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Article

Prevalence of drug-drug interactions and duplicate therapy in chronic patients in Switzerland: a real-world data study

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Abstract:

The primary purpose of this study was to determine the prevalence of drug-drug interaction (DDI) and duplicate therapy in chronic patients in a completely random study population engaged in digital health apps in Switzerland. In this cross-sectional study, polypharmacy checks for 100 completely anonymous patients were analyzed for the occurrence of DDIs and duplicate therapy. Logistic regression models were used to identify factors associated with DDIs and duplicate therapy. DDIs and duplicate therapy prevalence were 34% and 33%, respectively. Chi-Square test discovered a significant association between the DDIs and duplicate therapy variables. Logistic regression models showed a strong association between the number of medications taken and higher odds of DDIs occurring in our population only. In conclusion, our study shows that polypharmacy is a determining factor for the occurrence of unwanted DDIs, and the prevalence of duplicate therapy and DDIs is around 33%, increasing an issue regarding patient safety and its burden to the healthcare system.

Keywords: polypharmacy, duplicate therapy, digital health, inappropriate prescribing, contraindicated drugs, drug-drug interactions, pharmacoepidemiology.

1. Introduction

According to the World Health Organization (WHO), in 50% of the cases, medicines are irrationally prescribed or sold. Furthermore, up to half of the chronic illness patients do not adhere to their prescribed treatment regime[1]. Common examples of inappropriate drug use are polypharmacy, inadequate prescription of antibiotics, inappropriate self-medication by patients and the non-adherence to treatment[1].

Polypharmacy is known as the continuous co-prescription of various drugs to treat multiple chronic diseases or symptoms in a patient. Often, these drugs are prescribed using disease -specific guidelines and target specific disease goals without considering comorbidities and medications patients are already taking[2]. Consequently, the higher the number of medications taken by chronic patients, the more likely the occurrence of adverse drug reactions (ADR), medication

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errors, drug-drug interactions, low adherence, higher use of healthcare services, and higher mortality risk[3-6].

Apart from health risks, the inappropriate use of medicines presents elevated costs in the healthcare system. In the USA, adverse drug events make it to the top 10 causes of death, and its costs are calculated to range between $30 and $130 billion each year[7]. The same situation has also been observed in other countries like Japan[8], Germany[9] and Italy[10]. Therefore, finding ways to prevent and control patient medication errors is a substantial need.

Harmful DDIs due to polypharmacy are observed and assessed commonly in hospitalized patients and specific diseases [11-15]. However, until now, no work has studied the real-world polypharmacy patterns in patients by analyzing their intake of prescribed and over the counter (OTC) drugs and medication consumption using digital health apps.

In this cross-sectional study, it is described for the first time the distribution of DDIs and polypharmacy based on real-world data from chronic patients in Switzerland using the TOM Medications app. TOM medications is a digital health app that helps patients follow their therapy by reminding them daily when to take the medications, together with additional functionalities for keeping track of their well-being.

2. Results

Four hundred and five (405) medicines were taken by 100 patients included in this study with an average (SD) of 4.05 ± 1.226 medication intake per user.

Participants in our study used a combination of several formulations of medicines, including tablets, inhalators (nebulizers or nasal sprays), liquid formulations, parenteral injections, and ophthalmological preparations. The most frequent formulation used by TOM users were oral formulations with 90.9 %, followed by liquid preparations (3.7 %) and inhalators (2.7 %). In Figure 1, it is shown the distribution of pharmaceutical formulations in our study group.

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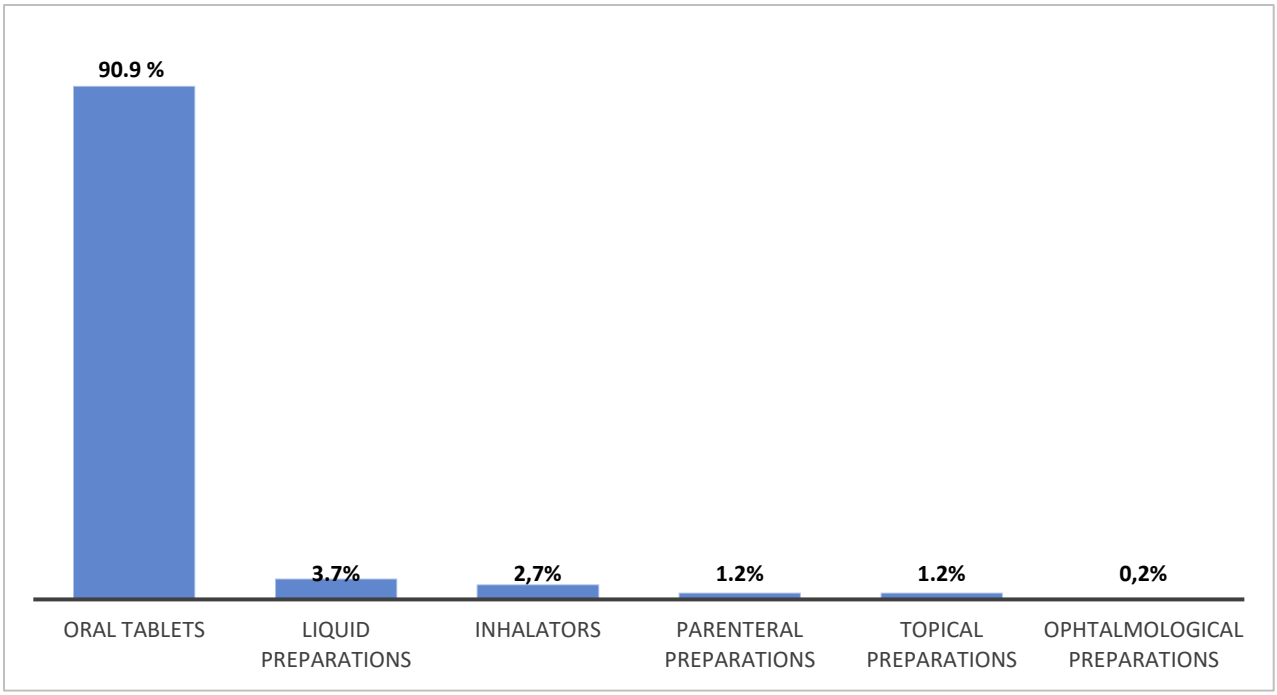

Figure 1: Distribution of medicines by pharmaceutical formulation.

The most frequently used medicines were pantoprazole (n=23) and aspirin cardio (n=15), taken by 22 % and 15% of our study population, respectively. These medicines were followed by paracetamol (n=11) and metformin (n=11), used by 11,11% of patients included in this study. On a higher level, when classifying by therapeutic class, the five most used drugs belong to anti-inflammatory and rheumatoid products (11,6%), antithrombotic medicines (7,4 %), drugs for related acid disorders (6,9%), antidiabetics (5,7%) and antihypertensives (5.2%). A descriptive frequency table of all used medicines can be found at Supplementary Table. 1.

Prevalence of potential drug-drug interactions (DDIs)

45 potential DDIs were detected in 34 % of the study population, with an average (SD) of 1.32 ± 0.589 per patient.

DDIs were then classified into five relevant classes based on the severity of the detected interaction. Our analysis showed that 6,7 % of the analyzed polypharmacy checks had at least one DDI classifiable as class 1 (the combination is contraindicated due to severe life-threatening consequences), whereas 11.1% were identified as class 2 (major interactions, where one of the medicines should be discontinued), and 51.1 % of the DDIs had at least one class 3 drug combination that needs clinical monitoring and dose adjustment to reach optimal therapy related outcomes. Similar distribution patterns were also seen in the confirmed DDIs with the two online drug databases, Medscape drug-drug interaction checker and Epocrates online, shown in Supplementary Table 2 and Supplementary Table 3.

Table 1: Frequency of potential DDIs

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Relevance Class of DDI	Frequency
Class 1: serious life-threatening interaction	6,7%
Class 2: life-threatening interaction, one of the drugs needs to be discontinued	11.1%
Class 3: moderate life-threatening, clinical monitoring and dose adjustment needed	51.1%
Class 4: minimal risk	8.9%
Class 5: slight/possible interaction	22.2%

Methylphenidate, Trazodone and Mirtazapine were the most frequent medicines involved in 8,88 % of the DDIs (n=4). They were followed closely by metformin, ibuprofen, bisoprolol and irbesartan hydrochlorothiazide and amlodipine valsartan hydrochlorothiazide involved in 7,14% of the DDIs (n=3). Figure 2 presents an overview of the prescription frequency and the incidence of DDIs. Interestingly, 8 out of 43 drugs (17,7 %) were involved in DDIs and interacted with more than one drug in the same therapy. The drugs involved in more than one DDI in the same therapy were clarithromycin, trazodone, mirtazapine, methylphenidate, bupropion hydrochloride, and irbesartan hydrochlorothiazide (Supplementary Table 4).

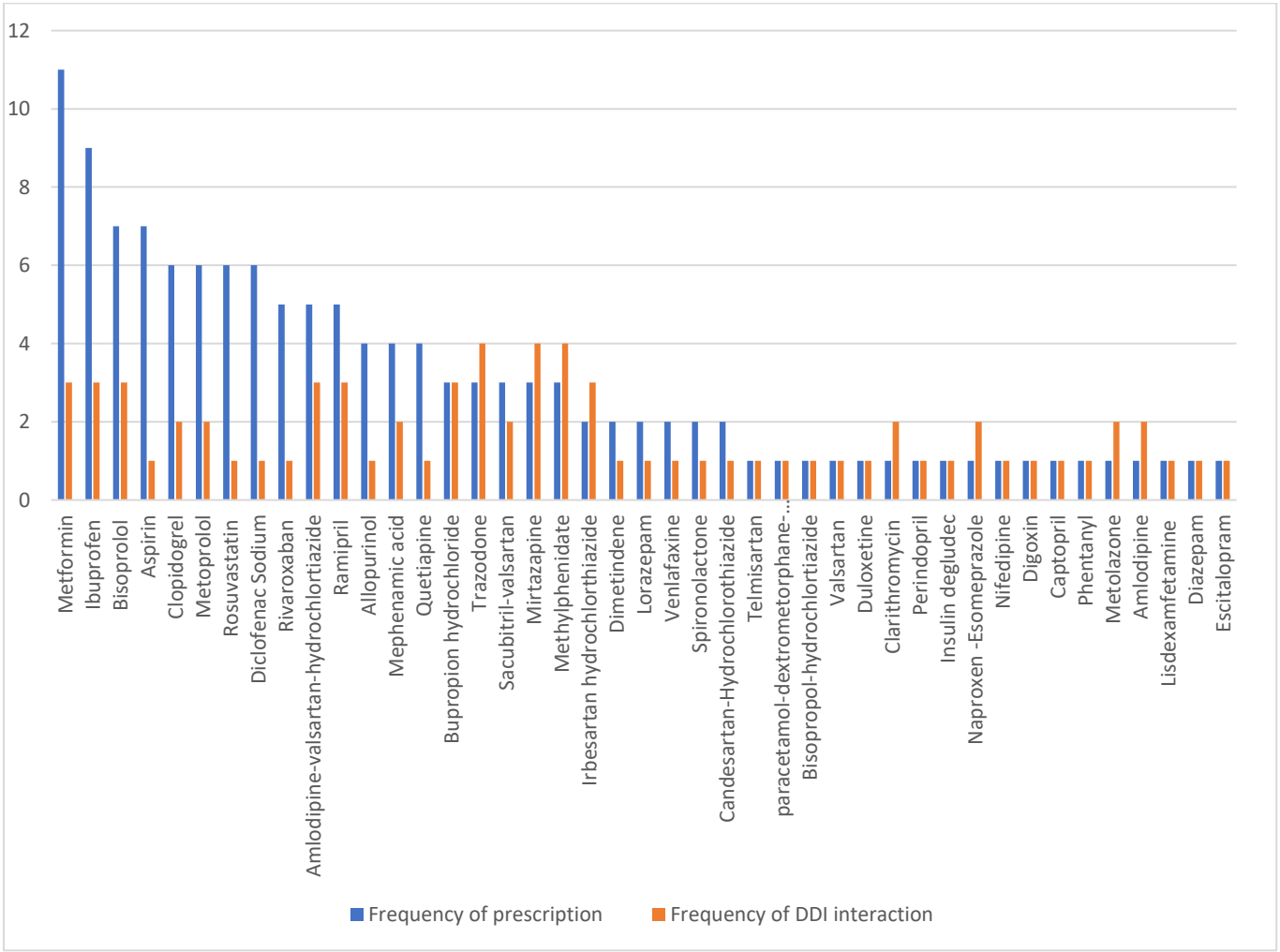

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Figure 2: Overview of the frequency of prescribed medicines and their involvement in DDIs.

The mechanism of action involved in the interactions was pharmacodynamic in 61 % (n=18) of the cases, pharmacokinetic in 4,2 % (n=2) and unknown in 31 % (n=9) of the time. Supplementary Table 5 presents a summary of interacting medicine pairs identified in this research study with a probability of clinical significance (moderate, major, and contraindicated).

To determine clinical severity on a deeper level, the organs affected physiologically by the occurrence of DDIs were analyzed. Our results show that 51,1 % of the DDIs affected the cardiovascular system, 22,2 % of the DDIs affected the nervous system, and 13,3 % affected the endocrine system. Only 2 % of the DDIs affect multiple organs in the organisms, causing an anaphylactic effect in the body (Fig. 3).

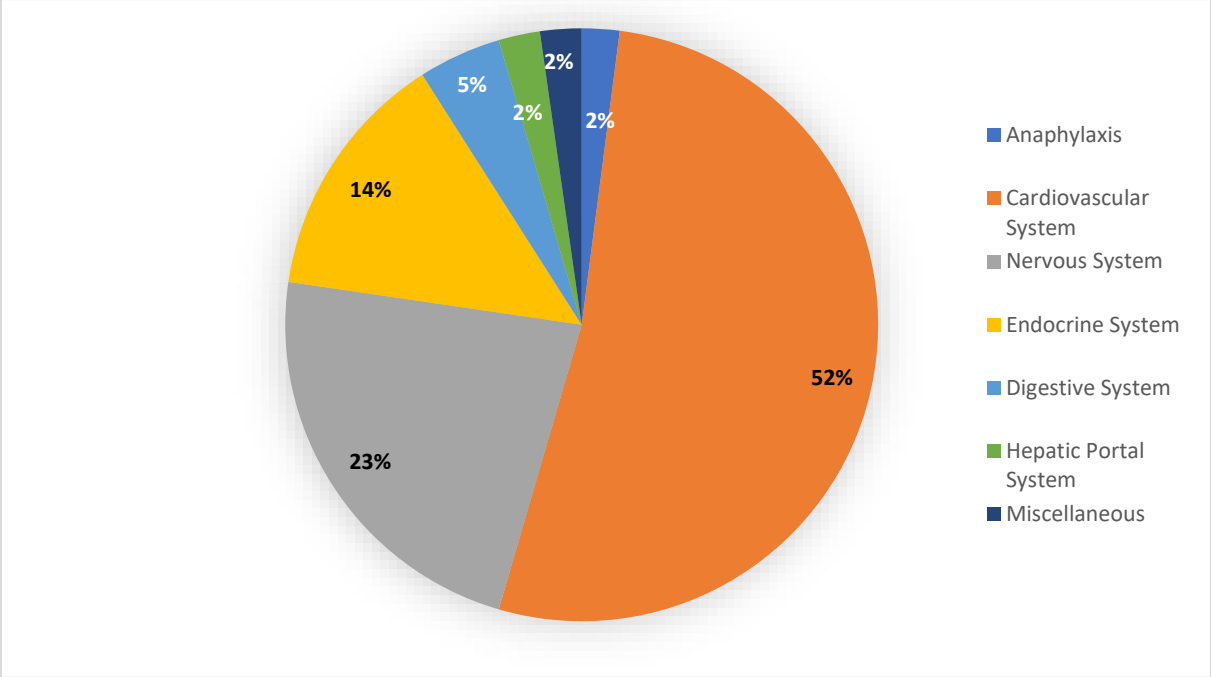

Figure 3: Distribution of DDIs effects among physiological organ systems.

Subsequently, the clinical effects of the moderate, major, and contraindicated DDIs were studied. By analyzing such interactions, an understanding is built about the symptoms and quality-of-life effects which patients experience when taking these medications together over time.

Hypotension (12,6%) was the most prevalent experienced symptom resulting from the potential DDIs, followed by bradycardia (9,2%), hyperglycemia (8%) and central nervous system (CNS) depression (6,9 %). This number correlates with the affected organ systems distribution shown above, where the cardiovascular system was the most affected, followed by the nervous and endocrine systems.

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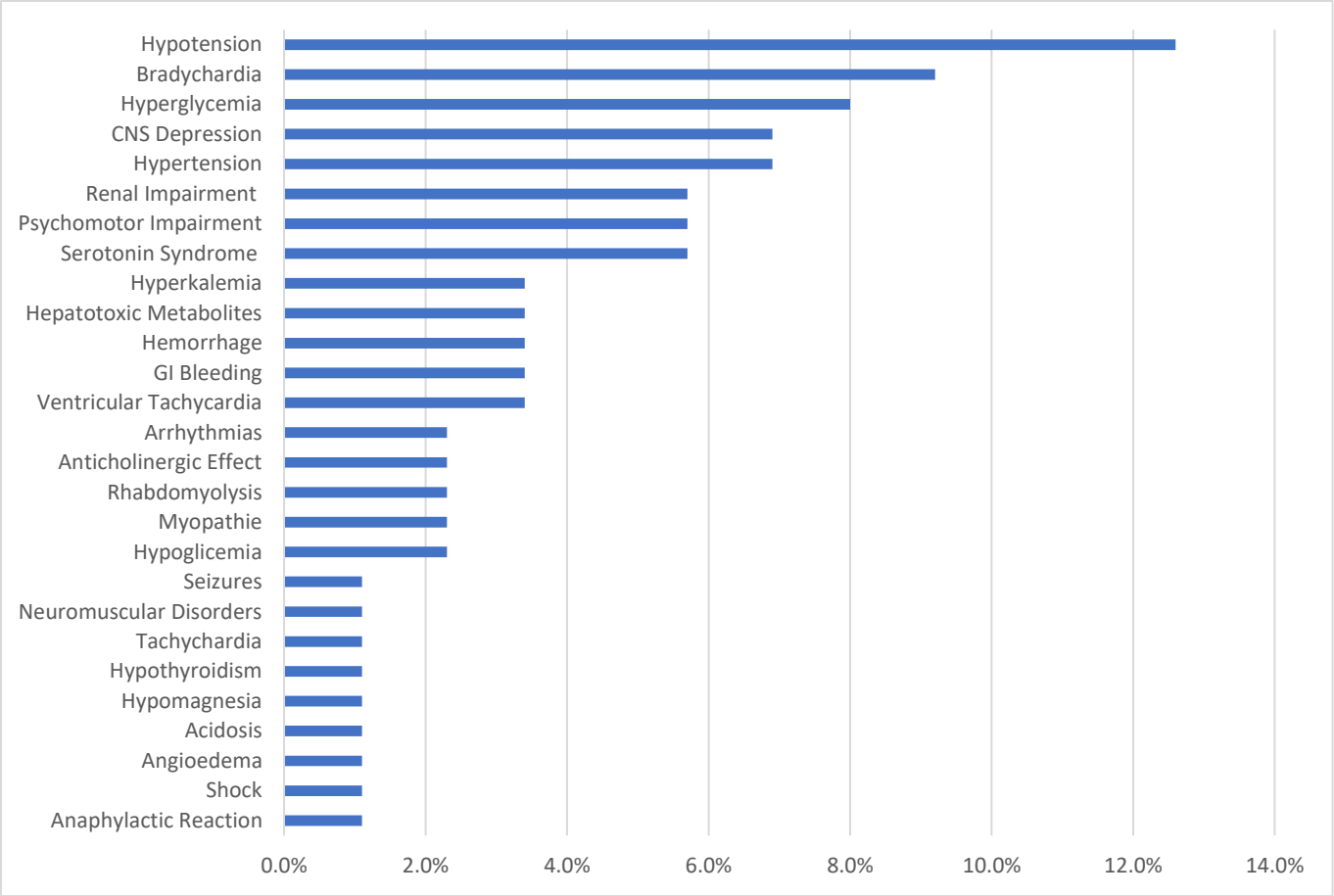

Figure 4: Frequency of potential DDI Symptoms

Prevalence of duplicate therapy

Apart from the potential DDIs in our study populations, the unwanted duplicate therapy prevalence were analyzed. Duplicate therapy is a common practice of prescribing two or more medications for the same purpose, indication or similar pharmacological activities without a clear distinction of when one agent should be administered over the other [16]. While sometimes a combination of drugs is deliberately prescribed to improve the patients' health, taking the same medication twice can result in toxic side effects and a reduction in their well-being.

Our analysis shows that 33 % of our study group were subject to duplicate therapy. A more detailed analysis of the data showed that 33,3 % of the positive duplicate therapy cases were unwanted duplicate therapies, and 45,5 % were potentially unnecessary duplicate therapies. According to our results, only in 21,2% the combination therapy is wanted (Supplementary Table. 6).

Further, indications for which drugs were mostly taken in duplicate therapies were analysed. In 42.4% of the cases, duplicate therapies were taken for the treatment of cardiovascular diseases, followed closely by drugs taken for the management of pain symptoms in 30,3 % of the cases, and nervous system disease and diabetes with 9,1 %.

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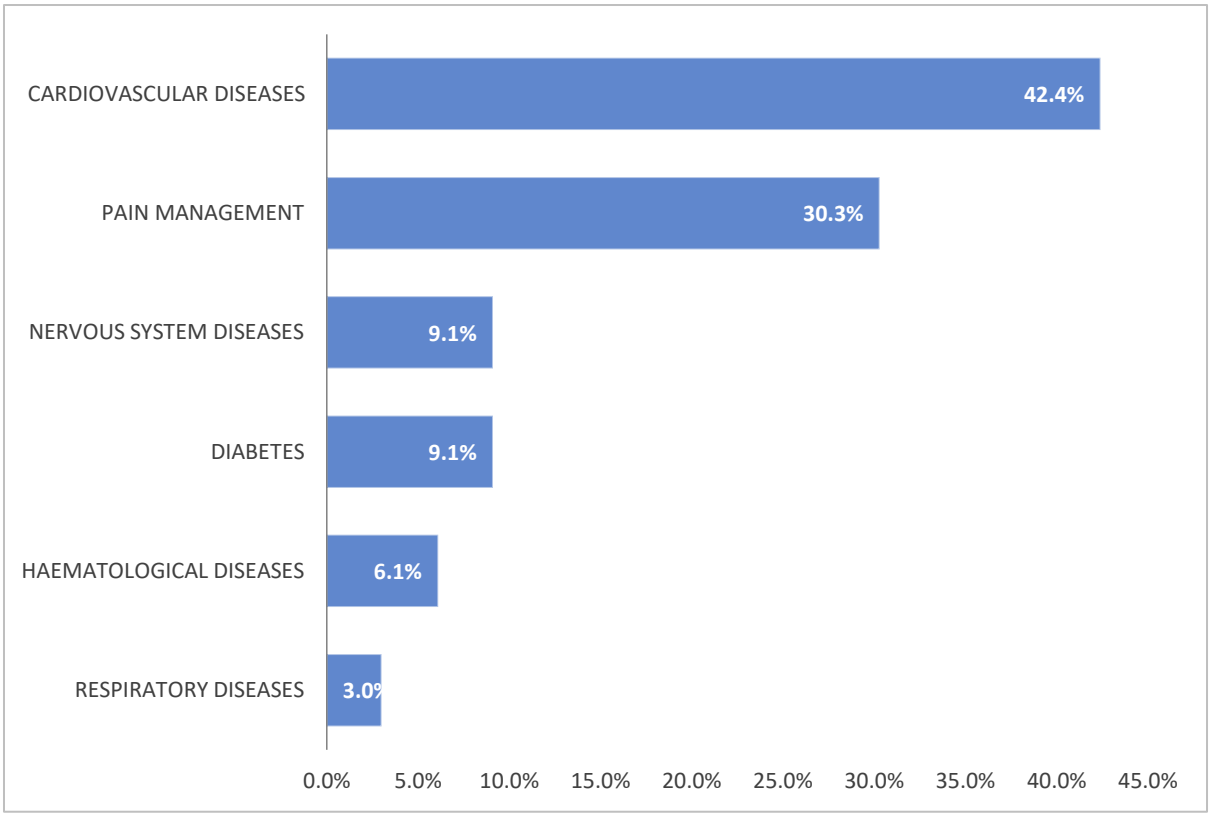

Figure 5: Distribution of possible indications in duplicate therapy

When classified according to the therapeutic class, the antihypertensive drugs make up 30,1 % of the medications used in duplicate therapy in our study populations. The second highest intake of medications belongs to the non-steroid anti-inflammatory drugs (NSAIDs) with 24,2 %, and the antithrombotic agents are the third group with 12,1 %.

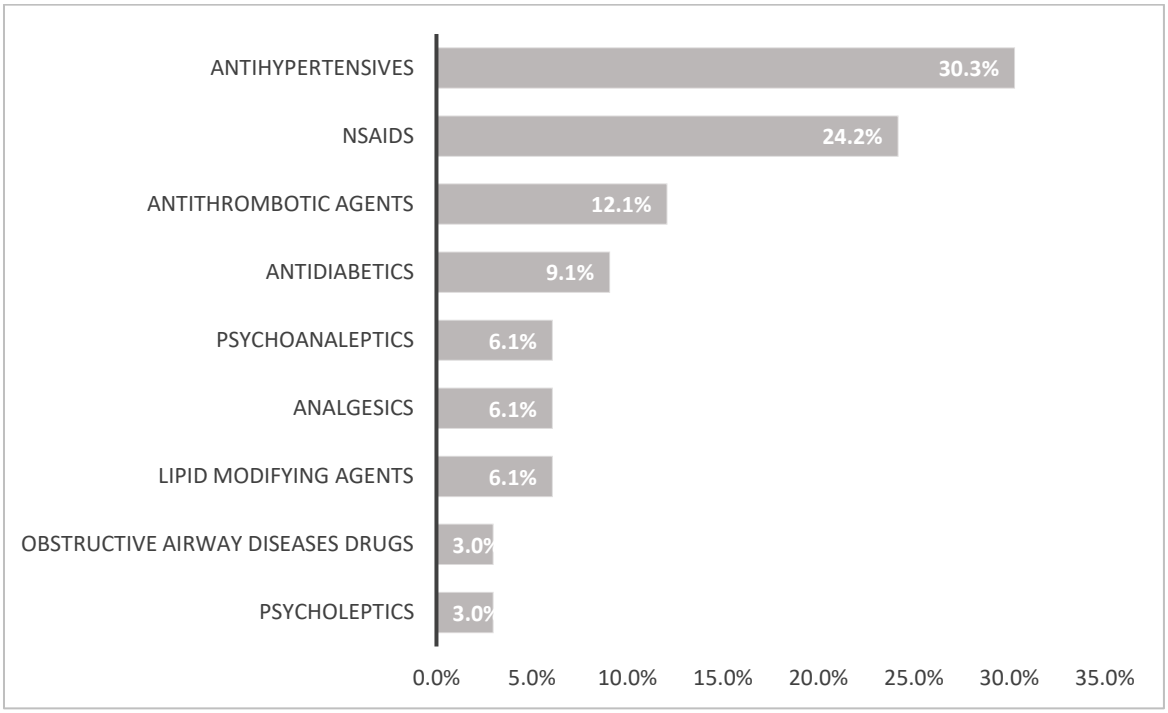

Figure 6: Frequency of therapeutic classes in duplicate therapy

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The Pearson Chi-Square test revealed a strongly significant positive association between the patients taking a duplicate therapy and the possibility of a DDI being present as well (Table 2. And Supplementary Table 7).

Table 2: Pearson Chi-Square and Likelihood Ratio Estimates

	Value	*df*	*Significance*
Pearson Chi-Square	9.265	1	0.002
Continuity Correction	7.949	1	0.005
Likelihood Ratio	9.073	1	0.003
Linear by Linear Association	9.172	1	0.002
N valid of cases	100	1	

The number of prescribed medications was strongly associated with an increased probability of DDIs with an odds ratio of 2.044 (95%CI 1.33-3.133, p=0.01). Contrary to the association identified with the Pearson Chi-Square test, our logistic regression model did not identify duplicate therapy as a strong variable for an increased number of DDIs (Table 4). Neither the medication number nor the DDIs were significantly associated with an increased probability of a duplicate therapy (Supplementary Table 8).

Table 3: Logistic regression model of predictors of DDIs.

Covariate	*OR (Exp (B))*	*95 % Confidence Interval*	*P value*
The total number of medications	2.044	(1.333, 3,133)	0.01
Is there a duplicate therapy present?	0.445	(0.167, 1.189)	0.107

3. Discussion

This study sheds light on the real-world prevalence of duplicate therapy and drug-drug interactions in Switzerland and its link to polypharmacy in the general swiss population using digital health tools. Our results show that DDIs were prevalent in our polypharmacy study population with a frequency of 34 %. Furthermore, 17 8% of patients with prevalent DDIs experience serious life-threatening side effects, whereas, for the majority, 51,1% of dose adjustments of the medicines and close monitoring are recommended to benefit from the therapy.

The most frequent drugs involved in DDIs belonged to the antihypertensives (15,9 %), psychoanaleptics (15,9%), NSAIDs (12.5 %) and ACE-I/ARB (9,1 %) therapeutic classes. Interestingly,

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these are similar to our study's therapeutic classes involved in duplication therapy. Antihypertensives (30,3 %) were the highest class being prescribed as duplicate therapy, followed by NSAIDs (21.2 %). When comparing the distribution of the therapeutic class in our study's entire medication usage, an interesting picture is seen. While NSAIDs are the highest taken medication class from all participants in this study (11, 6%), antihypertensives are the 5th most frequently used class (5,2%), and psychoanaleptics (4.7 %) and ACE-I/ARB (4.7%) are positioned lower. There is a higher likelihood of antihypertensives being the most predisposed therapeutic class to be involved in DDIs and duplicate therapies. This fact has been previously reported in a cross-sectional investigation. Drug-related problems (DRP) affected 50% of the patients and were most frequently encountered for "Drugs for the Cardiovascular System" and caused by inappropriate duplication of the therapeutic group or active ingredient. Our data show a similar pattern of DDI and duplicate therapy distribution [17].

Similarly, a study analyzing the effect of potential DDIs and polypharmacy in the Caribbean showed that polypharmacy and the presence of hypertension were associated with a higher risk of DDIs [18]. Patients suffering from cardiovascular diseases show higher rates of DDIs presence. This finding is vital since cardiovascular diseases are the leading cause of deaths, with 17,9 (32%) million people dying from cardiovascular diseases globally[19]. It can be possible that duplicate therapy and DDIs have their share in the high morbidity and mortality rate of CVD patients.

The prevalence of DDIs in our study group is 34% which is a similar rate to other published findings [20, 21]. Our results with 17,8% of the population carrying serious life-threatening DDIs are higher than the 4,4% of the Danish patients [22] and 3,8 % of HIV-infected patients in Spain [23], but much lower than the 69% of the American pediatric patients admitted to ICUs[24]. These differences can be explained by the difference in the study population groups. In the Danish population, only elderly patients and their prescription database are studied. However, patients have access in their day-to-day activities to many over the counter drugs which can interact with the prescribed drugs. In our analysis, we show that NSAIDs make up 12,5 % of the medicines that are involved in DDIs. NSAIDs are commonly sold as OTC drugs without prescription in every pharmacy.

Regarding the two other studies, the difference lies in the different population groups. One of the groups above consists of HIV patients, who, due to their immunocompromised system are not a good representative of the general population. The second study is focused only on pediatric patients admitted to the intensive care unit and is not representable of TOM's study population, where most of the patients suffer cardiovascular diseases, diabetes, and central nervous system diseases. Nevertheless, our results are similar to the 18,2 % of the severe DDIs seen in the emergency department patients in the Caribbean, where 18,2 % of the patients, both old and young, presented potential severe DDIs in their therapy [18].

The second finding in our study shows that the prevalence of duplicate therapy in our study populations is 33 %. This number is higher than 11,1 % of a real-world study performed in Catalonia [25], and the 2,5 % of the REPOSI study hospitalized elderly in Italy [26]. The difference in prevalence with the studies performed in Catalonia is explained with the fact that they only included geriatric patients and the contraindicated duplication therapies in their study. Our results show that 21,2 % of the analyzed duplication therapies could be wanted combinations. Regarding the REPOSI study, hospitalized old patients were included in the study. Patients using the TOM app are not hospitalized

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and are not in continuous observation by the nurses and doctors. Nevertheless, our finding is very similar to 39% observed in an American primary care study [27], which presents a closer resemblance to the conditions of chronic patients in our study group.

NSAIDs are the drugs leading the category of unwanted duplicate therapy, which comes with no surprise since they are easy to access drugs bought without a prescription, even in high doses. Several studies showed that although NSAIDs are generally considered safe can so easily, patients performing self-medication without control can easily exceed the daily dose limit for each drug [28-30]. According to Schiffman et al., in a one-week diary study, in 24,1 % of the cases, patients exceeded the daily dose (EDL) for these drugs, and EDL was associated with deviations from detailed dosing directions. These patients exhibited an attitude of "choosing my own dose" and not starting with the lowest dose, as well as poor knowledge of the recommended 1-time and 24-hours doses [29]. Following the findings in these studies, it is also possible for patients in our study group to exceed the daily dose of NSAIDs or pain killers.

Our study shows an association between polypharmacy and a higher odds ratio of the occurrence of the DDIs, but not with the presence of duplicate therapy. This association was shown in several studies on various diseases [31]. One study showed that even mild polypharmacy increases the risk of dementia in older adults and that the presence of DDIs is responsible for this effect in 70,4% of the cases [31]. On the contrary, the only study that could not show a significant association between polypharmacy and DDIs was done in Korean patients diagnosed with cancer [20]. However, the same study showed a significant association between polypharmacy and the hospitalization rate, which could be due to the presence of unidentified DDIs [20]. Further, our regression model could not show higher odds of duplicate therapy when a higher number of medicines are taken. While the Pearson correlation showed an association between DDIs and duplicate therapy, it was impossible to fit a significant logistic regression model for our correlation between the DDIs and duplicate therapy. Such an association has been seen in a study performed in Thailand among the elderly in primary care, where duplicate drug classes accounted for the highest proportion of potential DDIs [32]. One possible explanation could be the small sample size we have included in this study; it could be that more than 100 patients need to be included and fit into the model to establish such a correlation.

The results of this study draw attention to an important concern of the healthcare system. While treating critical diseases and making patients healthy is vital, it is equally important not to deteriorate their health and well-being due to inappropriate medication management practices. Data shows that in Germany, it is estimated that 16000 to 25000 patients die yearly due to polyreaction [33], compared to only 2700 people who die in car accidents [34]. Furthermore, studies in Switzerland, Finland and Sweden estimated that 3-5 % of all deaths could be traced back to unwanted medication events [34]. Several studies have analyzed the possibility of a better medication management system and its impact on reducing DDIs and duplicate therapies. A study where medical students performed in-home medication reviews showed that 86% of elderly patients were prescribed at least one inappropriate drug. Due to the medication reviews, changes to therapy were made to 57% of the study population. This resulted in a better health outcome for these patients and could improve patient safety [35]. While this approach proved to bring significant results, it should also be considered whether the healthcare system has the human capital capacity to rely on these approaches. While since

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the 80s, a repeat prescription card (also known as the pink card) has been suggested, it has not been implemented so far [36]. Such a card would prevent the duplication of drugs, thus helping to control both polypharmacy and iatrogenic disease.

Controlling duplication therapy is suitable not only for the patient but also for the healthcare system in general. A study performed in Japan showed that the cost of unwanted duplicated drugs was found to be 0,7 % of the total drug cost [37]. The estimated expenses for these unwanted duplicative medications were in the range of 5,2-7,2 billion yen (37,8-52,3 million $), which could be saved if the unwanted duplicative medications were eliminated nationwide [37]. Digital health advancements hold great promise in developing to improve medication management and reduce the costs of the healthcare system.

4. Materials and Methods

4.1. Study Design and sample size

This cross-sectional cohort study is based on the real-time collection of anonymous data from the polypharmacy check analysis of engaged patients in the TOM Medications app. 100 anonymous medication check results were analyzed to describe the drug-drug interaction and duplicate therapy prevalence among TOM's userbase.

The TOM medication app is an app that reminds chronic patients when to take the drug and increases adherence to therapy among human adults in the general population. The medications check is a service provided to TOM users to check for polypharmacy interactions in their therapy. This medication Check is carried out online by TopPharm Apotheke Witikon, a partner pharmacy, authorized to provide polypharmacy checks for patients.

4.2. Research Ethics and Permissions

This study is conducted using anonymous health-related personal data from TOM users. Users of the TOM Medications app do not undergo any registration process or have the possibility to insert personal data (e.g. Name or E-mail). Therefore, TOM users are anonymous at every step of the process. According to the Swiss association of the research ethics committee in the "Guidance for basic Research", this does not fall within the scope of the Human Research Act (HRA), and thus it does not require an ethics committee approval.

4.3. Study Design and sample size

Polypharmacy check data used in this study were collected from TOM Medications Content Management System (CMS). The study population consisted of 100 analyzed polypharmacy checks.

4.4. Data collection

Each TOM user's medication cabinet was analyzed for the occurrence of the DDIs with the Propharma X system provided from HCI solutions (Bern, Switzerland). The DDIs were classified based on their relevance on 5 classes: Class 1 (contraindicated interactions), class 2 (major interactions, avoid or use

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an alternative), class 3 (moderate, monitor or modify treatment), class 4 (minor, caution advised), and class 5 (observation). Subsequently, the identified DDIs were double-checked the Medscape drug interactions checker to analyze the mechanism of action of the drug-drug interactions into pharmacodynamic, pharmacokinetic or unknown, and Epocrates online. The results of the analysis were recorded in the data extraction sheet (Excel and SPSS database) used for this research study. Both the databases are considered reliable clinical support tools with sufficient sensitivity to provide dependable medical information [38]

4.5. Data and Statistical Analysis

Descriptive analysis for variables was calculated using *Statistical Package for Social Sciences SPSS* version 26, and the results from the analysis were expressed in mean and standard deviations for continuous variables and in percentages for categorical variables.

The Chi-Square test of associations was used to determine potential associated or relationships between the predictor variable (e.g. duplicate therapy) and the outcome variable (i.e. DDIs) [39]. Significant relationships identified with the Chi-Square test of associations were then fitted in logistic regression models to identify the factors associated with DDIs and duplicate therapy. The logistic regression models included the number of medications and the presence of DDIs or duplicate therapy. The analyses were carried out with SPSS for Mac, version 26 (SPSS, Chicago, IL). The significance level for statistical tests, the p values, was set at $p<0.05$.

Author Contributions: R.H. designed the statistical tests; A.B. generated the data. R.H. analyzed the data; R.H. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable

Data Availability Statement: The authors declare that all data supporting the findings of this study are available within this paper or within the Supplementary File and can be obtained from the corresponding author on request.

Conflicts of Interest: A.B. is an employee of Toppharm Apotheke Witikon, R.H. is an employee of TOM Medications (Innovation 6 AG). Otherwise, the authors declare no conflict of interest.

Abbreviations

ACE-I	Angiotensin Converting Enzyme Inhibitor
ADR	Adverse Drug Reactions
ARB	Angiotensin Receptor Blocker
CMS	Content Management System
CNS	Central Nervous System
CVD	Cardiovascular Diseases
DDI	Drug-Drug Interactions
DRP	Drug Related Problems
HIV	

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ICU	Human Immunodeficiency Virus
NSAID	Intensive Care Unit
OTC	Non-Steroid Anti-inflammatory Drugs
SD	Over the Counter
SPSS	Standard Deviations
WHO	Statistical Package for Social Sciences
	World Health Organization

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Supplementary data file:

Supl. Table 1: The frequency of all therapeutic classes used in our study population

	Frequency	*Percent*
Drugs for acid related disorders	28	6.9
Drugs for functional Gastrointestinal Disorders	5	1.2
Antiemetics and Antinauseants	2	.5
Drugs for Constipation	2	.5
Antidiarrheals, Intestinal Anti-inflammatory agents	1	.2
Antidiabetics	23	5.7
Vitamins	11	2.7
Mineral Supplements	4	1.0
Other Alimentary Tract and Metabolism products	3	.7
Antithrombotic Agents	30	7.4
Cardiac Therapy	1	.2
Antihypertensives	21	5.2
Diuretics	8	2.0
Beta blocking Agents	16	4.0
Calcium Channel Clockers	7	1.7
Agents acting on the Renin-Angiotensin-System	19	4.7
Lipid modifying agents	19	4.7
Antipruritic	1	.2
Corticosteroids, Dermatological preparations	2	.5

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Other Dermatological Preparations	1	.2
Sex hormones and modulators of gynecological system	1	.2
Urologicals	12	3.0
Pituitary and hypothalamic hormones	3	.7
Corticosteroids for systemic use	3	.7
Thyroid Therapy	9	2.2
Antibacterial	7	1.7
Antivirals	4	1.0
Antineoplastic Agents	1	.2
Anti-inflammatory and Antirheumatic products	47	11.6
Muscle Relaxants	2	.5
Antigout Preparations	4	1.0
Analgesics	15	3.7
Antiepileptics	10	2.5
Psycholeptics	12	3.0
Psychoanaleptics	19	4.7
Nasal Preparations	5	1.2
Drugs for Obstructive Airway Diseases	10	2.5
Cough and Cold Preparations	4	1.0
Antihistamines	6	1.5
Other Respiratory System Products	1	.2
Ophtalmologicals	1	.2
Other Nervous system Drugs	5	1.2
Herbal Products	20	4.9
Total	405	100.0

Suppl. Table 2: Distribution of DDI relevance classes using Medscape drug-drug interaction.

	Frequency	*Percent*
Class 1	3	6.7
Class 2	5	11.1
Class 3	19	42.2
Class 4	2	4.4
Class 5	1	2.2
Total	30	66.7
Missing System	15	33.3
Total	45	100.0

Suppl. Table 3: Distribution of DDIs using Epocrates online.

	Frequency	*Percent*
Class 1	1	2.2
Class 2	7	15.6
Class 3	22	48.9
Total	30	66.7
Missing System	15	33.3

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Total	45	100.0

Suppl. Table 4: Frequency of the medications involved in DDIs

	Frequency	*Percent*
Diazepam	1	1.1
Clarithromycin	2	2.3
Pantoprazol	1	1.1
Escitalopram	1	1.1
Allopurinol	1	1.1
Bisoprolol	3	3.4
Perindopril-Amlodipine-Indapamide	1	1.1
Torsemide	2	2.3
Quetiapine	1	1.1
Candesartan	1	1.1
Mephenamic Acid	2	2.3
Paracetamol	1	1.1
Aspirin	1	1.1
Ibuprofen	3	3.4
Diclofenac Sodium	1	1.1
Levothyroxine	1	1.1
Rivaroxaban	1	1.1
Ramipril	3	3.4
Rosuvastatin	1	1.1
Insulin deglutec	1	1.1
Metformin	3	3.4
Irbesartan-Hydrochlorothiazide	3	3.4
Naproxen	1	1.1
Clopidogrel	2	2.3
Sacubitril-Valsartan	2	2.3
Mirtazapine	4	4.5
Amlodipine	2	2.3
Dimentindene	1	1.1
Amlodipine-Valsartan-Hydrochlorothiazide	3	3.4
Lisdexamphetamine dimesylate	1	1.1
Bupropion hydrochloride	3	3.4
Valsartan	1	1.1
Metolazone	2	2.3
Perindopril-Amlodipine	1	1.1
Simvastatin	1	1.1
Lorazepam	1	1.1
Estradiol-Dydrogesterone	1	1.1
Acemetacin	1	1.1
Sitagliptin	1	1.1
Ramipril-Hydrochlorothiazide	2	2.3
Moxonidine	1	1.1
Metoprolol	2	2.3
Phenytoin	1	1.1
Telmisartan	1	1.1
Candesartan-hydrochlorothiaze	1	1.1

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Venlafaxine	1	1.1
Nifedipine	1	1.1
Digoxin	1	1.1
Captopril	1	1.1
Bisoprolol-Hydrochlorothiazide	1	1.1
Naproxen-Esomeprazole	1	1.1
Methylphenidate	4	4.5
Trazodone	4	4.5
Phentanyl	1	1.1
Duloxetine	1	1.1
Paracetamol-dextrometorphan-Pseudoephedrine-Doxylamine	1	1.1
Total	88	100.0

Suppl. Table 5: Drug-Drug Combinations mainly involved in moderate and major DDIs and their mechanism of action.

Drug-Drug Interaction		Severity	Mechanism of Action	Frequency (%)
Drug 1	Drug 2			
Allopurinol	Perindopril	Moderate	UNK	1
Bisoprolol	Insulin deglutec	Moderate	PD	1
Irbesartan-Hydrochlorothiazide	Naproxen	Moderate	PD	1
Dimentindene	Mirtazapine	Moderate	UNK	1
Mephenamic acid	Clopidogrel	Moderate	PD	1
Rivaroxaban	Ibuprofen	Moderate	PD	1
Telmisartan	Ibuprofen	Moderate	PD	1
Clopidogrel	Rosuvastatin	Moderate	PK	1
Quetiapine	Venlafaxine	Moderate	UNK	1
Bisoprolol	Nifedipine	Moderate	PD	1
Amlodipine-Valsartan-Hydrochlorothiazide	Digoxin	Moderate	PD + PK	1
Paracetamol-Dextrometorphan-Pseudoephedrine-Doxylamine	Captopril	Moderate	PD	1
Ramipril	Spironolactone	Moderate	PD	1

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Amlodipine-Valsartan-Hydrochlorothiazide	Ramipril	Moderate	PD	1
Bupropion hydrochloride	Methylphenidate	Moderate	PD	1
Bupropion hydrochloride	Trazodone	Moderate	UNK	1
Bisoprolol-Hydrochlorothiazide	Naproxen	Moderate	PD + PK	1
Amlodipine-Valsartan-Hydrochlorothiazide	Mephenamic acid	Moderate	PD	1
Lorazepam	Fentanyl	Moderate	PD	1
Valsartan	Metolazone	Moderate	UNK	1
Metoprolol	Amlodipine	Moderate	UNK	1
Metformin	Metolazone	Moderate	PD	1
Duloxetine	Mirtazapine	Moderate	UNK	1
Diclofenac Sodium	Aspirin	Moderate	PD	1
Candesartan-Hydrochlorothiazide	Ibuprofen	Moderate	PD	1
Bupropion-Hydrochloride	Lisdexamphetamine	Major	UNK	1
Trazodone	Methylphenidate	Major	PD	2
Methylphenidate	Trazodone	Major	PD	1
Clarithromycin	Diazepam	Contraindicated	PK	1
Clarithromycin	Escitalopram	Contraindicated	PD	1
Sacubitril-Valsartan	Ramipril	Contraindicated	PD	1

Suppl. Table 6: Distribution of duplicate therapies based on the intention of the duplicate therapy.

	Frequency	*Percent*
Unwanted	11	33.3
Potentially unwanted	15	45.5
Wanted	7	21.2
Total	33	100.0

Suppl. Table 7: Cross tabulation of Duplicate Therapy and DDI variables

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			Is a duplicate Therapy Present		
			Yes	No	Total
Is a DDI present?	Yes	Count	18	16	34
		Expected Count	11.2	22.8	34.0
	No	Count	15	51	66
		Expected Count	21.8	44.2	66.0
Total		Count	33	67	100
		Expected Count	33.0	67.0	100.0

Suppl. Table 8: Logistic regressiom model of predictors of duplicate therapy.

Covariate	*OR (Exp (B))*	*95 % Confidence Interval*	*P value*
The total number of Medication	1.795	(1.178, 2.737)	0.07
Is there a DDI present?	2.261	(0.850, 6.016)	0.102