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Working Paper: Results of Personalised Medicine Pilot

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1 Revision history

Version	Date	Changes made	Author(s)
1.0		Initial concept	
2.0		First Draft	
3.0		Version for internal review	

Statement of originality

This working paper contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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2 Working paper abstract

The present working paper D8.10, pertaining to Task T8.5 (IDMP Implementation for Personalised Medicine), reports the results of the “Personalized Medicine Pilot" that was performed at FOUND to integrate and extend the findings of the previous D8.9 working paper. Specifically, whereas in the working paper D8.9 we identified common perpetrator drug-gene combos that could be responsible for drug-drug-gene interactions in older adults, in the working paper D8.10 we pinpointed the actual victims of these combos in real-world drug prescriptions. To this aim we retrospectively examined the drug therapies of 348 older adults followed at FOUND and we selected those including the perpetrator drugs acting on either CYP3A4, CYP2C19, CYP2D6 or SLCO1B1 that were identified in D8.9. Then, in each of these subgroups we looked for the substrates of the respective CYP or of SCLCO1B1 by using the *drug bank* database and the Flockhart table, and for potential drug-drug interactions by using the drugs.com interaction checker. About 72% of the whole population was taking at least one drug perpetrator drug acting on CYP3A4; the most common drug victims were pantoprazole, esomeprazole omeprazole, amlodipine (which are also CYP3A4 inhibitors), atorvastatin, and clopidogrel, all found in more than 20% of the examined prescriptions. At least one drug perpetrator acting on CYP2D6 was found in around 30% of our patient cohort and the potential victims taken by more than 10% of the patients were carvedilol, simvastatin , doxazosin and tiotropium. Almost 69% of the patients were taking at least one of the drug perpetrators acting on CYP2C19, identified in D8.9. Esomeprazole, Clopidogrel, Doxazosin, Pantoprazole and Warfarin were the most commonly co-prescribed drug victims, with a prevalence higher than 10%. Finally, more than 65% of the patients in our cohort was taking at least one of the drug perpetrators acting on SLCO1B1 and the victim drugs more frequently combined with them were atorvastatin, digoxin, simvastatin, rosuvastatin, olmesartan, and valsartan, all with a prevalence higher than 6%. No serious adverse drug reaction ascribable to drug interactions was reported in any of the examined medical records.
In conclusion, we pinpointed the most common drug victims that could be involved in drug-drug-gene interactions with the perpetrator-drug-gene combos that occur more frequently in geriatric patients according to our previous investigations; These data could be helpful in designing new IDMP- and pharmacogenomic-based DDI/DDGI checkers.

Keywords: DDI, DDGI, CYP, SLCO1B1, polypharmacy, .

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the Description of Action?	✓ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
the international State of the Art?	✓ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
Is the quality of the working paper in a status						
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Is the structure and contents of the working paper						
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* Type of comments: M = Major comment; m = minor comment; a = advice

4 List of abbreviations

Abbreviation	Complete form
AIFA	Italian Medicines Agency
CDSS	clinical decision support system
CYP	Cytochrome P 450
DDI	Drug-drug interaction
DDGIs	drug-drug-gene interactions
FOUND	Azienda Ospedaliera Universitaria Federico II
IDMP	Identification of Medicinal Products
OsMed	Observatory on the Use of Medicines

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1 Executive summary

Polypharmacy, i.e. treating patients with 5 or more drugs, is a condition which can be responsible for important unwanted clinical consequences. Among them probably the most important are drug-drug interactions (DDIs) which can cause, depending on the drugs involved, either drug toxicity or loss of drug efficacy with therapy failure. DDIs occur when a perpetrator drug -i.e. a drug which can modify the response to other drugs- is combined with a victim drug -i.e. a drug whose effects can be modified by the perpetrator drug. In the some cases, the same drug can act both as a perpetrator and as a victim at the same time. In recent years it became clear that the effect of drug perpetrators may vary depending on the genotype of the patients exposed to these drugs and more specifically that variations in key pharmacogenes such as those encoding drug metabolizing enzymes are involved. To account for the relevance of genetic factors in DDIs, the term drug-drug-gene interactions (DDGIs) has been introduced. Serious DDIs and DDGIs can be prevented by an accurate analysis of drug therapy (and, possibly, patient genotype) with the aim of avoiding dangerous drug combinations. Medical doctors can be helped in this process by specific drug interaction checkers, some of which are incorporated in more complex clinical decision support systems (CDSS). A key factor for the efficient working of such informatic solutions is the univocal identification of the drugs included in the evaluated therapy, whose names may vary among different brands and across different countries. In this perspective, the design of IDMP-based DDI-checkers could greatly help. In this perspective, the activities of Task 8.5 were focused on identifying the most relevant DDGIs in older adults, who represent the category of patients in whom polypharmacy more frequently occurs. In the previous working paper D8.9, we identified the perpetrator drug-gene combos which may cause DDGIs, most commonly occurring in older adults from Southern Italy. In the present working paper D8.10, we extended and integrated these findings by identifying the victim drugs of these combos and the potential DDGIs in which they could be involved. To this aim we performed an observational, retrospective pilot study in which the drug therapy of 348 older adults followed at FOUND was examined. Specifically, we stratified these drug prescriptions in several groups based on the presence of one of more of the drug perpetrators that we previously identified in D8.9 and of the respective potential key pharmacogene involved (CYP3A4, CYP2C19, CYP2D6 or SLCO1B1), then, we looked in each of these subgroups for the substrate of the aforementioned enzymes and transporters, which could potentially act as victims. The main finding of this investigation is that drug victims of the drug perpetrators-gene combos identified in D8.9, occur frequently in older adults' drug prescriptions. That, in many cases, the same drugs may occur both as perpetrators and as victims. Although many of these perpetrator-victim combination may underlie significant DDIs (which were classified as serious in 18.4 % of cases) or the respective DDGIs, in the medical records examined we did not find any report of clinically relevant adverse drug reactions caused by DDIs. The list of drug perpetrators, drug victims and related pharmacogenes that we obtained in the present and in the previous working paper could help to prioritize the efforts in developing IDMP-based drug interaction checkers and related CDSS towards those drugs which are more likely involved in drug interactions in older adults.

2 Content of the working paper

2.1 Contents of the working paper

The present document contains the results of the pilot clinical study that we performed to identify victim drugs and the related DDIs, which more commonly occur in older adults. Data are reported in 12 tables: one of them summarizes the findings of the previous working paper D.9, in which we identified perpetrator drug-pharmacogene combos that could cause DDIs in older adults, five report the list of their victims and five the potential DDI that could occur by the combination of these perpetrator and victim drugs.

2.2 Authorship and responsibilities

The Project Coordinator is responsible of submitting the working papers in accordance with the timing and conditions set out in the DoA.

The leader of the Work Package to which the working paper is assigned is responsible for reporting to the Project Coordinator about the progress and completion of the output and the document, and to ensure that it has the required quality.

The lead beneficiary of each working paper, as identified in the Description of the Action (DoA), is responsible of editing the document. For that purpose he or she may count with the contribution of other partners. All authors that have made significant contributions to the working paper shall be listed in the table contained in the second page of the template.

3 Introduction

According to the World Health Organization polypharmacy is the concomitant use of multiple drugs in the same patient (WHO, 2019). Although no specific threshold has been defined, it is widely assumed that patients are on polypharmacy when they take 5 or more medicines; when 10 or more drugs are prescribed, polypharmacy is considered "excessive" (Masnoon et al., 2017). Only medicines taken "chronically" should be included in these calculations but, once again, no clear-cut indication has been provided on how long a specific medicine must be taken to be considered “chronic”; as a matter of fact, values within the wide interval between 90 and 240 days have been used in different studies.

The most common reason to combine multiple drugs in the same therapy is that several chronic diseases may occur together in the same patient (comorbidities); in addition, many of these chronic diseases do not respond adequately to treatment with only one active substance (e.g. diabetes mellitus and arterial hypertension). In these conditions, polypharmacy is, therefore, necessary, and useful. There are, however, circumstances in which the use of one or more of the drugs included in specific polypharmacy regimens is not supported by a solid clinical rationale; in these conditions, polypharmacy is considered "inappropriate".

Polypharmacy is highly prevalent in some categories of patients the most typical of which are older adults (according to the WHO definition, patients over 65 years of age). These patients, indeed, are very frequently affected with multiple age-related chronic diseases. Data from the National Observatory on the Use of Medicines (OsMed) of the Italian Medicines Agency (AIFA) showed that the average number of drugs taken per day in the age group between 80 and 84 years is 7.4 (Onder et al, 2016; Onder et al, 2014). In addition, the SIMPATHY Project (Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly) estimated that the prevalence of excessive polypharmacy (10 or more drugs) in people aged 70-74 years is about 20% (Mair et al., 2017).

Although polypharmacy is often required to address the therapeutic needs described above, it can also cause significant clinical problems; in particular, adherence to drug treatment is lower, and the incidence of delirium, mental confusion, and falls, and, in general, drug toxicity are higher in older adults on polypharmacy as compared with those who are not. One of the factors responsible for these unwanted consequences of polypharmacy is that when several drugs are combined, the risk that they interact with each other increases. The term “drug-drug interaction” (DDI) refers to the phenomenon whereby when different drugs are combined, the response to one or more of them is different from that observed when they are administered alone. DDIs may be pharmacokinetic, if they impact on absorption, distribution, metabolism or elimination, or pharmacodynamic, if they interfere with the mechanism of action. Typically, when two drugs do interact together, one of them causes the interaction, the so-called "perpetrator drug", whereas the other is affected by the interaction caused by the perpetrator, the so-called "victim drug"; in some cases, however, a given drug may behave both as a perpetrator and as a victim.

In some circumstances, drug interactions are useful, and combining interacting drugs may help achieve therapeutic goals, while in others, they can contribute to drug toxicity. This often happens when polypharmacy, as in many older adults, is inappropriate or excessive. As a matter of fact, Hanlon et al. (2017) showed that the prevalence of DDIs is about 25% in older adults on polypharmacy, aged 70-79 years. Therefore, special care should be taken in prescribing drugs to these patients to avoid dangerous DDIs. A useful strategy to prevent DDI-related problems is the so-called medicine review, a structured revision of therapy to identify inappropriate and dangerous drugs and potential DDIs, which is performed jointly by geriatricians, pharmacists and pharmacologists (Shaw et al., 2002). Medical doctors can be helped in this process by specific drug interaction checkers, some of which are incorporated in more complex clinical decision support systems (CDSS). A key factor for the efficient working of such informatic solutions is the univocal identification of the drugs included in the evaluated therapy, whose names may vary among different brands and across different countries. In this perspective, the design of IDMP-based DDI-checkers could greatly help.

An important limitation of medicine review is that many of the potential DDIs identified do not have any clinical consequence and this may cause doctors’ fatigue towards DDI warnings and related recommendations. As in other issues of personalized medicine, individual factors seem to be

involved in determining the susceptibility to severe events related to DDIs. These remain to date largely unknown.

In recent years, inter-individual variability in the susceptibility to DDI-related toxicity has been largely attributed to genetic factors; among those, polymorphisms in genes encoding proteins (typically enzymes, pumps or transporters) targeted by interacting drugs play a major role. For instance, a pharmacokinetic interaction due to the inhibition of a specific cytochrome by a perpetrator drug will be accentuated in patients who have a "slow metabolizer" phenotype since they bear polymorphic variants with low or no activity of the gene encoding such cytochrome.

In the light of these considerations, it has been suggested that the classic concept of DDI should be supplemented by the concept of drug-drug-gene interactions (DDGI): in DDGIs, the genotype acts as an interacting factor which operates in combination with specific perpetrators to generate a gene-drug combo perpetrator (Bahar et al., 2017; Verbeurgt et al., 2014).

In the context of the activities of Task 8.5, in the first part of the UNICOM project, we identified the most common gene-drugs combinations that could represent potential combo perpetrators in the pharmacological treatment of the elderly (Cataldi et al., Geriatrics). The detailed results of this investigation are reported in the previous working paper D8.9 whereas in Table 1 we show the list of the combo interactors that we identified. However, the potential victims of these combo perpetrators and the DDGIs in which they could be involved in real-world settings remained largely unknown. To fill this knowledge gap and to obtain useful information for the development of future IDMP-based DDI-checkers, we performed a retrospective study in a cohort of geriatric patients on polypharmacy followed at our institution. The results of this study are described in the present report.

Table 1. List of the drug perpetrator- gene variant combos commonly observed in older adults

Potential Perpetrator Drug (prevalence of use in older adults on polypharmacy)	**Involved Pharmacogene**	**Potentially interacting gene variants** (prevalence in European people)
Amlodipine (16,3%) Esomeprazole (12,2%) Omeprazole (10.0%) Pantoprazole (15,7%)	CYP3A4	CYP3A4*22 (5%) CYP3A4*1G (8%) CYP3A5*3 (92.4%)
Esomeprazole (12,2%) Omeprazole (10.0%) Pantoprazole (15,7%)	CYP2C19	CYP2C19*2 (14.66%) CYP2C19*8 (0.34%) CYP2C19*4 (0.20%) CYP2C19*3 (0.17%)
Rifaximin (6,0%)	CYP2C19	CYP2C19*17 (21.6%)
Amlodipine (16,3%) Omeprazole (10,0%)	CYP2D6	CYP2D6*4 (18.5%) CYP2D6*41 (9.4%) CYP2D6*5 (2.95%) CYP2D6*10 (1.57%) CYP2D6*9 (2.76%) CYP2D6*17 (0.39%)
Atorvastatin (30,0%) Digoxin (8,4%) Pantoprazole (15,7%) Rosuvastatin (6,0%) Simvastatin (8,4%)	SLCO1B1	SLCO1B1 *5 (2,04%) SLCO1B1 *15 (15.02%)

4 Patients and Methods

4.1 Study design

Study design was monocentric, non-interventional, observational, and retrospective. We retrieved prescription and clinical data (gender, age, number of comorbidities, evidence of clinically relevant drug interactions) from the medicine reviews of geriatric patients who attended the Multidimensional Assessment and Geriatric Therapy Outpatient Clinic and the Internal Medicine ward of FOUND from 2018 until study approval. After selecting the patients who met inclusion and exclusion criteria, we identified the records in which drug therapy included the different drugs reported in Table 1; for each of these perpetrator drugs, co-prescribed drugs that may be victims of such interactions were identified by using the Flockhart table of CYP substrates and the drug bank database (https://go.drugbank.com/). To identify potential DDIs caused by the combination drug perpetrators and victims we examined individual drug therapies with the free drugs.com DDI checker (https://www.drugs.com/drug_interactions.html). This DDI checker classifies drug interaction as major- therapy must be modified-, moderate- caution is advised- and minor- not clinically relevant.

4.2 Inclusion and exclusion criteria

Inclusion criteria:

- age > 65 years;
- "chronic" treatment (i.e. of at least 3 month duration) with at least 5 different active drug ingredients;
- the presence in therapy of at least one of the perpetrators drugs listed in Table 1.

Exclusion criteria:

- artificial, enteral or parenteral nutrition;
- continuous intravenous therapy;
- terminal renal failure in treatment with hemodialysis or peritoneal dialysis;
- Chronic Class C liver failure according to Child-Pugh;
- malignant neoplasms treated with chemotherapy;
- immunosuppressive therapy for systemic autoimmune diseases or organ transplantation.

4.3 Endpoints

Primary endpoint:

- Identification of the potential drug victims which are prescribed in combination with the drug-gene combos listed in Table 1;

Secondary endpoints:

- Prevalence of potential DDGI;
- Prevalence of symptomatic interactions.

4.4 Estimation of sample size and statistical analysis

To calculate sample size, we used the Statulator Sample Size Calculator for Estimating a Single Proportion (https://statulator.com) and the prevalence data from our pilot study, which are reported in Appendix 1. More specifically, we calculated the number of records to be examined to match the expected prevalence of drug use with a level of confidence of 95% and a precision interval of 5%. Considering that the closer to 0,5 is the expected prevalence, the larger will be the sample size, and considering that, amongst the active principles reported in Table 1, Atorvastatin (prevalence 0,3) is the drug with the prevalence closest to 0,5, we calculated sample size based on atorvastatin data. Calculations showed that 323 records had to be examined to be 95%

confident that between 25% and 35% of subjects in the population take atorvastatin. Lower values were obtained for all the other perpetrator drugs in Table 1.

5 Results

5.1.1 *Study population*

Table 2 reports the main characteristic of the study population which consisted of 348 patients (189 males) with a median age of 75 years [69-79]. As per inclusion criteria, recruited patients were all on polypharmacy and the median number of the drugs they were taking was 8 [6-10]. All patients were affected with multiple chronic diseases and the median number of comorbidities was 6 [5-8]. Specifically, arterial hypertension affected almost the 60% of patient cohort whereas type II diabetes and dyslipidaemia were observed in almost 30% of it. Also carotid artery stenosis, non-terminal chronic renal insufficiency, atrial fibrillation and BPCO were very frequently occurring diseases in our study population.

Table 2. Main characteristics of the study population

	n	Percentage
Age	75 [69-79]	
Gender	189 males	54.3
Number of taken drugs	8 [6-10]	
Number of comorbidities	6 [5-8]	
Most prevalent diseases		
arterial hypertension	202	57,9
Type II diabetes	104	29,8
dyslipidaemia	104	29,8
Carotid artery stenosis	100	24
chronic renal failure	68	19,5
Atrial fibrillation	63	18,1
BPCO	56	16
Benign prostatic hyperplasia	50	14,3
goiter	40	11,5
Diverticular disease	24	6,9
Mixed anxiety-depressive disorder	23	6,6
hypoacusia	18	5,2
Hypertensive cardiopathy	18	5,2
cognitive decline	17	4,9
hypothyroidism	17	4,9

5.2 Victims of perpetrator drugs acting on CYP3A4

Drug therapy included one of the CYP3A4 inhibitors listed in Table 1 (i.e. Amlodipine, Esomeprazole, Omeprazole, or Pantoprazole) in 251 patients (72.12% of the whole patient population). When we examined the drugs that were prescribed in combination with these CYP3A4 inhibitors we found that many of them are metabolized by CYP3A4 and, consequently, may be victim of CYP3A4-related DDIs or DDGIs. The most prevalent among them were the same CY3A4 inhibitors mentioned before (i.e. Amlodipine, Esomeprazole, Omeprazole, or Pantoprazole), which are, at the same time, CYP3A4 inhibitors and substrates. Clopidogrel, whose activation is partly CYP3A4-dependent, was taken by about 25% of the patients, whereas the two β-blockers bisoprolol and carvedilol were included in the drug therapy of about 20% of the patients. Table 3 reports the full list of the CYP3A4 substrates, which may be involved in DDIs and DDGIs caused by Amlodipine, Esomeprazole, Omeprazole, or Pantoprazole, that we identified in our patient cohort.

Table 3. CYP3A4 substrates which may be victim of DDIs and DDGIs caused by Amlodipine, Esomeprazole, Omeprazole, or Pantoprazole

Victim Drug	Number of patients	Percentage
Pantoprazole	93	37,05
Atorvastatin	81	32,27
Esomeprazole	80	31,87
Omeprazole	68	27,09
Clopidogrel	64	25,49
Amlodipine	60	23,90
Carvedilol	49	19,52
Bisoprolol	42	16,73
Warfarin	29	11,55
Simvastatin	26	10,35
Tiotropium	23	9,16
Doxazosin	19	7,56
Amiodarone	15	5,97
Nebivolol	15	5,97
Rifaximin	15	5,97
Rosuvastatin	15	5,97
Fluticasone	14	5,57
Omega 3	14	5,57
Escitalopram	13	5,17

Tamsulosin	13	5,17
Apixaban	12	4,78
Metoprolol	11	4,38
Salmeterol	11	4,38
Silodosin	11	4,38
Ranolazine	10	3,98
Prednisone	8	3,18
Ticagrelor	8	3,18
Alfuzosin	7	2,78
Alprazolam	7	2,78
Clonidine	7	2,78
Ivabradine	6	2,39
Losartan	6	2,39
Quetiapine	6	2,39
Sertraline	6	2,39
Fenofibrate	5	1,99
Paracetamol	5	1,99
Lansoprazole	4	1,59
Lercanidipine	4	1,59
Nifedipine	4	1,59
Repaglinide	4	1,59
Trazodone	4	1,59
Verapamil	4	1,59
Beclometasone	3	1,19
Bromazepam	3	1,19
Linagliptin	3	1,19
Propranolol	3	1,19

In the following Table 4, we list the main potential DDIs that we retrieved by crossing the drug perpetrators Amlodipine, Esomeprazole, Omeprazole, or Pantoprazole, with the drug victims identified in the present study. Most of these interactions were scored as moderate but two of them were rated as

major: the interaction between amlodipine and simvastatin and the interaction between the PPIs omeprazole and esomeprazole and clopidogrel. However, in the latter case, CYP3A4 inhibition only plays a minor role being the named PPIs also inhibitors of CYP2C19, the main cytochrome in the process of activation of this antiplatelet drug.

Table 4. Potential DDIs involving CYP3A4 and the drug perpetrators and victims identified in our older adult cohort.

Perpetrator	Victim	Interaction severity	Interaction
Amlodipine	Atorvastatin	moderate	Increased atorvastatin plasma levels and risk of atorvastatin toxicity
Amlodipine	Carvedilol	moderate	Increased carvedilol plasma levels and risk of carvedilol toxicity
Amlodipine	Bisoprolol	moderate	Increased bisoprolol plasma levels and risk of bisoprolol toxicity
Amlodipine	Simvastatin	Major	Increased simvastatin plasma levels and risk of simvastatin toxicity
Amlodipine	Nebivolol	moderate	Increased nebivolol plasma levels and risk of nebivolol toxicity
Amlodipine	Apixaban	moderate	Increased apixaban plasma levels and risk of apixaban toxicity
Amlodipine	Metoprolol	moderate	Increased metoprolol plasma levels and risk of metoprolol toxicity
Amlodipine	Prednisone	moderate	Increased prednisone plasma levels and risk of prednisone toxicity
Amlodipine	Alprazolam	moderate	Increased alprazolam plasma levels and risk of alprazolam toxicity
Amlodipine	Trazodone	moderate	Increased trazodone plasma levels and risk of trazodone toxicity
Amlodipine	Propranolol	moderate	Increased propranolol plasma levels and risk of propranolol toxicity
Omeprazole	Clopidogrel	Major	Decreased activation of the prodrug clopidogrel and loss of therapeutic efficacy

Omeprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Omeprazole	Atorvastatin	moderate	Increased atorvastatin plasma levels and risk of atorvastatin toxicity
Omeprazole	Escitalopram	moderate	Increased escitalopram plasma levels and risk of escitalopram toxicity (omeprazole also blocks CYP2C19)
Omeprazole	Nifedipine	Minor	Increased nifedipine plasma levels and risk of nifedipine toxicity
Omeprazole	Warfarin	moderate	Increased warfarin plasma levels and risk of warfarin toxicity
Omeprazole	Trazodone	Minor	Increased trazodone plasma levels and risk of trazodone toxicity
Esomeprazole	Clopidogrel	Major	Decreased activation of the prodrug clopidogrel and loss of therapeutic efficacy
Esomeprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Esomeprazole	Atorvastatin	moderate	Increased atorvastatin plasma levels and risk of atorvastatin toxicity
Esomeprazole	Escitalopram	moderate	Increased escitalopram plasma levels and risk of escitalopram toxicity (omeprazole also blocks CYP2C19)
Esomeprazole	Warfarin	moderate	Increased warfarin plasma levels and risk of warfarin toxicity
Pantoprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Pantoprazole	Warfarin	moderate	Increased warfarin plasma levels and risk of warfarin toxicity

5.3 Victims of perpetrator drugs acting on CYP2D6

The two CYP2D6 inhibitors, Amlodipine and Omeprazole, that we identified in working paper D8.9 as potential perpetrators of CYP2D6-related DDIs and DDGIs in older adults, were included in the drug therapy of 109 patients of our cohort (31.3% of the whole population). The list of CYP2D6 substrates that could act as a victim in DDIs and DDGIs involving these CYP2D6 inhibitors was smaller than in the case of CYP3A4. Carvedilol was the most prevalent among them as it was found in about 16% of cases, whereas simvastatin, doxazosin and tiotropium were included in about 10% of the prescriptions. The two β-blockers: atenolol and nebivolol were found in more than 7% of the drug prescriptions examined.

Table 5. CYP2D6 substrates which may be victim of DDIs and DDGIs caused by Amlodipine, or Omeprazole

Victim Drug	Number of patients	Percentage
Carvedilol	18	16,51
Simvastatin	13	11,92
Doxazosin	11	10,09
Tiotropium	11	10,09
Atenolol	8	7,33
Nebivolol	8	7,33
Tamsulosin	6	5,50
Ticlopidine	6	5,50
Metoprolol	4	3,66
Ranolazine	4	3,66
Escitalopram	3	2,75
Quetiapine	3	2,75
Trazodone	3	2,75
Clonidine	2	1,83
Formoterol	2	1,83
Nifedipine	2	1,83
Acetaminophen	2	1,83
Sertraline	2	1,83
Citalopram	1	0,91
Donepezil	1	0,91
Flecainide	1	0,91

The analysis of the potential DDIs involving CYP2D6 that could arise through the interaction of the drug perpetrators identified in D8.9 and the drug victims that we found in the present study showed two potential major DDIs: the first involving simvastatin and amlodipine and the second omeprazole and citalopram (Table 6). In both cases, however, the role played by CYP2D6 seems to be minor. In fact, both amlodipine and omeprazole also block other CYPs more significantly involved in the metabolism of the two mentioned victims. Specifically, amlodipine is expected to act on simvastatin mainly through the blockade of CYP3A4 whereas CYP2D6 is expected to play only a minor role in the metabolism of this statin. Likewise, most of citalopram is metabolized by CYP2C19 and CYP3A4 while CYP2D6 is involved in the generation of the minor metabolite didemethylcitalopram (Bezchlibnyk-Butler and Aleksic, 2000). The remaining interactions identified by the drug.com interaction checker were mostly scored as moderate. The most prevalent among them involved β-blockers in combination with amlodipine. Also in this case, it is quite obvious that this kind of interaction may involve other mechanisms independent from CYP2D6 blockade especially if we consider that, given that these drugs act on similar but non-identical pharmacological targets, their interactions are mainly pharmacodynamic in nature.

Table 6. Potential DDIs involving CYP2D6 and the drug perpetrators and victims identified in our older adult cohort.

Perpetrator	Victim	Interaction severity	Interaction
Amlodipine	Carvedilol	moderate	Increased carvedilol plasma levels and risk of carvedilol toxicity
Amlodipine	Simvastatin	Major	Increased simvastatin plasma levels and risk of simvastatin toxicity
Amlodipine	Atenolol	moderate	Increased atenolol plasma levels and risk of atenolol toxicity
Amlodipine	Nebivolol	moderate	Increased nebivolol plasma levels and risk of nebivolol toxicity
Amlodipine	Metoprolol	moderate	Increased metoprolol plasma levels and risk of metoprolol toxicity
Omeprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Omeprazole	Escitalopram	moderate	Increased escitalopram plasma levels and risk of escitalopram toxicity (omeprazole also blocks CYP2C19)
Omeprazole	Nifedipine	Minor	Increased nifedipine plasma levels and risk of nifedipine toxicity
Omeprazole	Citalopram	Major	Increased citalopram plasma levels and risk of citalopram

			toxicity (omeprazole also blocks CYP2C19)

5.4 Victims of perpetrator drugs acting on CYP2C19

In the analysis of geriatric drug prescriptions reported in the working paper D8.9 we found both CYP2C19 inhibitors (the PPIs esomeprazole, omeprazole and pantoprazole), which could synergize with loss of function genetic variants of this cytochrome, and inducers (rifaximin), which, instead, are expected to increase the effect of the CYP2C19*17 gain of function polymorphism. A total of 239 patients (68.7%) of the cohort examined in the present study was treated with one of the CYP2C19 inhibitors. Table 7 reports the CYP2C19 substrates that were co-prescribed with these inhibitors and could be victim in DDIs and DDGIs with them. As already described for CYP3A4, also in the case of CYP2C19, the involved CYP inhibitors (esomeprazole, omeprazole and pantoprazole) are also potential substrates of this enzyme and, as a matter of fact, they rank in the first three places of the “drug victim” list with a prevalence of about 30%. Notably, a quarter of the patients taking CYP2C19 inhibitors were also treated with clopidogrel, an antiplatelet prodrug which is activated upon CYP2C19 metabolism, and about 10% of them were taking warfarin or simvastatin.

Table 7. CYP2C19 substrates which may be victim of DDIs and DDGIs caused by esomeprazole, omeprazole and pantoprazole

Victim Drug	Number of patients	Percentage
Pantoprazole	93	38,5892
Esomeprazole	80	33,195
Omeprazole	68	28,2158
Clopidogrel	62	25,7261
Warfarin	27	11,2033
Simvastatin	25	10,3734
Doxazosin	18	7,4689
Nebivolol	14	5,8091
Amiodarone	13	5,3942
Escitalopram	12	4,9793
Apixaban	10	4,1494
Quetiapine	6	2,4896
Sertraline	6	2,4896
Bromazepam	3	1,2448
Propranolol	3	1,2448

Citalopram	2	0,8299
Diclofenac	2	0,8299
Formoterol	2	0,8299
Lansoprazole	1	0,4149
Paroxetine	1	0,4149

When we looked at the potential DDIs (and, consequently, DDGIs) that could involve the victim drugs listed in Table 8 and the drug perpetrators acting on CYP2C19 identified in working paper D8.9 and listed in Table 1, we found several interactions scored as major. More specifically, they were: 1 the interaction of the PPIs omeprazole and esomeprazole with the SSRI escitalopram, and 2 the interaction of omeprazole and esomeprazole with clopidogrel. The remaining interactions, which involved warfarin or simvastatin as victims, were rated as *moderate* by the drugs.com interaction checker.

Table 8. Potential DDIs involving CYP2C19 and the drug perpetrators and victims identified in our older adult cohort.

Perpetrator	Victim	Interaction severity	Interaction
Omeprazole	Clopidogrel	Major	Decreased activation of the prodrug clopidogrel and loss of therapeutic efficacy
Esomeprazole	Clopidogrel	Major	Decreased activation of the prodrug clopidogrel and loss of therapeutic efficacy
Omeprazole	Warfarin	moderate	Increased warfarin plasma concentration and risk of bleeding
Esomeprazole	Warfarin	moderate	Increased warfarin plasma concentration and risk of bleeding
Pantoprazole	Warfarin	moderate	Increased warfarin plasma concentration and risk of bleeding
Omeprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Esomeprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Pantoprazole	Simvastatin	moderate	Increased simvastatin plasma levels and risk of simvastatin toxicity
Omeprazole	Escitalopram	moderate	Increased escitalopram plasma

			levels and risk of escitalopram toxicity (omeprazole also blocks CYP2C19)
Esomeprazole	Escitalopram	moderate	Increased escitalopram plasma levels and risk of escitalopram toxicity
Omeprazole	Citalopram	Major	Increased citalopram plasma levels and risk of citalopram toxicity
Esomeprazole	Citalopram	Major	Increased citalopram plasma levels and risk of citalopram toxicity

Only 21 patients (6.0% of the whole population) were treated with the CP2C19 inducer rifaximin. As this drug is poorly absorbable, the clinical relevance of DDIs and DDGIs involving rifaximin is uncertain. Nonetheless, it has been suggested that generic rifaximin could be absorbed to a higher extent than brand preparations (Blandizzi et al., 2014). Moreover, some DDIs may take place in the intestinal mucosa, which is known to be involved in the presystemic metabolism of many drugs. Esomeprazole was the CYP2C19 substrate most frequently co-prescribed with rifaximin as it was found in about 50% of the patients taking this drug, followed by clopidogrel and doxazosin taken by almost 15% of the group (Table 9).

Table 9. CYP2C19 substrates which may be victim of DDIs and DDGIs caused by rifaximin

Victim Drug	Number of patients	Percentage
Esomeprazole	10	47,62
Clopidogrel	3	14,28
Doxazosin	3	14,28
Pantoprazole	3	14,28
Warfarin	3	14,28
Omeprazole	2	9,52
Escitalopram	1	4,76
Formoterol	1	4,76
Lansoprazole	1	4,76
Melatonin	1	4,76
Nebivolol	1	4,76
Quetiapine	1	4,76

Ticlopidine	1	4,76

We identified only one DDI involving the CYP2C19 inducer rifaximin and the oral anticoagulant warfarin. It was scored as moderate (Table 10).

Table 10. Potential DDIs involving CYP2C19, its inducer rifaximin and the drug victims identified in our older adult cohort.

Perpetrator	Victim	Interaction severity	Interaction
Rifaximin	Warfarin	moderate	Warfarin effects may be either increased or decreased

5.5 Victims of perpetrator drugs acting on SLCO1B1

Drug therapy included at least one of the SLCO1B1 inhibitors (Atorvastatin, Digoxin, Pantoprazole, Rosuvastatin or Simvastatin) in 229 patients (65.8% of the whole cohort). The SLCO1B1 substrates that were most frequently co-prescribed with these inhibitors and could act as their victims in DDIs and DDGIs were atorvastatin, digoxin, simvastatin, and rosuvastatin, all taken by more than 10% of the patients of this group. The full list of the SLCO1B1 substrates is reported in Table 11.

Table 11. SLCO1B1 substrates which may be victim of DDIs and DDGIs caused by Atorvastatin, Digoxin, Pantoprazole, Rosuvastatin or Simvastatin

Victim Drug	Number of patients	Percentage
Atorvastatin	121	52,83
Digoxin	34	14,84
Simvastatin	31	13,53
Rosuvastatin	23	10,04
Olmesartan	18	7,86
Valsartan	15	6,55
Ezetimibe	9	3,93
Enalapril	7	3,05
Repaglinide	7	3,058

The analysis of the potential DDIs involving SLCO1B1 and the perpetrator and victim drugs identified in the present study disclosed only one moderate interaction between digoxin and atorvastatin (Table 12). Interestingly, one of the drug victims identified in our cohort, namely enalapril, also behaves as a drug perpetrator and may cause an interaction in which digoxin is the victim. Also this interaction is scored as moderate.

Table 12. Potential DDIs involving SLCO1B1, and the drug perpetrators and victims identified in our older adult cohort.

Perpetrator	Victim	Interaction severity	Interaction
Atorvastatin	Digoxin	moderate	Increased digoxin plasma levels (about 20%) and risk of digoxin toxicity
Enalapril	Digoxin	moderate	Increased digoxin plasma levels (about 20%) and risk of digoxin toxicity

6 Discussion

Precision medicine aims to design and deliver the best therapy for every single patient based on his/her individual characteristics. Traditionally, the interest of precision medicine has been focused on genetic variability but many additional factors which, among the others, include age, gender, ethnicity, concomitant disease status and therapy may all impact on patient response to medicines and should be accounted for in tailoring individual treatments. Even though they have been neglected for a long time, older adults represent a very special case for precision medicine because of the many variables that may influence drug response in these subjects. In fact, they are very often affected by multiple diseases, are on polypharmacy and may have liver and kidney failure, which impair drug clearance. The issue of polypharmacy can be especially worrisome in these patients because of because of the many potential interactions that may arise that may arise among the different drugs taken. The severity of drug-drug interactions is affected by the individual genetic background since crucial pharmacogenes on which the interacting drug exert their effect often show a significant individual variability. Task 8.5, of which the present working paper represents the final report, focused on precision medicine in older adults, an issue in which IDMP may have important practical applications. In fact, to reduce the risk of dangerous DDIs medical doctors examine drug prescriptions with the help of DDI checkers, searching for potentially interacting drugs that should be replaced with safer non-interacting medicines. However, these DDI checkers have several intrinsic limitations such as not considering the effect of polymorphic variations in key pharmacogenes. In addition, available DDI checkers either work with commercial drug names and can be used only in the specific country for which they were developed, or they adopt active principles thus requiring the user to identify the ones contained in the medicines the patient is taking. IDMP coding could greatly help in designing DDI checkers to be used in different countries with no limitations related to commercial names.

The work that we performed in task 8.5 was intended to gather useful information for the future design, in the post-UNICOM era, of an IDMP- and pharmacogenomic-based DDI checker. Whereas in the first part of the project we identified the “perpetrator drug”-pharmacogene combos that could more frequently cause DDIs and DDGIs in older adults, in the second part of the project we performed a clinical pilot study, whose results are reported in the present working paper D8.10, to identify in real world conditions their victims and the most common DDIs (and DDGIs) in which they could be involved. The results shown in the 12 tables of the present report represent a list of drugs whose IDMP coding should be prioritized for the development of an IDMP/pharmacogenomic based DDI checker to be used in older adults.

Most of the potential interactions that we identified by using the drugs.com interaction checker were rated as moderate, meaning that caution should be taken but therapy does not necessarily need to be modified. Few serious potential interactions were identified. Among them, the interaction between simvastatin and amlodipine, two drugs which are very often used in combination in older adults but that can significantly increase the risk of statin-induced myopathy because of amlodipine-induced inhibition of simvastatin degradation. Another interaction rated as major was that occurring between citalopram and either omeprazole or esomeprazole. Different mechanisms could be involved in this interaction considering that PPIs may reduce the activity of multiple CYPs that take part in citalopram metabolism including CYP2C19 AND CYP2D6. Among the moderate interactions it is worth to mention those involving amlodipine and several beta blockers because these drugs can interact both by pharmacokinetic and by pharmacodynamic mechanisms leading to an increase in the risk of hypotension, bradycardia and bradyarrhythmia and, consequently, of syncope and falls.

The analysis of the medical records of the patients taking part in the study did not show any evidence of clinically significant events attributable to DDIs. This could be explained by several considerations: 1. we examined only pharmacokinetic DDIs which usually cause clinically relevant consequences when therapy is changed but not during chronic therapy; 2. The study population was quite small; 3. We did not stratify patients according to their pharmacogenotype and, therefore, we do not know whether any patient with risky genetic polymorphisms were recruited in the study.

7 Conclusions

In conclusion, with the present working paper D8.10 we have extended and integrated the findings of our previous working paper D8.9, by identifying the drug victims of common perpetrator drug-gene combos in the real-world conditions of older adults followed at geriatric clinics of a large University Hospital. We also examined the potential DDIs that could originate when these drug victims are given together with the mentioned perpetrator drug combos pinpointing those that are rated as major and, therefore, require changes in therapy to prevent serious clinical consequences.

The information gathered in working paper D8.9 and D8.10 can be considered instrumental for further steps to be taken in the post-UNICOM future research to develop IDMP-based DDI and DDGI checkers. We identified, indeed, some of the drugs and genetic variants that should be prioritized because of their relevance in older adults, the patient group in which more often serious DDI occur.

8 References

Bahar M, Setiawan D, Hak E, Wilffert B. Pharmacogenetics of drug–drug interaction and drug–drug–gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6. Pharmacogenomics 2017;18:701–39. doi: 10.2217/pgs-2017-0194. Epub 2017 May 8. PMID: 28480783.

Bezchlibnyk-Butler K, Aleksic I, Kennedy SH. Citalopram--a review of pharmacological and clinical effects. J Psychiatry Neurosci. 2000 May;25(3):241-54. PMID: 10863884; PMCID: PMC1407724.

Blandizzi C, Viscomi GC, Marzo A, Scarpignato C. Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers. Pharmacol Res. 2014 Jul;85:39-44. doi: 10.1016/j.phrs.2014.05.001. Epub 2014 May 14. PMID: 24836868.

Cataldi M, Celentano C, Bencivenga L, Arcopinto M, Resnati C, Manes A, Dodani L, Comnes L, Vander Stichele R, Kalra D, Rengo G, Giallauria F, Trama U, Ferrara N, Cittadini A, Taglialatela M. Identification of Drugs Acting as Perpetrators in Common Drug Interactions in a Cohort of Geriatric Patients from Southern Italy and Analysis of the Gene Polymorphisms That Affect Their Interacting Potential. Geriatrics (Basel). 2023 Aug 24;8(5):84. doi: 10.3390/geriatrics8050084. PMID: 37736884; PMCID: PMC10514861.

Hanlon, J. T., Perera, S., Newman, A. B., Thorpe, J. M., Donohue, J. M., Simonsick, E. M., et al. (2017). Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. J. Clin. Pharm. Ther. 42, 228–233. doi: 10.1111/jcpt.12502

Mair A, Fernandez-Llimos F, Alonso A, Harrison C, Hurding S, Kempen T, Kinnear M, Michael N, McIntosh J, Wilson M. and The SIMPATHY consortium Polypharmacy management by 2030: a patient safety challenge. Scotland: The Simpathy Consortium, 2017 https://ec.europa.eu/chafea/health/newsroom/news/documents/polypharmacy-handbook-second-edition_en.pdf (accessed on 10/18/2021)

Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017 Oct 10;17(1):230. doi: 10.1186/s12877-017-0621-2. PMID: 29017448; PMCID: PMC5635569.

Onder G, Marengoni A, Russo P, Degli Esposti L, Fini M, Monaco A, Bonassi S, Palmer K, Marrocco W, Pozzi G, Sangiorgi D, Buda S, Marchionni N, Mammarella F, Bernabei R, Pani L, Pecorelli S; Geriatrics Working Group of the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA); Medicines Utilization Monitoring Center Health Database Network. Advanced Age and Medication Prescription: More Years, Less Medications? A Nationwide Report From the Italian Medicines Agency. J Am Med Dir Assoc. 2016 Feb;17(2):168-72. doi: 10.1016/j.jamda.2015.08.009. PMID: 26441359.

Onder G, Vetrano DL, Cherubini A, Fini M, Mannucci PM, Marengoni A, Monaco A, Nobili A, Pecorelli S, Russo P, Vitale C, Bernabei R. Prescription drug use among older adults in Italy: a country-wide perspective. J Am Med Dir Assoc. 2014 Jul;15(7):531.e11-531.e15. doi: 10.1016/j.jamda.2014.04.005. Epub 2014 May 28. PMID: 24878216.

Shaw, J, Seal R, Pilling M. for the Task Force on Medicines Partnership, National Prescribing Centre, National Collaborative Medicines Management Services Programme (Great Britain). Room for review. A guide to medication review : the agenda for patients, practitioners and managers. 2002 London (United Kingdom) : Task Force on Medicines Partnership. ISBN 0954402804

Verbeurgt P, Mamiya T, Oesterheld J. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. Pharmacogenomics. 2014 Apr;15(5):655-65. doi: 10.2217/pgs.14.6. PMID: 24798722.

WHO Medication Safety in Polypharmacy. Geneva: World Health Organization; 2019 (WHO/UHC/SDS/2019.11). Licence: CC BY-NC-SA 3.0 IGO. (https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11)