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ORIGINAL RESEARCH

Prescription Advice Based on Data of Drug-Drug-Gene Interaction of Patients with Polypharmacy

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Purpose: Pharmacogenetic counselling is a complex task and requires the efforts of an interdisciplinary team, which cannot be implemented in most cases. Therefore, simple rules could help to minimize the risk of medications incompatible with each other or with frequent genetic variants.

Patients and Methods: One hundred and eighty-four multi-morbid Caucasian patients suffering from side effects or inefficient therapy were enrolled and genotyped. Their medication was analyzed by a team of specialists using Drug-PIN® (medication support system) and individual recommendations for 34 drug classes were generated.

Results: In each of the critical drug classes, 50% of the drugs cannot be recommended to be prescribed in typical drug cocktails. PPIs and SSRI/SNRIs represent the most critical drug classes without showing a single favorable drug. Among the well-tolerated drugs (not recommended for less than 5% of the patients) are metamizole, celecoxib, olmesartan and famotidine. For each drug class, a ranking of active ingredients according to their suitability is presented.

Conclusion: Genotyping and its profound analysis are not available in many settings today. The consideration of frequent alterations of metabolic elimination routes and drug–drug–gene interactions by using simple rankings can help to avoid many incompatibilities, side effects and inefficient therapies.

Keywords: single nucleotide polymorphisms, personalized medicine, precision medicine, DDGIs, CYPs, transporter

Introduction

The structure of deoxyribonucleic acid (DNA) was first described only less than 70 years ago.[1] This milestone opened an entirely new field of research, leading to a deeper understanding of heredity, diseases and their treatment.[2] Advances in molecular biology, especially regarding the human genome, led to the conception of a new scientific discipline known as pharmacogenetics or pharmacogenomics (PGx), which conflates genetics, pharmacology and biochemistry.[3] Thanks to PGx, it is possible to create a profile of a patient's gene variations, so-called single-nucleotide polymorphisms (SNPs), prior to administration of a drug. Subsequently, an optimized drug selection can be made which improves therapy outcomes and minimizes adverse drug reactions (ADRs).[3] This stands in contrast to the conventional drug therapy in which typically a wide patient population is considered to be relatively homogeneous and one-drug-fits-all or trial-and-error prescriptions are the reality.[3]

Besides the above-mentioned drug–gene interactions (DGIs), so-called drug–drug interactions (DDIs) are also known to affect both the efficacy and toxicity of drugs.[4] DDIs make up the most common causes of ADRs and occur especially in the elderly due to polymedication.[5]

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Combining DGIs and DDIs leads to a new concept called drug–drug–gene interactions (DDGIs) which improves the understanding of the drug metabolism of an individual patient, elevating Personalized Medicine to a new level.[4,6] The notion of DDGIs also helps to understand the so-called Phenoconversion, which describes a genotype–phenotype mismatch occurring due to nongenetic factors. On the one hand, Phenoconversion into a lower metabolizer phenotype can occur as a consequence of the concomitant use of CYP450-inhibiting drugs, increasing age, cancer, and inflammation. On the other hand, Phenoconversion into a higher metabolizer phenotype can result due to a concomitant use of CYP450-inducing drugs and smoking. Furthermore, pregnancy, alcohol and vitamin D exposure are suggested to be relevant factors for phenoconversion.[7]

In order to combine and analyze simultaneously the metabolic data, genomic profile and DDGIs of a patient, innovative medication support software like Drug-PIN® (Personalized Interactions Network) can be used, leading to an individual profile for each and every patient.[4]

There are several studies regarding Personalized Medicine and the administration of drugs tailored to a patient's genetic makeup. However, these studies have controversial outcomes and often only consider specific drugs or polymorphisms.[8–11] Furthermore, studies in which DDGIs as well as further traits and lifestyle habits of an individual patient have been investigated are rare and again only consider specific drug classes or diseases.[4,12,13]

This study aimed to establish a prescription ranking for drugs of commonly used drug classes, based on data of patients for which a DDGI profile was generated using the medication support software. This ranking should assist practitioners in their choice of the right drug(s) for those patients for whom no individual DDGI profile exists in order to minimize the risk of ADRs or inefficient therapies.

Patients and Methods

Study Design

We conducted a retrospective study in order to evaluate the metabolism of 281 drugs from 34 different drug classes (see Supplementary Table 1) within a collective of patients, considering their genetics as well as possible co-medication and further traits. The primary objective was to determine "critical" and "noncritical" drug classes and drugs. The secondary objective was to establish a prescription ranking for the drugs of the critical drug classes.

Study Population

Data from 184 multi-morbid Caucasian outpatients that were presented at the Centre of Personalized Medicine, Sant'Andrea University Hospital, Rome (Italy) between 2017 and 2020 were evaluated (Table 1).

Inclusion criteria were patients aged between 18 and 85 and written informed consent. Exclusion criteria were as follows: advanced age (>85 years), substance use disorders (except nicotine), neurological disorders (epilepsy, major

Table 1 Main Patient Characteristics (n = 184)

Patient Characteristics	Value
Age (years)	49.4 ± 16.5
Sex (F/M)	143/41
BMI	24.3 ± 6.2
Number of prescribed drugs	8 ± 4
GFR [mL/min]	93 ± 16
AST/ALT ratio	0.9
Number of clinically relevant polymorphisms	16.3 ± 4.6

Note: Variables are reported as mean ± standard deviation.
Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine aminotransferase.

neurocognitive disorder, Parkinson's disease) or severe acute organic illnesses (major cardiovascular disorders and hypertension, diabetes, malignancy, renal failure).

The patients' SNP data were compared with SNP data of the 1000 Genomes project and PharmGKB.

Ethical Approval

The study was approved by the Ethics Committee of the University of Rome and registered under Prot. 987/2014 and complies with the Declaration of Helsinki.

Data Collection

Genotyping

For the SNP analysis, the patients' DNA was extracted from samples of 5 mL of peripheral blood using an automatic QIAsymphony platform (Qiagen, Hilden, Germany). Subsequently, the DNA was processed using a next-generation sequencing platform (Ion Chef/Ion S5, Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer's instructions.

Drug-PIN

For each patient, an individual profile was generated using the Drug-PIN platform. It is a software that – through semantic analysis algorithms and deep learning – evaluates the pharmacological effectiveness of and interactions between drugs, considering all of the patient's traits such as: gender, age, weight, lifestyle habits, liver and kidney function, genetic data and concomitant therapies. Summarizing a single drug's grade of interaction and clinical and laboratory characteristics as well as genomic data of 100 SNPs (see Supplementary Table 2) with grade I or II clinical evidence (ref CPIC), the software generates a patient's individual score for each drug. Based on the score, drugs can be categorized into three groups: "usable", "non-preferable" and "not recommended".[4,13]

Analysis

As a first step, within each drug class the number of drugs that were considered to be either usable, non-preferable or not recommended was added up for each patient, resulting in a database for each category (usable, non-preferable and not recommended).

In a second step, the number of patients who had the same number of usable drugs within a drug class was counted and listed. The same procedure was applied to drugs considered to be non-preferable and to drugs considered to be not recommended.

In a third step, the different drug classes were compared with one another across a category. Some drug classes stood out because for many patients a high number of drugs were considered to be not recommended and/or non-preferable. These drug classes were therefore viewed as critical and subjected to further investigation.

Within the critical drug classes, we evaluated for each patient which specific drugs were considered to be not recommended. For each drug in the critical drug class, the number of patients for whom the respective drug was classified as not recommended was counted and the results were listed in a ranking as shown for PPIs in Table 2. As a last step, an overview containing all drugs from the critical drug classes was created, using data from the ranking tables.

Table 2 Ranking for PPIs

Rank	Drug	NR Patients*, n (%)
1.	Esomeprazole	11 (7.1)
2.	Rabeprazole	31 (19.9)
3.	Pantoprazole	34 (21.8)
4.	Lansoprazole	64 (41.0)
5.	Omeprazole	72 (46.2)

Notes: *n = 156. Tables for the other drug classes have been created in the same way and can be found in the supplementary materials (Supplementary Tables 3–7).
Abbreviation: NR, not recommended.

Additionally, a two-proportion Z-test was performed in order to evaluate if the SNP frequencies of the study sample and reference frequencies show the same distribution.

Results

The two-proportion Z-test shows that 49% of the SNP frequencies of the study group present the same distribution as found in the reference group ($p > 0.05$). When only considering the cytochromes P450 (CYPs), the number rises to 67%.

After evaluating the data, 6 out of 34 drug classes were considered to be critical since for over a third of the patients more than 25% of the drugs from these classes were not recommended (`ure 1A) The critical drug classes are proton-pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, H_2 antagonists, angiotensin II receptor blockers (ARBs) and selective serotonin reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs).

All of these six drug classes show a high number of patients for whom more than 25% of the drugs are not recommended. When also considering the non-preferable drugs, the number of patients doubles, peaking at 97% for SSRIs/SNRIs (Figure 1A). After only considering patients for whom more than 50% of the drugs are not recommended, the number of patient drops, with no or very few patients for COX-2 inhibitors, H_2 antagonists and ARBs. However, NSAIDs and especially PPIs and SSRIs/SNRIs still show a high number of patients. If considering also the non-preferable drugs, the number of patients rises strongly again for each drug class, peaking again for SSRIs/SNRIs at 80% (Figure 1B).

SSRIs/SNRIs represent the drug class with the highest number of patients for whom drugs are not recommended, followed by PPIs and NSAIDs and lastly by COX-2 inhibitors, H_2 antagonists and ARBs that show similar results.

The distribution of the patients for whom >25% of the drugs from the critical drug classes are considered to be not recommended or non-preferable shows a small variance (Figure 2A). A greater variance can be found when including only the patients for whom >50% of the drugs from the critical drug classes are considered to be not recommended or non-preferable (Figure 2B).

There are large differences among the rankings of the single drugs from the critical drug classes regarding the number of people for whom the drugs are not recommended (Table 2 and Supplementary Tables 3–7). Regarding PPIs, for instance, for about half of the patients, the administration of omeprazole is not recommended and for 1 patient out of 5 pantoprazole is not recommended. Esomeprazole, however, is listed as the best in the ranking and not recommended for 1 patient out of 14 (Table 2).

Within the drug classes NSAIDs, COX-2 inhibitors, ARBs and H_2 antagonists, (almost) half of the drugs are considered to be favorable since they are not recommended for only less than 5% of the patients. SSRIs/SNRIs and PPIs, on the contrary, show no favorable drug. In all drug classes except for H_2 antagonists, however, half of the drugs within the respective class are considered to be unfavorable since they were not recommended for more than 20% of the patients (Figure 3, Supplementary Tables 8–13).

Discussion

The interindividual drug response is influenced by numerous factors like age, nutrition, health status, environmental exposure, (epi)genetics and concurrent therapy.[3] More than one-tenth of patients are said to be less likely to respond to standard treatments and suffer unwarranted toxicity.[14] A systematic review of 25 prospective observational studies from 5 continents showed that 5.3% of hospital admissions were associated with ADRs. Children (<17 years) showed the lowest prevalence with 4.1%, followed by adults (17–60 years) with a prevalence of 6.3%. Elderly patients (>60 years) showed the highest prevalence with 10.7%. In adults and the elderly, the main medications that led to ADRs were cardiovascular drugs and NSAIDs.[15]

In the United States, however, the proportion of older adults taking five or more drugs tripled from 13.8% in 1994 to 42.4% in 2014. The greater the number of drugs a patient is administered, the greater the likelihood of experiencing ADRs. For elderly patients taking five or more drugs, the chance of ADRs increases by 88% compared to those taking less than three drugs. It is estimated that, due to medication overload – describing the use of multiple drugs for which the

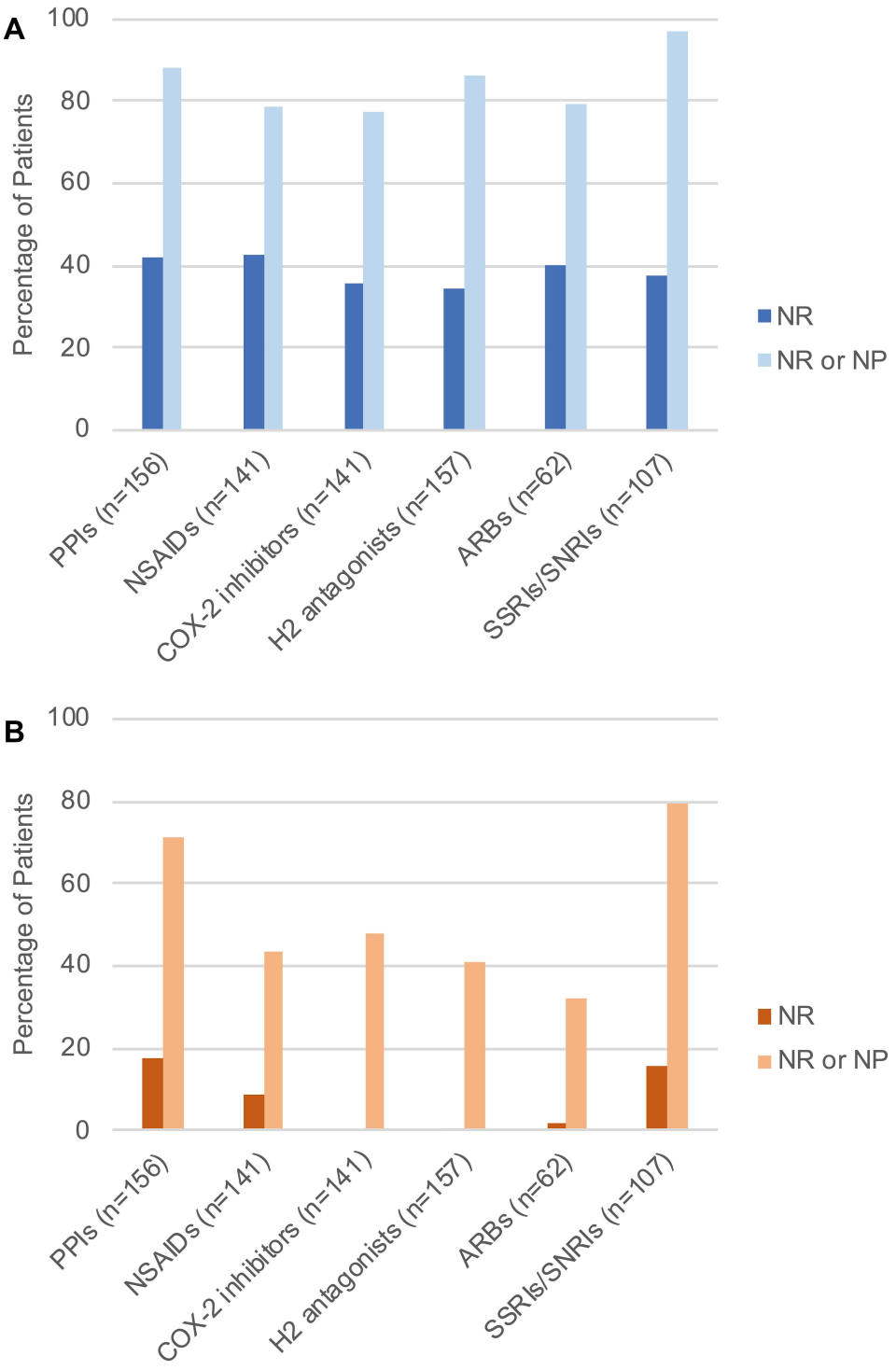

Figure 1 Percentage of patients for whom a certain share of drugs (**A** >25% and **B** >50%) of the critical drug classes were considered to be not recommended and not recommended or non-preferable, respectively.
Notes: (n = x) indicates the number of patients for whom data were available for the specific drug class. Data for this figure can be found in Supplementary Tables 8–13.
Abbreviations: NR, not recommended; NP, non-preferable.

harm to the patient is greater than the benefit – 4.6 million hospitalizations will occur between 2020 and 2030, causing costs of $62 billion and being responsible for the premature death of 150,000 elderly in the United States.[16]

Besides toxicity, the efficiency of drugs poses a problem in non-individualized drug therapy. When it comes to the ten highest-grossing drugs in the US, for every person a specific drug helps to improve the condition, between 3 and 24

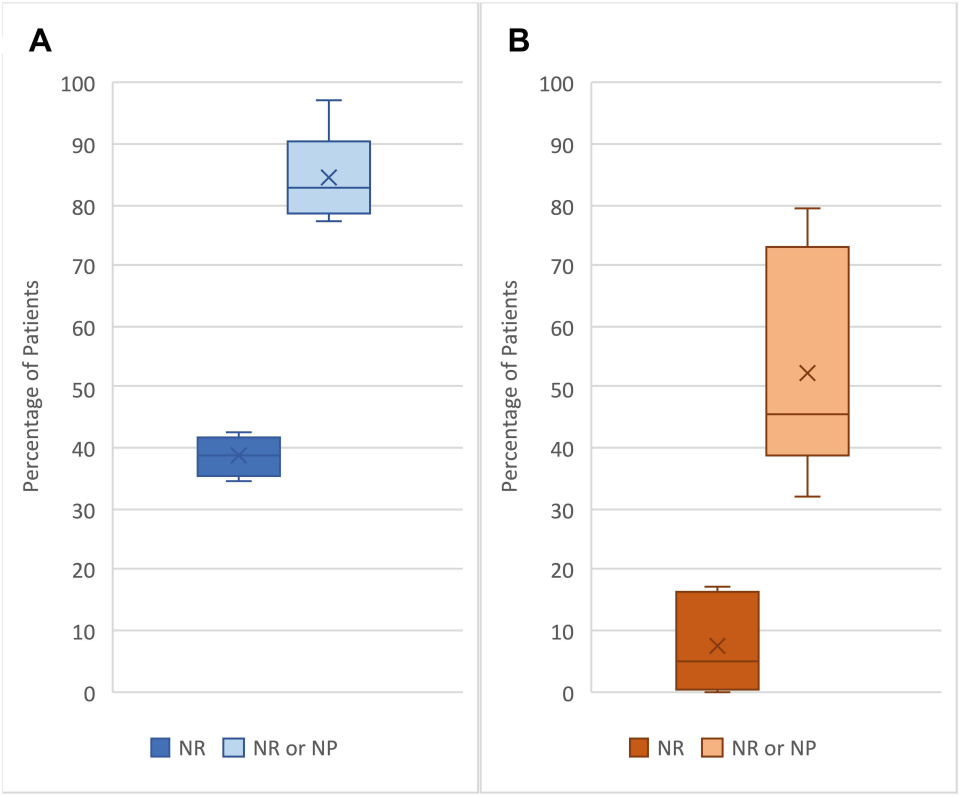

Figure 2 Distribution of patients for whom a certain share of drugs (**A** >25% and **B** >50%) were considered to be not recommended and not recommended or non-preferable, respectively. The respective boxplot shows the data of all six critical drug classes combined.
Abbreviations: NR, not recommended; NP, non-preferable.

PPIs	NSAIDs			ARBs	COX-2 Inhibitors	H_2 Antagonists	SSRIs/SNRIs
Esomeprazol	Tenoxicam	Zomepirac	Flurbiprofen	Olmesartan	Celecoxib	Nizatidine	Etoperidone
Rabeprazole	Metamizole	Naproxen	Meloxicam	Eprosartan	Lumiracoxib	Lafutidine	Escitalopram
Pantoprazole	Flufenamic acid	Acetylsalicylic acid	Ibuprofen	Telmisartan	Parecoxib	Famotidine	Duloxetine
Lansoprazole	Bufexamac	Benzydamine	Aminophenazone	Tasosartan	Valdecoxib	Roxaitidine	Paroxetine
Omeprazole	Morniflumate	Ketoprofen	Phenazone	Valsartan	Etoricoxib	Ranitidine	Fluvoxamine
	Sulindac	Mefenamic acid	Niflumic acid	Candesartan		Cimetidine	Venlafaxine
	Acemetacin	Etodolac	Diclofenac	Irbesartan			Citalopram
	Ketorolac	Lornoxicam	Indometacin	Losartan			Sertraline
	Aceclofenac	Nimesulide	Phenylbutazone				Fluoxetine
	Etofenamate	Piroxicam					

Figure 3 Overview and ranking of drugs from critical drug classes.
Notes: Drugs displayed in green are preferable drugs, since they were considered to be not recommended in <5% of the patients, drugs displayed in yellow were not recommended for 5–20% of the patients and drugs displayed in orange were not recommended for >20% of the patients. Detailed data for each drug class and drug can be found in Table 2 and Supplementary Tables 3–7.

people will not experience such an improvement.[17] The efficiency of prescribed drugs for the most common diseases lies between 50% and 60%; considering only cancer therapy, it even drops to 20%.[18] For migraine treatment, every second patient does not respond adequately to acute and prophylaxis therapies.[19] Especially for drugs with a narrow therapeutic index, the interindividual drug response has to be seriously considered.[8]

A crucial point in pharmacotherapy is to find the right dose of medication which, however, varies widely amongst patients. For instance, for the anticoagulant warfarin, dose requirements vary by 20-fold, for propranolol, an antihypertensive drug, they vary by 40-fold and for L-DOPA, used in the treatment of Parkinson's disease, the dosage even varies by 60-fold.[20]

A patient's genetic makeup regarding the enzymes and transporters involved in drug metabolism has a fundamental impact on the variability in drug response.[3] In almost every important enzyme involved in the metabolism of xenobiotics, genetic variants can be identified,[8] altering the function of an enzyme in a too rapid metabolization of a drug, rendering it ineffective, or in a too slow metabolization, provoking an increased blood concentration of the drug which potentially can lead to ADRs or, in the case of prodrugs, ineffective activation.[21] Allele frequencies differ not only between patients but also significantly among ethnic groups.[14] The large interethnic differences in both genotypes and phenotypes make the right drug choice even more complex.[22] For instance, in Caucasians, 26% of individuals are carriers of non-functional CYP2D6 alleles, which differs strongly from the proportion in other ethnic groups like Asians, Black Africans and African-Americans with a frequency of 6.4%, 6.6% and 14.7%, respectively.[23]

Besides individual genetic variability, co-medication and possible interaction between drugs have to be considered when administering drugs. Based on the fact that the ageing of the world population results in an increase in elderly people with multi-morbid conditions receiving multiple drugs, DDIs resulting in ADRs will increase and pose new challenges for physicians.[24]

The risk associated with the different drugs is calculated by the software not only on the basis of the pharmacodynamic properties but also taking into account certain patient characteristics, such as sex, age, weight, lifestyle habits (coffee, alcohol, nicotine consumption), liver and kidney function, pharmacogenetic profile and concomitant therapies.[25] The ranking is thus based on the likelihood of a drug having adverse effects in the overall context of multimorbid and poly-treated patients (which is the population most susceptible to drug-related adverse events).[26] In this way, an attempt is made to study the reality of the situation in which drugs give adverse events and to identify those that give them most often.

Although there is a large amount of evidence regarding the benefits of Personalized Medicine, it is still only rarely implemented in a practitioner's therapy. A recent review showed that the most studied PGx-driven approach can be found in CYP2C19 testing with antiplatelets, where relevant polymorphisms could be found in approximately 30% of the patients and where changing the antiplatelet reduced morbidity and mortality by more than 50%. Improved medication outcomes could also be found for other cardiovascular, psychiatric, analgesic, and gastrointestinal drugs, underlining the benefits of PGx.[27] Rodriguez-Escudero et al showed in their study that after implementing patients' PGx data to the traditional Comprehensive Medication Management pharmacists changed their pharmacotherapy-related recommendations for every patient with genetic variants, mainly due to "too high dosage" or potential DGI due to an altered metabolism. Potential DGIs based on PGx-guided Clinical decision support (CDS) reports could be found in over 20% of the total prescriptions, mostly in antidepressants, NSAIDs and PPIs[28] which corresponds with our findings.

A good example of the discrepancy between the compatibility and the frequency of prescription of a drug class is PPIs. As shown in the 2020 drug report for Germany, PPIs represent the most frequently prescribed drug class within gastrointestinal remedies, with a prescription volume of 3.65 billion defined daily doses (DDD) in 2019. Pantoprazole remains the most commonly prescribed PPI (2764 million DDD) – although there are no studies demonstrating the therapeutic superiority of pantoprazole over other PPIs – followed by omeprazole (644 million DDD) and esomeprazole (201 million DDD).[29]

Pantoprazole, omeprazole and lansoprazole are metabolized to 80% by CYP2C19 which, however, is known to be highly polymorphic.[30] Esomeprazole, on the contrary, is metabolized to a lesser extent by CYP2C19 than omeprazole.[31] Almost half of the patients in our study showed polymorphisms of CYP2C19 that influenced the phenotype (PM 3.8%, IM 23.4%, UM 21.2%). Therefore, prescribing those patients drugs that are mainly metabolized through CYP2C19, like omeprazole and lansoprazole, may lead to an unfavorable drug response due to drug-gene mismatches. This can also be shown in our results, where esomeprazole is not recommended for only 7% of the patients; pantoprazole and omeprazole, however, show figures that are about three and over six times higher, respectively. Our findings and the prescription frequencies therefore show a reverse ranking.

A similar finding can be made in other drug classes. Commonly prescribed drugs like ibuprofen (553 million DDD), diclofenac (202 million DDD), candesartan (2.281 million DDD), etoricoxib (111 million DDD), ranitidine (32 million

DDD), citalopram (261 million DDD) and venlafaxine (208 million DDD) all show an unfavorable profile within our patient collective while at the same time a much more favorable drug is available as alternative medication as displayed in Figure 3.

A key limitation of this study is its retrospective design. The patients that underwent the genotyping suffered from different diseases and therefore their concurrent medication varied in the type and number of drug(s). Furthermore, the number of patients for whom data were available varied for every drug class, ranging from 62 patients for ARBs to 156 patients for PPIs. Since only Caucasians were included in this study, our findings are not applicable to patients of other ethnicities because of the already-mentioned interethnic differences in SNP frequencies.

Lastly, the classification of the drugs does not completely correspond to the ATC codes.

Conclusion

Today, a lot of patients are still administered drugs that turn out to be unfavorable for them. The wrong choice and dosage of drug(s) leads to ADRs and failure of treatment. Genotyping patients prior to drug administration helps practitioners to choose the right drug(s) and to protect patients from unnecessary side effects. Often, the possibility of genotyping and conducting a profound individual analysis is not available. However, using simple prescription rankings can help avoid many incompatibilities and side effects as well as inefficient therapies since in most cases a more favorable medication is available.

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Disclosure

Associate Professor Robert Preissner and Professor Maurizio Simmaco are members of the Advisory Board of Drug-PIN AG. Drug-PIN AG is the holder of the patent PCT/IB2019/052310. Mr Andreas Eckert reports personal fees from Drug-Pin AG, outside the submitted work. Dr Sara Spirito reports personal fees from Drug-PIN, during the conduct of the study; personal fees from Drug-PIN, outside the submitted work. The remaining authors declare that they have no conflict of interest.

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