979. Epub 2012 Jul 19. PubMed PMID: 22747187.
•• The Gaussian Ensemble Screening (GES) approach represents a cluster of molecules with similar molecular properties as a Gaussian distribution with respect to a selected center molecule. Calculating the Gaussian overlap between pairs of such clusters allows the similarity between drug classes to be calculated analytically without requiring thousands of bootstrap comparisons, as in current promiscuity prediction approaches. The approach is widely open to whatever are the molecular properties that are wished to be encoded. In the example of this specific paper, spherical harmonic surface shapes.

136. Pérez-Nueno VI, Souchet M, Karaboga AS, Ritchie DW. GES-SE: Predicting Drug Side Effects from Drug-Target Relationships. J.

Chem. Inf. Model. 2015 (55) 1804-23. doi: 10.1021/acs.jcim.5b00120. PubMed PMID: 26251970
•• The GESSE approach predicts potential SEs of drugs from their physicochemical properties (three-dimensional shape plus chemistry) and targets protein data extracted from predicted drug-target relationships. The GESSE approach uses a canonical correlation analysis of the full drug-target and drug-SE matrices, and it then calculates a probability that each drug in the resulting drug-target matrix will have a given SE using a Bayesian discriminant analysis (DA) technique.

137. http://www.nextgov.com/health/health-it/2015/11/fda-crowdsourcing-its-way-precision-medicine-what-about-security/124001/

138. Pérez-Nueno VI. Using quantitative systems pharmacology for novel drug discovery. Expert Opin. Drug Discov. (2015) 10(12). doi: 10.1517/17460441.2015.1082543
•• Interesting review on systems pharmacology.

4. DISCUSSION

The demographic shift towards an older population is dramatically increasing the public health burden. The average 70-year- old now takes seven different prescription medications. The use of multiple medications is often referred to as polypharmacy. This causes many problems such as drug-drug interactions, serious side effects, and non-adherence to treatment. National health agencies are clearly interested in reducing polypharmacy, given the huge sums of money they spend on the resulting side effects and hospitalizations.

Eliminate all taken drugs by the elderly is not yet possible, but reducing the number of medications taken can greatly improve the quality of life of the patients. Current existing approaches to tackle polypharmacy follow an experimental test and adjust methodology, which makes them very tedious and costly. Hence, the great number of challenges associated with exploiting systems pharmacology, and in silico chemo- and bio-informatic methods combined with data mining, to tackle polypharmacy in the elderly should be seen as a great source of opportunities for the future, for experimental and computational scientists alike.

Current evidence suggests that the implementation of tools such as Beers or STOPP lists, although still imperfect, reduces inappropriate drug use and drug-drug interactions [Gallaguer Clin Pharmacol Ther 2011:89:845-54, Blozizik, Drugs Aging 2010;27:1009-17]. However these tools are not systematically implemented and used

in the clinical care of older people. As Schoenenberger and Stuck point out in their review, these tools, as well as START list to avoid drug underuse or the CRIME recommendations for complex patients, could be incorporated in electronic databases which clinicians can automatically check for potential inappropriate drug use and drug-drug interactions or by building computer-based decision-support and electronic prescribing systems. The digitization of the healthcare system is one of the strong points in prevention, intervention strategies and current policies trying to better manage polypharmacy. Regarding this aspect, there has been quite controversy. The majority of European governments consider that the biggest trend in healthcare IT these days it is big data. “It aims to bridge the innovation gap in personalized medicine One example of a computer-based decision-support and electronic prescribing systems is IBM’s Watson technology

The system was presented as the “big hero behind the Health Deal”, being able to access to several 100 million anonymised patient profiles and scanning nearly 300 medical journals, more than 200 textbooks plus 12 million pages of free text, trained by 1000 doctors over 3 years. Moreover, if we add the possibility of having a joint data centre that integrates patient data from various IT solutions such as Watson, this brings the possibility of having big-data networks to be used to do clinical research or identify patients for clinical trials. The analysis of this big-data is very interesting for policy makers and hospitals in order to identify medical risks for their patients.

However, last June 2017 there was a big scandal when several doctors checked the fact that Watson was not working as expected. For example, regarding the prescription field, Watson was returning several times either obvious prescriptions or nonsense prescriptions.
The perception now is that Watson has not met lofty expectations. This may make us think that just the integration of databases for rational drug deprescribing might not help. The full integration of data-driven healthcare might not be the solution.

Until which point can be useful gathering databases and extracting data for AI predictions? A combination from different sources is normally the virtue. The same argument can be used when talking about crowsourced data.

Society is changing. People now gain medical literacy through Internet searches. The digital traces left by searches can improve medicine and properly deprescription of drugs by revealing insights into health that are difficult to obtain in other ways. “An example of this is when people find it difficult to report side-effects that appear months after they begin taking a drug because they do not associate the adverse reaction with the drug.” Instead of that, they search time after the side effect and the drug and can be associated. Hence, extracting information from Internet searches can be useful to propose a rational drug deprescribing and avoid important drug-drug interactions and side effects. The search engine can even in cases provide

more sensitive data than the currently available to health authorities. For example, only a small fraction of the people who has flu will visit a medical provider to see what they can do about their aliments, but much more people will search that into Internet than go to the doctor. Furthermore, there are certain areas in which the Internet is the primary venue for people to search and discuss their conditions. However, it is important to take into account that one problem would be assuming that crowdsourced data explains everything.

With the digitization of healthcare, the patient takes center stage. The citizen will need to be more self-aware of his health. Regarding mhealth and healthacare wearables, the process of deprescribing could be monitored by mobile applications, the data saved and stored to take conclusions. Only doing this for several patients in each country/hospital and sharing the information would increase the data available, that after being analysed, could give new insights into rational drug deprescribing. Computer-based decision-support and electronic prescribing systems could be applied to older patients with polypharmacy and monitored by mhealth applications, the results obtained would be analyzed and would help to propose rational drug deprescription, as well as calibrate and refine the AI systems. This would still take significant time and would not be still very efficient, but it is a step forward managing better polypharmacy. The gathering of big data and data driven healthcare allows going from intervention to preventive medicine.

What it is clear is that there is enough evidence that the systematic use of tools such as STOPP, Beers list, START or CRIME, in the clinical routine is helpful to manage polypharmacy and improve patients' outcomes. It is essential, then, to refine these tools and document their effectiveness, and determine how much we rely on big data and data-driven healthcare and how much on the traditional approaches.

Polypharmacy is necessary for the elderly condition and cannot be prevented. However, it is essential to assess the risks associated to it in order to properly manage it. Current European health policies focus on the digitization of healthcare given the increasing digitization of today's society. Data-driven healthcare and the analysis of the big-data generated is very interesting for policy makers and hospitals in order to identify medical risks for their patients. Current and future prevention and intervention strategies to inappropriate prescribing are significatively based on e-health measures. However, several examples shown here demonstrate that the unique use of data-driven healthcare and just gathering databases and extracting data for AI predictions might not be enough to better manage polypharmacy and the effects associated to it. Therefore, we are facing a complex situation.

The classical view of drug action, "one molecule interacts with one target to give one therapeutic effect" has been replaced by the new polypharmacology paradigm "one molecule (or more) interacts with

several targets to give several therapeutic effects and certain side effects". These targets are in a complex cellular network. The emerging discipline of Quantitative systems pharmacology (QSP) aims to understand how drugs modulate cellular networks in space and time in order to predict drug targets and their role in human pathophysiology. It is worth mentioning that although QSP might be considered to be a new approach, the principle of drug "repurposing" is well-established in the pharmaceutical industry as a way to identify new targets for drug molecules which have failed at the clinical testing stage for their original target. However, it has never been applied to polypharmacy.

This project aims to exploit multiple chemical and biological databases to build drug-target-SE-CO networks. By analyzing these diverse databases containing structural features of compounds, their bioactivity profiles, their relationships to the phenotypic effects observed, gene–SE and gene-disease associations, related molecular functions, and target-related pathways, we can (a) predict the SEs associated with a given target, (b) re-purpose drugs for two or more medical conditions, (c) reduce SEs, (d) predict drug-drug interactions, and (e) generate biologically meaningful hypotheses for reducing drugs in simultaneous prescription medications.
If successful, this work has the potential to transform current strategies for reducing polypharmacy. Many studies have found that simultaneous drug treatments for different conditions are associated with negative health outcomes, but more research is needed to fur-

ther delineate the consequences associated with unnecessary drug use in elderly patients. De-prescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes. Currently, it is very difficult to de-prescribe drugs rationally to achieve the desired effect in a clinical setting. However, evidence is emerging in support of a structured approach to de-prescribing. For example, doctors may follow a series of steps to manage polypharmacy in practice comprising: (a) a patient assessment, (b) identification of inappropriate drugs from an accurate list of medications using software tools (e.g. the Screening Tool of Older Person's Prescriptions (STOPP) criteria, STOPP/START of the NHS Cumbria toolkit, Beers Criteria updated 2012,the FORTA (Fit FOR The Aged) list, the NHS Highland system, the MAI tool, the NO TEARS and ARMOR systems or decision algorithms, (c) assess each drug for specific risks versus benefits (consecutive take one drug at a time and discontinue it over weeks to months),(d) agree to stop/reduce dose and withdraw slowly,(e) communicate with prescriber,(f) monitor, review and adjust regularly.

However, beyond this structured and practical approach, there are very few rigorously designed intervention studies that have been shown to reduce unnecessary polypharmacy. Moreover, the current approach is very tedious and costly. Most patients using it get tired before a proper statement of polypharmacy reduction can be made and they normally see multiple specialists that do not always agree in a consensus. By using in silico methods in combination

with a large amount of bioactivity and bioinformatics information available in databases, we can advance the understanding of D-T-SE-CO relationships and open the way to rational drug de-prescribing.

5. CONCLUSIONS

- A database of drug metabolites (DMdb) by careful extraction, curation, and storage of their chemical structures from public and bibliographic sources have been constructed. The DMdb contains 6124 drug metabolites and 1149 drugs, with their smiles, molecular weight, and reference article.

- A new knowledge-based statistical approach to predicting drug metabolites based on the contents of Dmdb has been developed. The quality of its contents, both in terms of correctness and coverage, is reflected in the quality of the metabolite predictions made by a new purposely designed statistical method.ur method can be regarded as the state-of-the-art in the field and it represents an incremental contribution towards developing safer, more effective, drugs.

- A database of drug-drug interactions (DDIdb) by careful extraction, curation, and storage of pairs of drug names annotated with the safety issues associated with their co-administration have been created. A DDIdb includes 49120 DDIs, 859 safety conditions, and 865 compounds. We concluded that drug-

classes do have similar side-effects, especially cardiovascular system, nervous system, sensory organs, and antineoplastic and immunomodulating agents.

- An analysis of DDIdb to identify trends among drug classes most susceptible to be involved in drug-drug interactions. High propensity drug classes to interactions and side effects have been identified. Nervous and cardiovascular system drug classes have the highest propensity, the most consumed prescriptions belong to these classes.

- Based on the data data and knowledge acquired in the previous points, an extensive review of current worldwide policies on polypharmacy have been made. The best strategies that could help to reduce the number of co-administered drugs and towards a more cost-effective health system have been explained, together with a new methodology, MINIMED, to tackle polypharmcy, de-prescribe and reduce economic cost.

6. OUTLOOK

Identifying and predict drug interactions, and adverse effects of drugs is extremely complicated, but many times we tend to forget to step back and see the whole picture. Treat a disease with a pill is the easy solution, and many cases the disease could be prevented and treated with lifestyle changes, such as nutrition and physical exercise. We believe we need to take more data into account in order to make the best suggestion of medicines and treatment. That's why our further goal is the creation of MINI-MED & NUTRI-BÉ.

MINI-MED & NUTRI-BÉ is a tool aimed at improving the quality of life and well-being of elderly people, aimed both at guiding patients and giving support to doctors in order to make the most appropriate decisions when prescribing medications for elderly people prioritising the welfare of patients, along with a diet that increases this well-being.

The MINI-MED & NUTRI-BÉ platform will also include a space for digital consultations and online courses focused on nutrition for elderly people, balanced and protective food to improve the quality of life during aging, which helps to benefit from the combination of drugs taken by the patient. The platform will use chemoinformatics and system pharmacology methods in order to advise which drugs could be reduced in the medical history of an elderly patient. According to the result, the platform will propose what nutrients and

what diet enhance this action, always with the aim of reducing secondary effects and improving the patient's well-being.
MINI-MED & NUTRI-BÉ will have mobile app support, PC platform, and web server. It is intended both to guide patients and to help/support doctors in order to make the most appropriate decisions when prescribing medications to the elderly prioritizing the welfare of patients, along with a diet that increases this well-being.
The platform will include a space for digital consultations, online courses focused on nutrition for the elderly, food balanced and protective to improve the quality of life during aging, which helps benefit from the combination of drugs taken by the patient trying to reduce their adverse effects The platform portal will always be updated with news of interest according to the most common clinical cases in the elderly. Advices, recipes, diets and menus enriched with certain types of nutrients and trace elements when there are certain deficiencies in the most common medical history of polypharmacy in elderly patients.

Following the trend of today's society with regard to the digitalisation of the industry, the health field is not far behind. We want to create, therefore, a digital product of support for both patients and doctors.

Bibliography

1. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9

2. http://www.fda.gov/.

3. Shepherd G, Mohorn P, Yacoub K, May DW. Adverse drug reaction deaths reported in United States vital statistics, 1999-2006. *Ann Pharmacother*. 2012;46(2):169-175. doi:10.1345/aph.1P592

4. Light DW, Lexchin J, Darrow JJ. Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs. *J Law, Med Ethics*. 2013;14(3):590-610.

5. PA C. How many deaths occur annually from adverse drug reactions in the United States? *Am J Med*. 2000;109(2):122-130. https://www.ncbi.nlm.nih.gov/pubmed/10967153.

6. Centers for Disease Control and Prevention. Health, United States, 2015 With Special Feature on Racial and Ethnic Health Disparities. *Heal United States*. 2015;3:216. doi:76-641496

7. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J A, T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG A, C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ BD, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*.

2012;380(9859):2095-2128. doi:10.1016/S0140-6736(12)61728-0

8. Cadieux RJ. Drug interactions in the elderly. How multiple drug use increases risk exponentially. *Postgrad Med*. 1989;86(8):179-186. doi:10.1080/00325481.1989.11704506

9. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: A review. *Am J Geriatr Pharmacother*. 2011;9(6):364-377. doi:10.1016/j.amjopharm.2011.10.004

10. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. *Ther Adv Drug Saf*. 2016;7(1):11-22. doi:10.1177/2042098615615472

11. Smith W. Adverse drug reactions: Allergy? Side-effect? Intolerance? *Aust Fam Physician*. 2013;42(1):12-16.

12. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med*. 2016;176(4):473-482. doi:10.1001/jamainternmed.2015.8581

13. Schmiedl S, Rottenkolber M, Hasford J, et al. Self-medication with over-the-counter and prescribed drugs causing adverse-drug-reaction-related hospital admissions: Results of a prospective, long-term multi-centre study. *Drug Saf*. 2014;37(4):225-235. doi:10.1007/s40264-014-0141-3

14. Saw JT, Bahari MB, Ang HH, Lim YH. Potential drug-herb interaction with antiplatelet/anticoagulant drugs. *Complement Ther Clin Pract*. 2006;12(4):236-241. doi:10.1016/j.ctcp.2006.06.002

15. Cooper RJ. “I can” t be an addict. I am.’ Over-the-counter medicine abuse: A qualitative study. *BMJ Open*. 2013;3(6):1-68. doi:10.1136/bmjopen-2013-002913

16. Mullan J, Weston KM, Bonney A, Burns P, Mullan J, Rudd R. Consumer knowledge about over-the-counter NSAIDs: they don’t know what they don’t know. *Aust N Z J Public Health*. 2017;41(2):210-214. doi:10.1111/1753-6405.12589

17. Chiba T, Sato Y, Suzuki S, Umegaki K. Concomitant use of dietary supplements and medicines in patients due to miscommunication with physicians in Japan. *Nutrients*. 2015;7(4):2947-2960. doi:10.3390/nu7042947

18. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: A tabular compilation of reported cases. *Liver Int*. 2012;32(10):1543-1556. doi:10.1111/j.1478-3231.2012.02864.x

19. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother*. 2013;4(5):73. doi:10.4103/0976-500X.120957

20. Urban L, Maciejewski M, Lounkine E, et al. c. *Toxicol Res (Camb)*. 2014;3(6):433-444. doi:10.1039/c4tx00077c

21. Knowles SR, Shapiro LE, Shear NH. Reactive metabolites and adverse drug reactions: Clinical considerations. *Clin Rev Allergy Immunol*. 2003;24(3):229-238. doi:10.1385/CRIAI:24:3:229

22. Kaufman G. Adverse drug reactions: classification, susceptibility and reporting. *Nurs Stand*. 2016;30(50):53-63. doi:10.7748/ns.2016.e10214

23. Gundert-Remy U, Bernauer U, Blömeke B, et al. Extrahepatic metabolism at the body’s internal-external interfaces.

Drug Metab Rev. 2014;46(3):291-324. doi:10.3109/03602532.2014.900565

24. Boros-Majewska J, Turczyk, Wei X, Milewski S, Williams DW. A novel in vitro assay for assessing efficacy and toxicity of antifungals using human leukaemic cells infected with Candida albicans. *J Appl Microbiol*. 2015;119(1):177-187. doi:10.1111/jam.12817

25. Crettol S, Petrovic N MM. Pharmacogenetics of phase I and phase II drug metabolism. *Curr Pharm Des*. 2010;16(2):204-219.

26. Nehlig A. Interindividual Differences in Caffeine Metabolism and Factors Driving Caffeine Consumption. *Pharmacol Rev*. 2018;70(2):384-411. doi:10.1124/pr.117.014407

27. Nieminen LRG, Makino KK, Mehta N, Virkkunen M, Kim HY, Hibbeln JR. Relationship between omega-3 fatty acids and plasma neuroactive steroids in alcoholism, depression and controls. *Prostaglandins Leukot Essent Fat Acids*. 2006;75(4-5):309-314. doi:10.1016/j.plefa.2006.07.012

28. Stepan AF, Walker DP, Bauman J, et al. Structural alert/reactive metabolite concept as applied in medicinal chemistry to mitigate the risk of idiosyncratic drug toxicity: A perspective based on the critical examination of trends in the top 200 drugs marketed in the United States. *Chem Res Toxicol*. 2011;24(9):1345-1410. doi:10.1021/tx200168d

29. Chagas CM, Moss S, Alisaraie L. Drug metabolites and their effects on the development of adverse reactions: Revisiting Lipinski's Rule of Five. *Int J Pharm*. 2018;549(1-2):133-149. doi:10.1016/j.ijpharm.2018.07.046

30. Guengerich FP, MacDonald JS. Applying mechanisms of chemical toxicity to predict drug safety. *Chem Res Toxicol*. 2007;20(3):344-369. doi:10.1021/tx600260a

31. Food and Agriculture Organization of the United Nations World Health Organization. Evaluation of certain food additives. *World Heal Organ Tech Rep Ser 928, 1–156 (World Heal Organ 2005)*. doi:10.1089/bfm.2018.0001

32. Attia SM. Deleterious effects of reactive metabolites. *Oxid Med Cell Longev*. 2010;3(4):238-253. doi:10.4161/oxim.3.4.13246

33. Thompson RA, Isin EM, Ogese MO, Mettetal JT, Williams DP. Reactive Metabolites: Current and Emerging Risk and Hazard Assessments. *Chem Res Toxicol*. 2016;29(4):505-533. doi:10.1021/acs.chemrestox.5b00410

34. Hopkins PN, Polukoff GI. Risk of valvular heart disease associated with use of fenfluramine. *BMC Cardiovasc Disord*. 2003;3:1-13. doi:10.1186/1471-2261-3-5

35. Weill A, Païta M, Tuppin P, et al. Benfluorex and valvular heart disease: A cohort study of a million people with diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2010;19(12):1256-1262. doi:10.1002/pds.2044

36. Bushra R, Aslam N, Khan AY. Food-drug interactions. *Oman Med J*. 2011;26(2):77-83. doi:10.5001/omj.2011.21

37. Cascorbi I. Drug interactions--principles, examples and clinical consequences. *Dtsch Arztebl Int*. 2012;109(33-34):546-556. doi:10.3238/arztebl.2012.0546

38. Boobis A, Watelet JB, Whomsley R, Benedetti MS, Demoly P, Tipton K. Drug interactions. *Drug Metab Rev*. 2009;41(3):486-527. doi:10.1080/10837450902891550

39. O. Nettleton D, J. Einolf H. Assessment of Cytochrome P450 Enzyme Inhibition and Inactivation in Drug Discovery and Development. *Curr Top Med Chem*. 2011;11(4):382-403. doi:10.2174/156802611794480882

40. Marcucci C, Hutchens MP, Wittwer ED, et al. A case approach to perioperative drug-drug interactions. In: *A Case Approach to Perioperative Drug-Drug Interactions*. Springer, New York, NY; 2015:81-85. doi:10.1007/978-1-4614-7495-1

41. van Laarhoven T, Nabuurs SB, Marchiori E. Gaussian interaction profile kernels for predicting drug-target interaction. *Bioinformatics*. 2011;27(21):3036-3043. doi:10.1093/bioinformatics/btr500

42. Heuberger R. Polypharmacy and Food-Drug Interactions Among Older Persons: A Review. *J Nutr Gerontol Geriatr*. 2012;31(4):325-403. doi:10.1080/21551197.2012.729902

43. Zhang L, Zhang Y (Derek), Zhao P, Huang S-M. Predicting Drug–Drug Interactions: An FDA Perspective. *AAPS J*. 2009;11(2):300-306. doi:10.1208/s12248-009-9106-3

44. Kirchmayer U, Mayer F, Basso M, et al. Polypharmacy in the elderly: A population based cross-sectional study in Lazio, Italy. *Eur Geriatr Med*. 2016;7(5):484-487. doi:10.1016/j.eurger.2016.05.008

45. Venturini CD, Engroff P, Ely LS, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. *Clinics (Sao Paulo)*. 2011;66(11):1867-1872. doi:10.1590/S1807-59322011001100004

46. Delgado-Silveira E, Fernández-Villalba EM, Freire MGM, Pérez MSA, Lagranja MPC, Martí JFP. The impact of Pharmacy Intervention on the treatment of elderly multi-

pathological patients. *Farm Hosp*. 2015;39(4):192-202. doi:10.7399/fh.2015.39.4.8329

47. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer Prescribing — A Trial of Education, Informatics, and Financial Incentives. *N Engl J Med*. 2016;374(11):1053-1064. doi:10.1056/NEJMsa1508955

48. Vetrano DL, Foebel AD, Marengoni A, et al. Chronic diseases and geriatric syndromes: The different weight of comorbidity. *Eur J Intern Med*. 2016;27:62-67. doi:10.1016/j.ejim.2015.10.025

49. Shrivastava A, Kukreja S, Kalra G, Shah N. Polypharmacy in psychiatry: A review. *Mens Sana Monogr*. 2013;11(1):82. doi:10.4103/0973-1229.104497

50. Stawicki SP, Gerlach AT. Polypharmacy and medication errors: Stop, Listen, Look, and Analyze…. *OPUS 12 Sci*. 2009;3(1):6-10. http://journal.opus12.org/o12-ojs/ojs-2.1.1/index.php/o12sci/article/viewfile/257/85.

51. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. *J Am Acad Nurse Pract*. 2005;17(4):123-132. doi:10.1111/j.1041-2972.2005.0020.x

52. MA S. Polypharmacy—time to get beyond numbers. *JAMA Intern Med*. 2016;176(4):482-483. doi:10.1001/jamainternmed.2015.8597.Polypharmacy

53. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995-2010. *BMC Med*. 2015;13(1):1-10. doi:10.1186/s12916-015-0322-7

54. Sevilla-Sanchez D, Molist-Brunet N, Amblàs-Novellas J, Roura-Poch P, Espaulella-Panicot J, Codina-Jané C. Adverse

drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. *Eur J Clin Pharmacol*. 2017;73(1):79-89. doi:10.1007/s00228-016-2136-8

55. Maher RL, Hanlon J HE. Clinical Consequences of Polypharmacy in Elderly Robert. *Expert Opin Drug Saf*. 2014;80(1):1051-1052. doi:10.1517/14740338.2013.827660.

56. Shah BM, Hajjar ER. Polypharmacy, Adverse Drug Reactions, and Geriatric Syndromes. *Clin Geriatr Med*. 2012;28(2):173-186. doi:10.1016/j.cger.2012.01.002

57. Heuberger RA, Caudell K. Polypharmacy and nutritional status in older adults: A cross-sectional study. *Drugs and Aging*. 2011;28(4):315-323. doi:10.2165/11587670-000000000-00000

58. Campanelli CM. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2012;60(4):616-631. doi:10.1111/j.1532-5415.2012.03923.x

59. Lee R.D. Polypharmacy: A case report and new protocol for management. *J Am Board Fam Pr*. 1998;11(2):140-144. doi:10.3122/15572625-11-2-140

60. Weiss BD, Brega AG, LeBlanc WG, et al. Improving the Effectiveness of Medication Review: Guidance from the Health Literacy Universal Precautions Toolkit. *J Am Board Fam Med*. 2016;29(1):18-23. doi:10.3122/jabfm.2016.01.150163

61. Scott IA, Gray LC, Martin JH, Mitchell CA. Minimizing inappropriate medications in older populations: A 10-step

conceptual framework. *Am J Med*. 2012;125(6):529-537.e4. doi:10.1016/j.amjmed.2011.09.021

62. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: A systematic review. *Drugs and Aging*. 2013;30(5):285-307. doi:10.1007/s40266-013-0064-1

63. Hood L, Balling R, Auffray C. Revolutionizing medicine in the 21st century through systems approaches. *Biotechnol J*. 2012;7(8):992-1001. doi:10.1002/biot.201100306

64. Pavelić K, Martinović T, Kraljević Pavelić S. Do we understand the personalized medicine paradigm? Personalized medicine marks the beginning of a new attitude in medicine. *EMBO Rep*. 2015;16(2):133-136. doi:10.15252/embr.201439609

65. Mair, A; Fernandez-Llimos, F; Alonso, A; Harrison, C; Hurding, S; Kempen, T; Kinnear, M; Michael, N; McIntosh, J; Wilson, M SC. SIMPATHY - Polypharmacy Management by 2030: a patient safety challenge. *Coimbra SIMPATHY Consort*. 2017;39(5):Coimbra SIMPATHY Consort. http://www.simpathy.eu/sites/default/files/Managing_polypharmacy2030-web.pdf.

66. Stewart D, Mair A, Wilson M, et al. Guidance to manage inappropriate polypharmacy in older people: systematic review and future developments. *Expert Opin Drug Saf*. 2017;16(2):203-213. doi:10.1080/14740338.2017.1265503

67. Stankuniene A, Stankunas M, Avery M, et al. Use of medications amongst older persons in Kaunas, Lithuania. *Open Med*. 2013;8(6):855-860. doi:10.2478/s11536-013-0237-7

68. Krause J, Van Lieshout J, Klomp R, et al. Identifying determinants of care for tailoring implementation in chronic diseases: An evaluation of different methods. *Implement Sci*. 2014;9(1). doi:10.1186/s13012-014-0102-3

69. Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2018;2018(9). doi:10.1002/14651858.CD008165.pub4

70. Stantchev MO-BGMGMA-AA-AS. Smart healthcare services: a patient oriented cloud computing solution. In: Bilbao; 2015. doi:10.3926/serv2014

71. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, et al. Polypharmacy Patterns: Unraveling Systematic Associations between Prescribed Medications. *PLoS One*. 2013;8(12):1-10. doi:10.1371/journal.pone.0084967

72. Twillman RK, Kirch R, Gilson A. Efforts to control prescription drug abuse: Why clinicians should be concerned and take action as essential advocates for rational policy. *CA Cancer J Clin*. 2014;64(6):369-376. doi:10.3322/caac.21243

73. FRIENDD: A STUDY GROUP ON DRUG INTERACTIONS IN POLYPHARMACY IN THE ELDERLY. https://ec.europa.eu/eip/ageing/commitments-tracker/a1/friendd-study-group-drug-interactions-polypharmacy-elderly_en.

74. Arcopinto M, Cataldi M, De Luca V, et al. Implementing an ICT-Based Polypharmacy Management Program in Italy. *Transl Med @ UniSa*. 2017;16(4):24-29. http://www.ncbi.nlm.nih.gov/pubmed/28775966%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5536159.

75. Crome P, Cherubini A, Oristrell J. The PREDICT (increasing the participation of the elderly in clinical trials) study: The charter and beyond. *Expert Rev Clin Pharmacol*. 2014;7(4):457-468. doi:10.1586/17512433.2014.922864

76. Icare4u project. http://www.icare4eu.org/.

77. Methods for Improving Compliance with Medicine Intake (MICMI). https://www.sites.google.com/site/micmiproject/.

78. EU-ADR project. https://www.euadr-project.org/.

79. eTOX. http://www.etoxproject.eu/.

80. Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management (eTRANSAFE) project. http://etransafe.eu/.

81. NHS Cumbria. STOPP START Toolkit supporting Medication Review. *NHS Cumbria*. 2013;46(February):1-12. doi:10/f6xfw4

82. O'mahony D, O'sullivan D, Byrne S, O'connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing*. 2015;44(2):213-218. doi:10.1093/ageing/afu145

83. Polypharmacy guidance for prescribing in frail adults http ___www.nhshighland.scot.nhs.uk_publications_documents_guidelines_polypharmacy_20guidance_20for_20prescribing_20in_20frail_20a.pdf.

84. Hanlon JT, Schmader KE. The medication appropriateness index at 20: Where it started, where it has been, and where it may be going. *Drugs and Aging*. 2013;30(11):893-900. doi:10.1007/s40266-013-0118-4

85. Lewis T. Using the NO TEARS tool for medication review. *Bmj*. 2004;329(7463):434. doi:10.1136/bmj.329.7463.434

86. Haque R. ARMOR: A Tool to Evaluate Polypharmacy in Elderly Persons. *Ann Long-Term Care*. 2009;17(6) (January):26-30.

87. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: A French consensus panel list. *Eur J Clin Pharmacol*. 2007;63(8):725-731. doi:10.1007/s00228-007-0324-2

88. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: A national consensus panel. *Cmaj*. 1997;156(3):385-391.

89. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: A randomized controlled trial. *Arch Intern Med*. 2009;169(9):894-900. doi:10.1001/archinternmed.2009.71

90. Stefanie Holt, 1 Sven Schmiedl, Dr. med., 1 2 and Petra A. Thürmann. Potentially Inappropriate Medications in the Elderly: The PRISCUS List. *Dtsch Arztebl Int*. 2010;107(31-32):543–551. doi:10.3238/arztebl.2010.0543

91. FAERS. https://open.fda.gov/data/faers/.

92. Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK "Yellow card scheme": Literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess (Rockv)*. 2011;15(20):1-234. doi:10.3310/hta15200

93. European database of suspected adverse drug reaction reports. http://www.adrreports.eu/.

94. OECD Health Statistics 2018. http://www.oecd.org/els/health-systems/health-data.htm.

95. Cognitive Computing: Enabling breakthrough discoveries for the life sciences industry. https://www.ibm.com/blogs/insights-on-business/healthcare/digital-transformation-for-life-sciences/.

96. Has IBM Watson's AI Technology Fallen Victim to Hype? http://fortune.com/2017/06/28/ibm-watson-ai-healthcare/.

97. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. *J Am Med Informatics Assoc*. 2008;15(5):585-600. doi:10.1197/jamia.M2667

98. National Clearinghouse for Alcohol and Drug Information (NCADI). https://www.urc-chs.com/projects/national-clearinghouse-alcohol-and-drug-information-ncadi.

99. Lardiere M., Jones E, Perez M. NACHC 2010 Assessment of Behavioral Health Services In Federally Qualified Health Centers. 2011;(December):17.

100. Fialová D, Onder G. Medication errors in elderly people: Contributing factors and future perspectives. *Br J Clin Pharmacol*. 2009;67(6):641-645. doi:10.1111/j.1365-2125.2009.03419.x

101. Sönnichsen A, Trampisch US, Rieckert A, et al. Polypharmacy in chronic diseases-Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): Study protocol for a randomized controlled trial. *Trials*. 2016;17(1):1-9. doi:10.1186/s13063-016-1177-8

102. Haux R. Health information systems - Past, present, future. *Int J Med Inform*. 2006;75(3-4 SPEC. ISS.):268-281. doi:10.1016/j.ijmedinf.2005.08.002

103. Wishart DS, Feunang YD, Marcu A, et al. HMDB 4.0: The human metabolome database for 2018. *Nucleic Acids Res*. 2018;46(D1):D608-D617. doi:10.1093/nar/gkx1089

104. Hoffmann MF, Preissner SC, Nickel J, Dunkel M, Preissner R, Preissner S. The Transformer database: Biotransformation of xenobiotics. *Nucleic Acids Res*. 2014;42(D1):1113-1117. doi:10.1093/nar/gkt1246

105. Davis AP, Grondin CJ, Johnson RJ, et al. The Comparative Toxicogenomics Database: Update 2017. *Nucleic Acids Res*. 2017;45(D1):D972-D978. doi:10.1093/nar/gkw838

106. Foodb. http://foodb.ca/.

107. Gaulton A, Hersey A, Nowotka ML, et al. The ChEMBL database in 2017. *Nucleic Acids Res*. 2017;45(D1):D945-D954. doi:10.1093/nar/gkw1074

108. Chempider. http://www.chemspider.com/.

109. Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. *Nucleic Acids Res*. 2016;44(D1):D1075-D1079. doi:10.1093/nar/gkv1075

110. eTOXsys. http://etoxsys.com/.

111. Japic. https://www.japic.or.jp/.

112. Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: Towards evidence-based deprescribing of drugs in older populations. *Evid Based Med*. 2013;18(4):121-124. doi:10.1136/eb-2012-100930

113. Zhang ASR and S. Polypharmacology: drug discovery for the future. *Expert Rev Clin Pharmacol*. 2013;6(1). doi:10.1586/ecp.12.74.

114. Hewett M, Oliver DE, Rubin DL, Easton KL, Stuart JM, Altman RB KT. PharmGKB: the Pharmacogenetics Knowledge Base. *Nucleic Acids Res*. 2002.

115. Kim D, Lee J, Lee S, Park J, Lee D. Predicting unintended effects of drugs based on off-target tissue effects. *Biochem Biophys Res Commun*. 2016;469(3):399-404. doi:10.1016/j.bbrc.2015.11.095

116. Iyengar ADB and R. Systems approaches to polypharmacology and drug discovery Aislyn. *Curr Opin Drug Discov Devel*. 2010;13(3):297-309. doi:10.1126/scisignal.2001965.Introduction

117. Iyengar SZ and R. Systems Pharmacology: Network Analysis to Identify Multiscale Mechanisms of Drug Action. *Annu Rev Pharmacol Toxicol*. 2012;(52):505-521. doi:10.1146/annurev-pharmtox-010611-134520.

118. Pérez-Nueno VI. Using quantitative systems pharmacology for novel drug discovery. *Expert Opin Drug Discov*. 2015;10(12):1315-1331. doi:10.1517/17460441.2015.1082543

119. Antolin A, Workman P, Mestres J, Al-Lazikani B. Polypharmacology in Precision Oncology: Current Applications and Future Prospects. *Curr Pharm Des*. 2017;22(46):6935-6945. doi:10.2174/1381612822666160923115828

120. Campillos M, Kuhn M, Gavin AC, Jensen LJ, Bork P. Drug target identification using side-effect similarity. *Science*

(80-). 2008;321(5886):263-266. doi:10.1126/science.1158140

121. Lucas Brouwers1, Murat Iskar1, Georg Zeller1, Vera van Noort1 PB. Network Neighbors of Drug Targets Contribute to Drug Side-Effect Similarity. *PLoS One*. 2011;6(7):469-474. doi:10.1371/journal.pone.0022187

122. Wang Z, Liang L, Yin Z, Lin J. Improving chemical similarity ensemble approach in target prediction. *J Cheminform*. 2016;8(1):1-10. doi:10.1186/s13321-016-0130-x

123. Pérez-Nueno VI, Souchet M, Karaboga AS, Ritchie DW. GESSE: Predicting Drug Side Effects from Drug-Target Relationships. *J Chem Inf Model*. 2015;55(9):1804-1823. doi:10.1021/acs.jcim.5b00120

124. Cobanoglu MC, Liu C, Hu F, Oltvai ZN, Bahar I. Predicting drug-target interactions using probabilistic matrix factorization. *J Chem Inf Model*. 2013;53(12):3399-3409. doi:10.1021/ci400219z

125. Informatics B, Program T. Data-Driven Prediction of Drug Effects and Interactions Nicholas. *Sci Transl Med*. 2013;4(125):1-26. doi:10.1126/scitranslmed.3003377.Data-Driven

126. Koutkias V, Kilintzis V, Stalidis G, et al. Constructing Clinical Decision Support Systems for Adverse Drug Event Prevention: A Knowledge-based Approach. *AMIA Annu Symp Proc*. 2010;2010:402-406. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041377/pdf/amia-2010_sympproc_0402.pdf.

127. Harpaz R, Callahan A, Tamang S, et al. Text Mining for Adverse Drug Events: the Promise, Challenges, and State of the

Art. *Drug Saf*. 2014;37(10):777-790. doi:10.1007/s40264-014-0218-z

128. White RW, Tatonetti NP, Shah NH, Altman RB, Horvitz E. Web-scale pharmacovigilance: Listening to signals from the crowd. *J Am Med Informatics Assoc*. 2013;20(3):404-408. doi:10.1136/amiajnl-2012-001482

129. Cañada A, Capella-Gutierrez S, Rabal O, Oyarzabal J, Valencia A, Krallinger M. LimTox: A web tool for applied text mining of adverse event and toxicity associations of compounds, drugs and genes. *Nucleic Acids Res*. 2017;45(W1):W484-W489. doi:10.1093/nar/gkx462

130. Prötzl E, Thielert M, Lechner V. Molecular docking. *Methods Mol Biol*. 2008;443:365-382. doi:10.1007/978-1-59745-177-2_19

131. Pérez-Nueno VI, Venkatraman V, Mavridis L, Ritchie DW. Detecting drug promiscuity using Gaussian ensemble screening. *J Chem Inf Model*. 2012;52(8):1948-1961. doi:10.1021/ci3000979

132. Lee A, Lee K, Kim D. Using reverse docking for target identification and its applications for drug discovery. *Expert Opin Drug Discov*. 2016;11(7):707-715. doi:10.1080/17460441.2016.1190706

133. Rastelli G, Pinzi L. Computational polypharmacology comes of age. *Front Pharmacol*. 2015;6(JUL):1-4. Doi:10.3389 /f phar.2015.00157

Appendix A

Supplementary information for Result session 3.1 DMDB

Metabolite id	MW drug	MW metabolite	Diff. MW	Smiles	Chembl ID	Inchi Key	Reference
1-nitronaphthalene.metabolite.G	173,17	143,19	29,98	C1=CC=CC2C=CC=C	CHEMBL57394	RUFPHBVGCFYCNW-UH	Drug Metab Dispos.
1-nitronaphthalene.metabolite.i1	173,17	189,17	-16	C1=CC2OC2C2C=CC	not found	GSAMVXYBVGOJMK-UH	Drug Metab Dispos.
1-nitronaphthalene.metabolite.i2	173,17	189,17	-16	C1=CC=CC2=CC3OC	not found	FZZLDSFTICXCRO-UH	Drug Metab Dispos.
1,2-dibromoethane.metabolite.m1	187,86	138,95	48,91	C(=O)(O)CBr	CHEMBL60851	KDPAWGWELVVRCH-UH	Drug Metab Dispos.
1,2-dibromoethane.metabolite.m2	187,86	124,97	62,89	C(O)CBr	CHEMBL468583	LDLCZOVUSADOIV-UH	Drug Metab Dispos.
1,2-dibromoethane.metabolite.m3	187,86	178,16	9,7	C(=O)(O)CSCC(=O)C(	CHEMBL259106	FDUKYMHTXNDQPD-UH	Drug Metab Dispos.
1,2-dibromoethane.metabolite.m4	187,86	150,16	37,7	C(=O)(O)CSCC(O)=O	CHEMBL1570500	UVZICZIVKIMRNE-UH	Drug Metab Dispos.
17-alpha-hydroxy-progesterone caproate.metabolite.1	428,61	330,47	98,14	C1CC(=O)C=C2CCC(]	not found	DBPWSSGDRRHUNT-WI	Drug Metab Dispos
17-alpha-hydroxy-progesterone caproate.metabolite.pr	428,61	314,47	114,14	C1CC(=O)C=C2CCC([	CHEMBL1489845	RJKFOVLPORLFTN-GK	Drug Metab Dispos
18-methoxycoronaridine.metabolite.18-hc	368,47	354,45	14,02	c1:c:c:c:c2NC3C(C(	CHEMBL607049	FRCVRUHRFLXLAI-UH	Drug Metab Dispos.
2-allylthio-pyrazine.metabolite.m1	152,21	142,18	10,03	N1=CC=NC(S(C)=O)=	not found	FHTBBZMYISOPBI-UH	Drug Metab Dispos.
2-allylthio-pyrazine.metabolite.m2	152,21	168,22	-16,01	N1=CC=NC(S(CC=C)=	not found	KALRQHIHOGSAEC-UH	Drug Metab Dispos.
2-allylthio-pyrazine.metabolite.m3	152,21	184,22	-32,01	N1=CC=NC(S(=O)(CC	not found	NUZRWVGVIVNVRG-UH	Drug Metab Dispos.
2-allylthio-pyrazine.metabolite.m4	152,21	142,18	10,03	N1=C(O)C=NC(SC)=C	not found	XEHFWBQFLYETFK-UH	Drug Metab Dispos.
2-allylthio-pyrazine.metabolite.m5	152,21	168,22	-16,01	N1=C(O)C=NC(SCC=C	not found	OKIWTIJWAAVEAG-UH	Drug Metab Dispos.
2-phenylpropionic acid.metabolite.R-2-ppa.glucuronid	150,17	326,3	-176,13	C1(=CC=CC=C1)[C@	not found	YDYDFDAUGYHMIG-VV	Drug Metab Dispos.
2-phenylpropionic acid.metabolite.S-2-ppa.glucuronid	150,17	326,3	-176,13	C1(=CC=CC=C1)[C@	not found	YDYDFDAUGYHMIG-HR	Drug Metab Dispos.
2,4-dichlorophenoxyacetic acid.metabolite.2.4-d-gluc	221,03	397,16	-176,13	c(OCC(OC1OC(C(=O)n	not found	VWTUPYKAIBDFAG-UH	Drug Metab Dispos.
2,4-dichlorophenoxyacetic acid.metabolite.2.4-d-glyci	221,03	278,09	-57,06	c(OCC(NCC(=O)O)=C	not found	ZSUWKPLZWNKGFI-UH	Drug Metab Dispos.
2,4-dichlorophenoxyacetic acid.metabolite.2.4-d-tauri	221,03	328,17	-107,14	c(OCC(NCCS(=O)(=O)n	not found	KMIBHQUPOLCZOA-UH	Drug Metab Dispos.
20s-protopanaxadiol.metabolite.M1-1-1	460,74	476,74	-16	C1C[C@H](O)[C@H0	CHEMBL3527019	NZMLWOMSTXSMTL-GD	Drug Metab Dispos.
20s-protopanaxadiol.metabolite.M1-1.6	460,74	476,74	-16	C1C[C@H](O)[C@H0	CHEMBL3527019	NZMLWOMSTXSMTL-GD	Drug Metab Dispos.
20s-protopanaxadiol.metabolite.M1-2.2	460,74	476,74	-16	C1C[C@H](O)[C@H0	CHEMBL466363	DOAJFZJEGHSYOI-GL	FYDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M1-3.3	460,74	476,74	-16	C1C[C@H](O)[C@H0	CHEMBL466363	DOAJFZJEGHSYOI-GL	ZDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M2-1.4	460,74	474,73	-13,99	C1CC(=O)[C@H0](C)(	CHEMBL2426028	MOCDJPYINJXPKU-RA	NDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M2-2.5	460,74	474,73	-13,99	C1CC(=O)[C@H0](C)(	CHEMBL2426028	MOCDJPYINJXPKU-HZ	VDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M6-1	460,74	494,76	-34,02	C1C[C@H](O)[C@H0	CHEMBL3526681	ROUZPBFWHICWJH-GL	IDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M6-2	460,74	494,76	-34,02	C1C[C@H](O)[C@H0	CHEMBL3526681	ROUZPBFWHICWJH-GL	Drug Metab Dispos.
20s-protopanaxadiol.metabolite.M7-1	460,74	652,87	-192,13	C1C[C@H](O)[C@H0	CHEMBL3527036	IXIGZEZCKFQBLU-BN	VDrug Metab Dispos.
20s-protopanaxadiol.metabolite.M7-2	460,74	652,87	-192,13	C1C[C@H](O)[C@H0	CHEMBL3527036	IXIGZEZCKFQBLU-XW	EDrug Metab Dispos.
24,25-dihydroxyvitamin d 3.metabolite.24-oxo-1-25-	416,64	430,63	-13,99	C(=C/C=C1/C2CCC(C	not found	BWFQMABKLLTETH-ZF	Physiological Revie
24,25-dihydroxyvitamin d 3.metabolite.24,25-trihydr	416,64	432,65	-16,01	C(=C/C=C1/C2CCC(C	CHEMBL3351075	WFZKUWGUJVKMHC-ZJ	Physiological Revie
24,25-dihydroxyvitamin d 3.metabolite.25-26-trihydr	416,64	432,65	-16,01	C(=C/C=C1/C2CCC(C	not found	LUMQIGNPUDCMLN-MI	Physiological Revie
24,25-dihydroxyvitamin d 3.metabolite.25-dihydroxyv	416,64	444,61	-27,97	C(=C/C=C1/C2CCC(C	not found	WMYIVSWWSRCZFA-AI	Physiological Revie
24,25-dihydroxyvitamin d 3.metabolite.Calcitroic.acid	416,64	374,52	42,12	C(=C/C=C1/C2CCC(C	CHEMBL3544529	MBLYZRMZFUWLOZ-HP	Physiological Revie
3-butene-1,2-diol.metabolite.2-hydroxy-3-butenal	88,1	86,09	2,01	C=CC(O)C=O	not found	PPNVQCFSKPIRKK-UH	F Drug Metab Dispos.
3-butene-1,2-diol.metabolite.acrolein	88,1	56,06	32,04	C=CC=O	CHEMBL721	HGINCPLSRVDWNT-UH	Drug Metab Dispos.
3-butene-1,2-diol.metabolite.epoxybutane.diol	88,1	104,1	-16	C1OC1C(O)CO	not found	KRBIHOANUQUSRV-UH	Drug Metab Dispos.
3-butene-1,2-diol.metabolite.hydroxymethylvinyl.ket	88,1	86,09	2,01	C=CC(=O)CO	not found	LHBQGXZUVXFJRH-UH	Drug Metab Dispos.
3-butene-1,2-diol.metabolite.m1	88,1	30,02	58,08	C1C2C3C=C([2H])C(	not found	JNSKNJBMFAKLY-UO	RJ. Chromatogr. B 73
3-hydroxybenzo-a-pyrene.metabolite.benzo.a.pyrene-3	268,31	444,44	-176,13	C12=CC=C3C=CC(O	not found	SJYHOQLSWMWVSY-UH	Drug Metab Dispos.
3-hydroxybenzo-a-pyrene.metabolite.benzo.a.pyrene-3	268,31	332,38	-64,07	C12=CC=C3C=CC(S(	not found	MQHMCTZTWIOPSS-UH	Drug Metab Dispos.
3-hydroxybenzo-a-pyrene.metabolite.benzo.a.pyrene-3	268,31	282,3	-13,99	C12=CC=C3C=CC(=C	not found	MYRYNZSMCVOJHZ-UH	Drug Metab Dispos.
3-methylindole.metabolite.2.3-epoxide	131,17	147,18	-16,01	C1=CC=CC2NC3OC3	not found	WHTZCVZCHNDLHB-UH	Drug Metab Dispos.
3-methylindole.metabolite.3-hydroxy-3-methylindoler	131,17	147,18	-16,01	C1=CC=CC2[NH+]=C	not found	HYZSAMREMMAXPO-UH	Drug Metab Dispos.
3-methylindole.metabolite.3-hydroxy-3-methyloxindo	131,17	163,18	-32,01	C1=CC=CC2NC(=O)C	not found	XCHBYBKNFIOSBB-UH	Drug Metab Dispos.
3-methylindole.metabolite.3-methyleneindolenine	131,17	129,16	2,01	C1=CC=CC2[NH+]=C	CHEMBL3623240	BCNUXXXHEIUHJB-UH	Drug Metab Dispos.
3-methylindole.metabolite.3-methyloxindole	131,17	147,18	-16,01	C1=CC=CC2NC(=O)C	not found	BBZCPUCZKLTAJQ-UH	Drug Metab Dispos.
3-methylindole.metabolite.3minac	131,17	292,36	-161,19	C1=CC=CC2NC=C(C	not found	GPAMNSHJZSIQCJ-UH	FDrug Metab Dispos.
3-methylindole.metabolite.indole-3-cabinol	131,17	147,18	-16,01	C1=CC=CC2NC=C(C	CHEMBL155625	IVYPNXXAYMYVSP-UH	Drug Metab Dispos.
3-nitrobenzanthrone.metabolite.3-aba	275,26	245,28	29,98	C1C=CC=C2C(=O)C3	not found	ZXPXRBDYCANCCU-UH	Drug Metab Dispos.
3-nitrobenzanthrone.metabolite.I-1	275,26	245,28	29,98	C1C=CC=C2C(=O)C3	not found	ZXPXRBDYCANCCU-UH	Drug Metab Dispos.
3-nitrobenzanthrone.metabolite.I-2	275,26	245,28	29,98	C1C=CC=C2C(=O)C3	not found	ZXPXRBDYCANCCU-UH	Drug Metab Dispos.
3-nitrobenzanthrone.metabolite.N-oh-aba	275,26	261,28	13,98	C1C=CC=C2C(=O)C3	not found	WCPKDLWOWHLXNO-UH	Drug Metab Dispos.
3-nitrobenzanthrone.metabolite.NAT-1	275,26	291,31	-16,05	C1C=CC=C2C(=O)C3	not found	DEJHBLOVSUCGJL-UH	FDrug Metab Dispos.
3-nitrobenzanthrone.metabolite.NAT-2	275,26	341,34	-66,08	C1C=CC=C2C(=O)C3	not found	MBBWEJFOKGQOKS-UH	Drug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.2-oh-tcb	291,98	307,99	-16,01	C1(=C(O)C(Cl)=C(Cl)	not found	PMUPQKIUSIWQCV-UH	IDrug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.4-oh-tcb	291,98	307,99	-16,01	C1(=CC(Cl)=C(O)C(Cl	not found	RQGVZEFZWFEKQR-UH	Drug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.4.5-epoxide	291,98	307,99	-16,01	C1(C=C(Cl)C2(OC2C=c	not found	ZOEYQLPQDMENKR-UH	Drug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.5-oh-tcb	291,98	307,99	-16,01	C1(=CC(Cl)=C(Cl)C(Cl	not found	KMGGIEHZQDAYLW-UH	Drug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.5.6-epoxide	291,98	307,99	-16,01	C1(=CC(Cl)=C(Cl)C2	not found	WQAFZHJGQMPBHM-UH	Drug Metab Dispos.
3,3',4,4'-tetrachlorobiphenyl.metabolite.6-oh-tcb	291,98	307,99	-16,01	C1(=CC(Cl)=C(Cl)C=	not found	GPHKIEYWDKDZEA-UH	Drug Metab Dispos.
3,4-methylenedioxyamphetamine.metabolite.hha	179,21	167,2	12,01	OC1C(=CC=C(CC(C)N	CHEMBL28278	KSRGADMGIRTXAF-UH	Journal of analytica
4-aminophenol.metabolite.apap	109,12	151,16	-42,04	c(NC(=O)C)1:c:c:c(O):	CHEMBL112	RZVAJINKPMORJF-UH	F Drug Metab Dispos.
4-aminophenol.metabolite.apap-gluc	109,12	327,29	-218,17	c(NC(=O)C)1:c:c:c(OC	CHEMBL1647	IPROLSVTVHAQLE-UH	FDrug Metab Dispos.
4-aminophenol.metabolite.fpap	109,12	139,15	-30,03	c(NCO)1:c:c:c(O):c:c:	not found	DXFHTRGLOOTEFS-UH	IDrug Metab Dispos.
4-aminophenol.metabolite.i1	109,12	153,14	-44,02	c(NC(=O)O)1:c:c:c(O):	not found	MSMJEQQYVMQBSR-UI	Drug Metab Dispos.
4-aminophenol.metabolite.i2	109,12	107,11	2,01	C(=N)1C=CC(=O)C=C	not found	WELKBINNNXKQQS-UH	Drug Metab Dispos.
4-aminophenol.metabolite.pap-gluc	109,12	285,25	-176,13	c(N)1:c:c:c(OC2C(O)(	not found	ZARKEMJKQOXOSQ-UH	Drug Metab Dispos.
4-methylthioamphetamine.metabolite.	181,29	197,29	-16	C1=CC(SCO)=CC=C1	not found	KTCMDZMUYKEXKX-UJ	Journal of analytica
4-methylthioamphetamine.metabolite.4-methylthioben	181,29	168,21	13,08	C1=CC(SC)=CC=C1C	CHEMBL99816	KWHCPERWLHBLOT-UJ	Journal of analytica
4-methylthioamphetamine.metabolite.4-methylthioph	181,29	197,29	-16	C1=CC(SC)=CC=C1	not found	NHDBTQFIBYMJRB-UH	Journal of analytica
4-phenylbut-3-yn-2-one.metabolite.pba	144,17	146,19	-2,02	C1=CC=CC=C1/C=C/	CHEMBL73639	BWHOZHOGCMHOBV-BE	Drug Metab Dispos.
4-phenylbut-3-yn-2-one.metabolite.pbaol	144,17	148,2	-4,03	C1=CC=CC=C1/C=C/	CHEMBL1490851	ZIJWGEHOVHJHKB-BQ	YDrug Metab Dispos.
4-phenylbut-3-yn-2-one.metabolite.pbo	144,17	146,19	-2,02	C1=CC=CC=C1/C=C/	CHEMBL1490851	BWHOZHOGCMHOBV-BE	Drug Metab Dispos.

Appendix B

Supplementary information for Result session 3.2 Propensity of drug-classes to drug interactions

Appendix B.1

UMLS	safety term	Number of DDIs involving drug and linked to safety term	Number of DDIs involving drug and not linked to safety term	Number of drugs in DDI with this side effect	Number of drugs in DDI without this side effect
C0231274	heat intolerance	2675	554	0	83
C0038271	stereotypy	2582	503	0	80
C0235299	right upper quadrant pain	763	4108	0	171
C1412278	rage	705	17330	0	288
C0948429	diuretic effect	461	387	0	54
C0542203	water retention	440	284	0	45
mU292	nervous system toxicity	339	305	0	49
C0013537	eclampsia	321	142	0	39
C0520758	prolonged neuromuscular block	261	905	0	67
mU359	reduced cardiac contractility	252	178	0	34
mU33	mild cognitive impairment	228	2751	0	80
C0005974	bone resorption	225	731	0	58
C1578561	gastrointestinal injury	214	3722	0	126
C0392684	irregular pulse	188	1876	0	85
C2210463	collapse	186	2971	0	97
C0160420	kidney injury	184	952	0	63
C0153690	bone metastases	182	396	0	50
C0392171	flu-like symptoms	182	1818	0	113
C0425945	prolonged periods	176	256	0	43
C0017067	ganglion	175	1245	0	63
C2037199	sudden loss of vision	141	1195	0	71
mU108	vestibular toxicity	130	239	0	37
C0740411	delayed gastric emptying	128	182	0	28
C0344375	stomach cramps	119	177	0	26
C0423798	easy bruising	99	687	0	72

Appendix B.1. List of safety terms, that are annotated to DDI, but neither of the interacting drug.

Appendix B.2

ATC code of the level	Description of the level	UMLS	Safety term	Number of DDIs involving drugs in ATC level and linked to safety term
N06AA	Non-selective monoamine reuptake inhibitors	C0080203	tachyarrhythmia	1253
N05BA	Benzodiazepine derivatives	C0011570	depression	1202
A10BB	Sulfonamides, urea derivatives	C0020615	hypoglycemia	1182
N06AA	Non-selective monoamine reuptake inhibitors	C0012833	dizziness	1168
C08CA	Dihydropyridine derivatives	C1568272	tendinopathy	981
C08CA	Dihydropyridine derivatives	C0024031	hypotension	961
C09AA	ACE inhibitors, plain	C0024031	hypotension	960
C03AA	Thiazides, plain	C0024031	hypotension	948
C03AA	Thiazides, plain	C0012833	dizziness	945
C09AA	ACE inhibitors, plain	C1568272	tendinopathy	924
N06AA	Non-selective monoamine reuptake inhibitors	C0039070	syncope	917
N06AA	Non-selective monoamine reuptake inhibitors	C0849963	nervous	907
C07AB	Beta blocking agents, plain, selective	C0684167	hypertension	861
N06AA	Non-selective monoamine reuptake inhibitors	C0264886	arrhythmias	860
C07AB	Beta blocking agents, plain, selective	C1568272	tendinopathy	852
C03AA	Thiazides, plain	C0684167	hypertension	830
C03AA	Thiazides, plain	C0039070	syncope	820
C03AA	Thiazides, plain	C1568272	tendinopathy	806
C07AB	Beta blocking agents, plain, selective	C0012833	dizziness	805
N06AX	Other antidepressants	C0011570	depression	804
N05BA	Benzodiazepine derivatives	C0398353	hypoventilation	779
A10BB	Sulfonamides, urea derivatives	C0013144	somnolence	764
N05BA	Benzodiazepine derivatives	C0849963	nervous	764
N06AA	Non-selective monoamine reuptake inhibitors	C0030193	pain	762
N06AA	Non-selective monoamine reuptake inhibitors	C1568272	tendinopathy	754
A10BB	Sulfonamides, urea derivatives	C0030193	pain	736
A10BB	Sulfonamides, urea derivatives	C0234369	tremors	732
A10BB	Sulfonamides, urea derivatives	C0018681	headache	730
A10BB	Sulfonamides, urea derivatives	C0012833	dizziness	724
A10BB	Sulfonamides, urea derivatives	C0020175	hunger	723
N06AA	Non-selective monoamine reuptake inhibitors	C0237314	irregular heartbeat	723
C09AA	ACE inhibitors, plain	C0684167	hypertension	719
C07AB	Beta blocking agents, plain, selective	C0039070	syncope	719
C09AA	ACE inhibitors, plain	C0012833	dizziness	711
C08CA	Dihydropyridine derivatives	C0684167	hypertension	695
C07AB	Beta blocking agents, plain, selective	C0024031	hypotension	689
C07AA	Beta blocking agents, non-selective	C0012833	dizziness	688
N06AA	Non-selective monoamine reuptake inhibitors	C1704628	hyperthermia	687
N06AA	Non-selective monoamine reuptake inhibitors	C0036572	seizures	685
N06AA	Non-selective monoamine reuptake inhibitors	C0684167	hypertension	674

Appendix B.2. List of safety issues that appear most often linked toDDIs involving drugs from certain drug classes (ATC 4th level).

Appendix B.3

ATC code	Name of the ATC code	ATC code	Name of the ATC code	Nº common safety
N06AA	Non-selective monoamine reuptake inhibitors	N06AX	Other antidepressants	80
C03AA	Thiazides, plain	N06AX	Other antidepressants	62
C08CA	Dihydropyridine derivatives	N06AX	Other antidepressants	62
N05AX	Other antipsychotics	N06AX	Other antidepressants	61
N05AX	Other antipsychotics	N06AA	Non-selective monoamine reuptake inhibitors	59
J05AE	Protease inhibitors	N06AX	Other antidepressants	58
J01MA	Fluoroquinolones	N06AX	Other antidepressants	57
C09AA	ACE inhibitors, plain	N06AX	Other antidepressants	55
L01XX	Other antineoplastic agents	N06AX	Other antidepressants	55
C07AA	Beta blocking agents, non-selective	C07AB	Beta blocking agents, plain, selective	52
M03BX	Other centrally acting agents	N06AX	Other antidepressants	52
C01BD	Antiarrhythmics, class III	N06AX	Other antidepressants	51
M03BX	Other centrally acting agents	N06AA	Non-selective monoamine reuptake inhibitors	51
N06AX	Other antidepressants	S01AA	Antibiotics	51
B01AC	Platelet aggregation inhibitors excl. heparin	N06AX	Other antidepressants	50
J01MA	Fluoroquinolones	N06AA	Non-selective monoamine reuptake inhibitors	49
L01XX	Other antineoplastic agents	L04AX	Other immunosuppressants	49
N05BA	Benzodiazepine derivatives	N06AX	Other antidepressants	49
C03AA	Thiazides, plain	C03BA	Sulfonamides, plain	48
C08CA	Dihydropyridine derivatives	C09AA	ACE inhibitors, plain	48

Appendix B.3 Number of shared safety terms between ATC 4th level drug classes