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A pharmacovigilance study of pharmacokinetic drug interactions using a translational informatics discovery approach

PK DDI and ADE translational discovery

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L.W, A.S, Pe.Z, and L.L conceived the study; all authors contributed to the design of the study; L.W, A.S and CW.C acquired and analyzed the data; L.W, A.S, and Pe.Z drafted the manuscript; all authors interpreted the results and made manuscript revisions; and all authors have read and agreed to the published version of the manuscript.

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US FDA's Adverse Event Reporting System
US FDA's Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers
Cytochrome P450 Drug Interactions Table

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What is already known about this subject?

Drug-drug interactions (DDIs) as well as DDI-related adverse drug events (ADEs) have been extensively studied using diverse data sources, statistical methods, and informatics approaches. These studies, although informative, tend to be disparate. Therefore, a translational approach that combines known pharmacokinetic data with pharmacovigilance data may be more informative in identifying DDI-associated ADEs.

What this study adds?

The current study used a translational informatics approach to determine ADEs associated with known cytochrome P450-related substrate and inhibitor pairs. Evidence was found for 590 ADEs related to 38 substrates and 2,085 PK DDI pairs. Overlapping analysis revealed several common ADEs that were shared among substrates of the same or different CYP isoforms. Specifically, our paclitaxel-clopidogrel interaction associated with peripheral neuropathy was supported by clinical and experimental evidence. Additionally, we found potentially novel DDI and ADE associations which should be validated in future studies.

ABSTRACT

Background: While the pharmacokinetic (PK) mechanisms for many drug interactions (DDIs) have been established, pharmacovigilance studies related to these PK DDIs are limited. Using a large surveillance database, a translational informatics approach can systematically screen adverse drug events (ADEs) for many DDIs with known PK mechanisms.

Methods: We collected a set of substrates and inhibitors related to the Cytochrome-P450 (CYP) isoforms, as recommended by the FDA and Drug Interactions Flockhart Table. FDA's Adverse Events Reporting System (FAERS) was used to obtain ADE reports from 2004 to 2018. The substrate and inhibitor information were used to form PK DDI pairs for each of the CYP isoforms and MedDRA preferred terms for ADEs in FAERS. A shrinkage observed-to-expected ratio (Ω) analysis was performed to screen for potential PK DDI and ADE associations.

Results: We identified 149 CYP substrates and 62 CYP inhibitors from the FDA and Flockhart tables. Using FAERS data, only those DDI-ADE associations were considered that met the disproportionality threshold of Ω>0 for a CYP substrate when paired with at least two inhibitors. In total, 590 ADEs were associated with 2,085 PK DDI pairs and 38 individual substrates, with ADEs overlapping across different CYP substrates. More importantly, we were able to find clinical and experimental evidence for the paclitaxel-clopidogrel interaction associated with peripheral neuropathy in our study.

Conclusion: In this study, we utilized a translational informatics approach to discover potentially novel CYP-related substrate-inhibitor and ADE associations using FAERS. Future clinical, population-based and experimental studies are needed to confirm our findings.

1. INTRODUCTION

Adverse drug events (ADEs) have been a matter of public health concern for over half a century and still continue to impose a great burden on clinical and non-clinical systems.[1-6] The incidence of ADEs has varied considerably across different studies, however, a meta-analysis of 39 prospective studies from the United States estimated an overall incidence of 15.1% for all ADEs from the combined out- and in-patient settings.[2] Polypharmacy has been consistently reported as one of the major contributing factors for ADEs, consequently increasing the risk of drug-drug interactions (DDIs).[5,7-9] A recent epidemiological review focused on the incidence of DDI-related ADEs, reporting incidences as high as 14.3% for in-hospital patients from published studies.[8] As such, drug interactions and their associated ADEs remain a matter of intense investigation, with studies using diverse data sources, statistical methods, and more recently informatics approaches to explore and identify previously unknown DDI-ADE associations.[10-13]

Food and Drug Administration's (FDA) post-marketing surveillance reporting system (SRS) called Adverse Event Reporting System (FAERS) is one of many data sources that have been evaluated for DDI-ADE associations.[14-19] Of the various statistical methods used to determine these associations,[12,20,21] disproportionality analysis (DPA) has been used frequently and refers to several frequentists and Bayesian methods that compare the observed frequency of a drug-ADE pair to its baseline frequency, assuming the drug and ADE are not related. Most of these methods were initially used to detect only single-drug effects but were later expanded to include two- and even higher-order drug combinations.[20-22] However, evaluation of two drug combinations using these SRS data sources often do not take into account the relationship between the two drugs.[23] Thus, to address this shortcoming, we focused on known pharmacokinetic (PK) mechanisms to determine a relationship between drug pairs in our study.[24,25]

Of the two broad DDI classifications, PK DDIs are more commonly evaluated,[26] and involve a precipitant drug changing either the absorption, distribution, metabolism or elimination of a victim drug. Of these, drug metabolism and its enzymes (DMEs) have been extensively studied in vitro and in vivo and

involve the different cytochrome P450 (CYP) isoforms and their related substrates and inhibitors.[27-29] These CYP isoforms are involved in metabolizing 70-80% of the drugs, with CYP2D6 alone metabolizing ~25% of the drugs.[30,31] CYP inhibitor-induced changes increase a substrates' peak concentration or exposure, thereby increasing the risk of an ADE associated with the substrate. Thus, substrate-inhibitor pairs that share the same CYP enzyme are likely to result in higher ADEs when co-prescribed and were thus used as known PK DDI pairs in our study.

In the current study, we employed a translational informatics approach to determine PK DDI and ADE associations, involving three stages (Table 1). Stage 1 was characterized by the identification of a set of known CYP-related substrates and inhibitors from existing databases. Stage 2 involved data processing of drugs, indications and ADEs in FAERS to identify unique cases with normalized drug and ADE information. Stage 3 involved disproportionality analysis of the FAERS data after identifying substrate-inhibitor pairs using information from both stage 1 and stage 2 and ADE information from stage 2 to determine substrate-inhibitor-ADE associations. The stage 3 DPA also included subsanalyses that evaluated ADEs using validated Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) and their association with a chosen subset of substrate-inhibitor pairs reported in our study.

2. METHODS

2.1 Data for PK DDIs

Several pharmacologic databases, such as DrugBank,[32] TWOSIDES,[23] DIDB,[33] have integrated a variety of DDI information. However, it is often difficult to delineate the type (PK or PD) of DDIs or the evidence for DDIs through these databases. Moreover, the underlying evidence for some of these DDIs is derived from either the FDA's tables for drug development and drug interactions[24] and Drug Interactions Flockhart Table[25]. Therefore, these two data sources were utilized in our study to identify the CYP isoform related substrates and inhibitors.

2.1.1 List of clinical substrates

Information on substrates was collected from the FDA list recommended for use in clinical DDI studies or concomitant use in clinical DDI studies and drug labeling.[24] The substrates are classified based on the extent of increase in their exposures by strong inhibitors – sensitive substrates are those that demonstrate an area under the concentration (AUC) of ≥5-fold and moderate substrates demonstrate an AUC of ≥2 to <5-fold. We collected both sensitive and moderate substrates in FDA's clinical index and clinical lists for further analysis.

Drug Interactions Flockhart Table also contains a list of substrates that are categorized based on the CYP isoforms that metabolize them, if there is published evidence to support their relationship.[25] We collected all the substrates listed in the Flockhart Table, albeit without annotation of substrate intensity. Then, all the substrates from the FDA and Flockhart tables were combined to remove drugs that were identified as substrates for multiple CYP isoforms (Table S1).

2.1.2 List of clinical inhibitors

FDA's and Flockhart's DDI tables also provide lists of inhibitors for a variety of CYP isoforms with proper annotations of inhibition potency. FDA classifies strong, moderate, and weak inhibitors as drugs that increase the AUC of sensitive index substrates ≥5-fold (≥10-fold for CYP3A), ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. We used the strong and moderate inhibitors for our analysis in this study, except for CYP2B6 for which information was only available on weak inhibitors (Table S1).

We did not encounter any disagreements between the FDA and Flockhart's data with respect to the CYP substrates and inhibitors identified.

2.1.3 Nomenclature of Targets and Ligands

Key protein and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to Pharmacology 2019/2020.[34]

2.2 FAERS data processing

For this study, we downloaded all the FAERS reports from 01/01/2004 to 9/30/2018. FAERS is a critical post-marketing drug safety surveillance system where reports on adverse events (AEs), medication errors, and quality complaints from healthcare professionals, consumers/patients and manufactures are recorded.[14] Given the mandatory reporting required by the FDA for manufactures, case duplication for an adverse event can occur if information is sent to the manufacturer but is also reported by consumers or healthcare professionals. Similarly, drug names are not uniform resulting in multiple entries for the same drug and therefore need normalization before further analysis can be conducted.

2.2.1 Drug name mapping

After an exploratory analysis of drug names in the FAERS data, we found parts in an unmapped drug name such as drug form (e.g., tablet), strength (e.g.,10 mg), and pharmaceutical salt forms (e.g., hydrochloride) which were uninformative for our analysis. Therefore, after removing these redundancies, DrugBank and RxNorm[35] were utilized to capture drug brand names (including international brands). Subsequently, all drug names were mapped into RxNorm standard ingredients. For the remaining unmapped drug names, USAGI[36] was used for the manual mapping process.

2.2.2 Case deduplication

In FAERS, one or more follow-up case versions may exist in addition to the initial case version because of the multiple reporting sources as well as data structure changes that occurred in 2012 Q3 (data reported before 2012 Q3 was called LAERS). In our study, all the available cases were extracted from the database based on the case id, case initial/follow-up code ('I' or 'F'), demographic information, prescribed drugs, and reported ADEs. If all of these fields were the same, the most recent case version was selected. If a case existed both in LAERS and FAERS data, then the most recent FAERS (current data) case version was kept.

2.2.3 Indications and ADE mapping

FAERS utilizes MedDRA[37] preferred terms (PT) to describe all drug indications and adverse events. Lower level terms (LLT) are also used in certain

situations. In our study, we used the MedDRA PT for all the indication and adverse event data fields, also incorporating any LLTs that had been mapped to PT terms previously. Then cases with matching terms for indications and adverse events were removed because they may not represent a drug-induced ADE. After drug mapping and removing duplicate reports, a total of 8,888,579 case reports from FAERS were extracted for further analysis. Lastly, the case reports were filtered based on the frequency of the individual drug and ADE terms (the frequency threshold being set at 99 and 999 for the drug and the ADE terms, respectively).

2.3 DDI-ADE signal detection

In this paper, we implemented a shrinkage observed-to-expected ratio statistical model proposed by Noren et. al.[38], the details of which are described below.

2.3.1 Definitions and notations

If ADE A is denoted as an adverse drug event of interest, n_{111} denotes the number of case reports on A and $n_{11.}$ the total number of reports listing both drugs D1 and D2; n_{101} denotes the number of reports on A and $n_{10.}$ the total number of reports listing D1, but not D2; n_{011} denotes the number of reports on A and $n_{01.}$ the total number of reports listing D2, but not D1; and n_{001} denotes the number of reports on A and $n_{00.}$ the total number of reports in the absence of both D1 and D2. Thus, based on a two-by-two contingency table, we generated a four-by-two contingency table for DDI signal evaluation (Table 2).

Let

$$f_{00} = \frac{n_{001}}{n_{00.}}$$

$$f_{01} = \frac{n_{011}}{n_{01.}}$$

$$f_{10} = \frac{n_{101}}{n_{10.}}$$

$$f_{11} = \frac{n_{111}}{n_{11.}}$$

denote the corresponding observed relative reporting rates for A.

2.3.2 Statistical analysis to detect suspected DDIs

The method to detect suspected DDIs in FAERS database is based on a disproportionality measure that compares the observed relative reporting rate, f_{11} of A, with its expected value $E[f_{11}]$, given the co-prescription of two drugs and under the baseline assumption that the two drugs do not interact. Although $E[f_{11}]$ is unknown, it can be estimated from the relative reporting rates of A, given a prescription of at most one of D1 and D2.

The estimator g_{11} of $E[f_{11}]$ is given as follows:

$$g_{11} = 1 - \frac{1}{\frac{f_{10}}{1-f_{10}} + \frac{f_{01}}{1-f_{01}} - \frac{f_{00}}{1-f_{00}} + 1} \quad (1)$$

To avoid the possible misleading influence of negative estimates, g_{11} is written as

$$g_{11} = 1 - \frac{1}{\max(\frac{f_{10}}{1-f_{10}}, \frac{f_{00}}{1-f_{00}}) + \max(\frac{f_{01}}{1-f_{01}}, \frac{f_{00}}{1-f_{00}}) - \frac{f_{00}}{1-f_{00}} + 1} \quad (2)$$

Norén et al. also provide a Ω shrinkage measure for detecting ADEs with two drugs as follows:

$$\Omega = log_2(\frac{n_{111}+\alpha}{E_{111}+\alpha}) \quad (3)$$

Where $E_{111} = g_{11} \times n_{11}$ and α is a tuning parameter determining shrinkage strength, set at 0.5 in our analysis.

The tuning parameter and the resulting shrinkage ensure that extreme values, in our case, very few ADE reports observed for a given pair of drugs, do not affect the Ω measure substantially, thus reducing the sample variances. As such, spurious associations are avoided by reducing the sensitivity of Ω to sparse data.

Since the Ω measure of disproportionality is a binary logarithm of the observed-to-expected ratio, a Ω value is interpreted as 2^{Ω} times the number of ADE reports associated with a combination of two drugs versus what would be expected given the individual ADE profiles of each drug.

2.4 Selection criteria to determine PK DDI and ADE associations

After the FAERS database-wide screening for PK DDI signals using the Ω shrinkage method, we determined the evidence for PK DDI and ADE associations by employing two selection criteria. First, all the substrate-inhibitor-ADE associations should meet the threshold disproportional reporting rate of Ω>0. Second, the ADE should be associated with a substrate that was paired with at least two distinct inhibitors at Ω>0. This indicated a positive interaction between the substrate-inhibitor pair and higher than expected number of ADE reports observed for that substrate with multiple inhibitors. The association of the same ADE, in the same direction, for the same substrate and with multiple inhibitors was considered consistent evidence of a PK DDI signal (Fig 1).

2.5 SMQ analysis

"Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the PT level that relate to a defined medical condition or area of interest."[39] Thus, SMQs describe a clinical syndrome that can characterize an adverse event due to drug exposure through the use of narrow and broad terms. The SMQ terms are validated after extensive review, testing, analysis and discussion by the Council for International Organizations of Medical Sciences (CIOMS) working groups. They were created to help in the identification and retrieval of safety reports and therefore can be used to extract ADE-related cases from pharmacovigilance databases.

Three SMQs that characterized two adverse clinical events were used to determine the substrate-inhibitor-ADE associations in case of two sets of DDIs in the current study. The SMQs were considered as positive terms if they represented known ADEs and negative terms if they represented previously unknown ADEs in case of paclitaxel or pethidine, respectively. Evaluation as a positive or negative term with each of the DDIs was performed to assess whether our findings conformed to clinical events observed with the substrates. The first DDI set included paclitaxel paired with clopidogrel and gemfibrozil independently; and the second included pethidine paired with clopidogrel and voriconazole independently. The SMQ terms used in the analysis included hematopoietic cytopenia affecting more than one type of blood cell (SMQ code: 2000028) and hematopoietic leukopenia (SMQ code: 2000030) as positive and negative terms for the paclitaxel and pethidine DDIs,

respectively. Additionally, Neuroleptic Malignant Syndrome (NMS, SMQ code: 2000044), that includes PT representing serotonin syndrome (SS) in the SMQ, was used as a positive term for pethidine and a negative term for paclitaxel. We again applied the shrinkage observed-to-expected ratio model for evaluating the PK DDI and SMQ associations.

3. RESULTS

3.1 PK DDI identification

After collecting information on drug names, metabolic enzymes, CYP substrates and inhibitors from FDA's website and the Drug Interaction Flockhart's Table, we normalized the drug names and removed those that are not FDA approved or withdrawn (e.g., grapefruit juice, cisapride, etc.). Overall, we collected 149 substrates and 62 inhibitors involving seven distinct CYP enzyme isoforms, respectively. Table 3 lists the statistics for each CYP isoform and Table S1 lists the substrates and inhibitors analyzed in our study. For CYP2B6, we selected some weak inhibitors because there are no FDA recommended strong or moderate inhibitors for this enzyme. CYP3A had the maximum number of substrates and inhibitors followed by CYP2D6, while CYP2C8 had the minimum.

3.2 Evidence of PK DDIs in FAERS

The database-wide screening using the Ω shrinkage method found 343,950 substrate-inhibitor-ADE triplets with $\Omega>0$. After applying our selection criteria, we found 640 substrate-ADE pairs at $\Omega>0$. Of these, 37 were associated with only single substrate-inhibitor pairs and 13 with MedDRA PT that were not drug-related and thus removed from further examination. As a result, we found evidence for 590 substrate-ADE pairs involving 38 individual substrates, 2,085 substrate-inhibitor pairs, and 347 distinct ADEs. Table 4 shows the number of substrates, substrate-inhibitor pairs and their associated ADEs by each CYP isoform while Table S2 shows the substrate-inhibitor-ADE triplets along with their Ω values. The number of substrates involved were <10 across all CYP isoforms. Among these, CYP2C9 had the highest (9) whereas CYP2C8 had the lowest (1) number of substrates involved. The number of ADEs associated showed a wide range, with 173 ADEs associated with eight CYP2B6 substrates whereas only eight ADEs were associated with three CYP2D6 substrates.

3.2.1 Substrate-ADE associations

Although the number of ADEs related to the substrates of each CYP enzyme differed, the ADEs themselves overlapped across different substrates and CYP enzymes (Tables S2 and S3). Individually, paclitaxel, a CYP2C8 substrate, was associated with the highest number of ADEs (115), followed by pethidine (103) and piroxicam (75). Of these, the proportion of known dose-related ADEs was 27.0% for paclitaxel, 17.5% for pethidine, and 26.7% for piroxicam. We also determined shared toxicity profiles across different CYP substrates (Fig S1), for example, pethidine and paclitaxel had 23 shared ADEs between them. Additionally, among all ADE terms, anxiety, edema peripheral, and osteoarthritis were the most frequent across the 38 CYP substrates.

Table 5 presents the shared ADEs (using PT terms) between paclitaxel and pethidine associated DDIs (Ω range: 0.10 – 2.50), with the highest Ω values associated with each DDI-ADE highlighted in bold. For example, the highest number of ADE reports associated with the paclitaxel – clopidogrel DDI were for neutropenia (Ω = 1.99), with ~4 times as many reports associated with both in combination verses what would be expected with either paclitaxel or clopidogrel alone. For paclitaxel – gemfibrozil, Ω (2.50) was highest for fluid overload. In case of pethidine, the highest number of ADE reports were observed for mental status change (Ω=2.17) and pancytopenia (Ω=1.88) associated with clopidogrel and voriconazole, respectively.

3.2.2 CYP-specific substrate-ADE overlaps

Table 6 compares ADE Ω values for seven overlapping ADEs related to the CYP2C9 substrates piroxicam and zafirlukast when paired with three different inhibitors. Similar trends in the degree of disproportionality for certain ADEs can be observed between DDIs of the two drugs. For example, when piroxicam and zafirlukast are combined with amiodarone and paroxetine, respectively, Ω values for gastro-esophageal reflux disease (GERD) are higher compared to their combinations with fluconazole. CYP-specific substrate-ADE associations were also visualized for all CYP enzymes except CYP2C8 since it only included one substrate (Fig S2).

3.3 Substrate-SMQ associations

The number of narrow scope terms included for each of the three SMQs in our analysis are listed in Table S4. These included 10 MedDRA PT for hematopoietic cytopenia affecting more than one type of blood cell, 32 PT for hematopoietic leukopenia, and three for NMS. Table 5 also includes the Ω disproportionality values for each of the SMQs with respect to the two PK DDIs associated with paclitaxel and pethidine, respectively. The highest Ω value for hematopoietic cytopenia affecting more than one type of blood cell was noted with the pethidine – voriconazole combination (Ω=2.05). On the other hand, the highest Ω value for hematopoietic leukopenia was observed with the paclitaxel – clopidogrel combination (Ω=1.26). Lastly, with NMS, only the pethidine – voriconazole combination had an Ω value greater than zero.

4. DISCUSSION

Drug interactions research has expanded from the initial small in vitro and in vivo experiments to the current use of big data and informatics approaches to screen and discover previously unknown DDIs and their ADEs.[10,11] The use of pharmacometrics approaches to detect DDIs is advantageous in several ways but still requires clinical as well as experimental validation. As such, the need for translational research where different disciplines of DDI research are combined to provide comprehensive knowledge has been emphasized and explored.[13,40] Therefore, in this study we employed a translational approach by first identifying a list of previously known CYP substrates and inhibitors and then using this information to detect DDI-associated ADEs from a pharmaco-surveillance database. By employing specific selection criteria to provide strong associations, we were able to curate our list and identify a total of 590 DDI-related ADEs. Additionally, the positive terms used in the SMQ analysis conformed to known ADEs for both paclitaxel and pethidine and the negative term for unknown ADEs in case of paclitaxel.

We focused on known CYP substrates and inhibitors to examine DDI-ADE associations based on the hypothesis that CYP-mediated inhibition of a substrate can result in PK changes that in turn can instigate an ADE. By mapping the ADEs to their CYP-related substrates (Fig S1 and S2), we were able to observe the most

commonly reported ADEs with respect to the different CYP substrates in our study. For example, the CYP2B6 pethidine and the CYP2C8 paclitaxel had the maximum overlap, with 23 ADEs in common (Table 5). Several of the ADEs in table 5 are listed in the paclitaxel FDA drug label but only in relation to the drug since DDIs with other drugs were not reported in the 2011 revision of the label.[41] Nonetheless, the label cautions concomitant use of the drug with CYP2C8 as well as CYP3A substrates, inhibitors, and inducers.

Clopidogrel is not listed as a known inhibitor of CYP2C8 in the paclitaxel FDA drug label. But recent retrospective studies have shown that the interaction of clopidogrel with paclitaxel increases the risk of peripheral neuropathy and neutropenia.[42-45] Shinoda et. al. conducted a small case study where all cases on paclitaxel and clopidogrel were reported to have neutropenia, with half of the patients discontinuing their treatment due to severe toxicity.[43] Additionally, the comparison in neutrophil counts before and after clopidogrel treatment was found to be significantly different in these cases. This study supports our paclitaxel-clopidogrel-neutropenia association but larger studies are needed to confirm these findings and provide clinical evidence. On the other hand, Agergaard et. al. reported a hazard ratio of 1.7 and 2.3 for peripheral neuropathy with overall and high dose clopidogrel administration among 48 cases and 88 matched controls on paclitaxel, using medical records and registry data.[42] Additionally, Tornio et. al. conducted both clinical and in vitro studies, demonstrating up to 5-fold increase in the AUC of the CYP2C8 substrate repaglinide and >70% inhibition of the CYP2C8 enzyme, in the presence of clopidogrel.[46] Bergmann et. al. also demonstrated in vitro inhibition of CYP2C8 by the clopidogrel metabolite, resulting in 50% decrease in the depletion rate of paclitaxel.[47] Thus, our findings of a DDI between paclitaxel and clopidogrel and its association with peripheral neuropathy and neutropenia were corroborated by previous pharmacoepidemiological studies. And, although the Ω value for peripheral neuropathy was lower in our study compared to neutropenia, the study by Agergaard et. al. shows that the increased risk of peripheral neuropathy associated with paclitaxel-clopidogrel interaction is clinically relevant.[42]

In contrast to paclitaxel, a search for the table 5 ADE terms in the pethidine FDA label showed few known adverse events such as hypotension, tachycardia,

nausea, and those related to cardiopulmonary depression.[48] Atelectasis, or lung collapse, can lead to respiratory depression, a severe adverse event of pethidine, but is not a known ADE. Nonetheless, the label does include both clopidogrel and voriconazole as known inhibitors of CYP2B6 which may alter the pharmacokinetics of pethidine.[48] However, some of the previously unknown ADE associations we report may denote an indication bias or drug-disease interactions. For example, colitis may serve as a direct or indirect indication for pethidine use as a sedative,[49,50] or renal failure as a condition that affects the pharmacokinetics of pethidine.[51] Therefore, our findings still need to be verified through future clinical, pharmacoepidemiological or experimental studies in order to confirm these DDI-ADE associations.

The CYP-specific evaluation including the CYP2C9 substrates piroxicam and zafirlukast also showed overlap of 7 ADEs with the known CYP2C9 inhibitors amiodarone, fluconazole, and paroxetine (Table 6). Five of the seven ADEs in table 6 have been mentioned for piroxicam in its FDA drug label except for cataract and disc degeneration,[52] whereas only arthralgia, depression, and GERD (dyspepsia) have been mentioned for zafirlukast.[53] A check of the ADE list for indication bias shows none related to zafirlukast but piroxicam is used to treat arthralgias.[54] Thus, arthralgias may serve as an indication or an ADE if the patient experiences a hypersensitivity reaction related to piroxicam. Thus, validation studies using different populations are needed to confirm these associations.

Even though quite of few of the ADEs are known dose-related adverse events of the drugs, especially piroxicam, no evidence for associations with the DDIs exist for both substrates so far. The drug labels also do not mention any interactions with the three inhibitors listed here, but a literature search of these DDIs revealed in vitro, in vivo and clinical PK studies that show an association of the two substrates with fluconazole. While fluconazole was shown to increase the plasma concentration of zafirlukast,[55] two studies on piroxicam showed contradictory effects of the drug on fluconazole, one reporting synergistic/additive effect while the other an antagonistic effect for the drug interaction.[56,57] While these three studies were found to report a DDI between the two CYP2C9 substrates and fluconazole, none were found for the DDIs with amiodarone or paroxetine or the ADEs related to the DDIs. Thus, these

DDIs and their related ADEs may represent associations that are novel but future studies are needed to determine their validity and causal relationships.

The SMQ-based analysis allowed us to evaluate the Table 5 ADE associations in terms of clinically relevant entities. Since the SMQs include a set of PTs that characterize a clinical condition/syndrome, PTs that represent the same or similar clinical entities were thus evaluated together. As such, table 5 associations with febrile neutropenia, neutropenia, pancytopenia, and white blood cell count decreased, that are very similar events, were represented by the SMQs "hematopoietic cytopenia affecting more than one cell type" and "hematopoietic leukopenia". Similarly, ADEs including mental status change, diarrhea, tachycardia, hypotension and renal failure associated with Table 5 DDIs in our analysis, that are part of NMS and/or SS were evaluated using the SMQ "NMS". Broadly, the hematopoietic cytopenia-related SMQ had a higher number of case reports associated with both the paclitaxel and pethidine DDIs compared to the hematopoietic leukopenia, except for the paclitaxel-clopidogrel combination. These SMQs did support our findings in relation to paclitaxel as a positive term but not as a negative term for pethidine. Although pethidine or the DDIs investigated have not been previously associated with cytopenia or leukopenia, the higher Ω value observed with voriconazole may illustrate the use of pethidine in the management of fever and rigors in patients with cancer-therapy related febrile neutropenia.[58-61] Cancer pain management is also an indication for pethidine[62] and thus this substrate-inhibitor pair maybe indirectly related to the ADE. In case of NMS, our approach supported the use of NMS as a negative term for paclitaxel. However, the Ω value for the pethidine-NMS association was small and may be a result of the narrow scope terms we used to increase the specificity of the SMQs representing our ADEs. Moreover, as NMS/SS involve a constellation of signs and symptoms, it may be possible that the patients did not experience or report all the signs and symptoms required to meet the criteria for SS, thus reducing the frequency of the terms represented by the SMQ in our analysis.[63] Thus, the SMQs were able to corroborate our findings, serving as good positive and negative terms for paclitaxel but not pethidine.

Our study has both strengths and limitations. First, data quality issues with using surveillance databases such as FAERS are unavoidable. However, we implemented multiple steps to reduce them and were able to successfully map the drug names to generic names and remove duplicate versions of the case reports from our analysis. Additionally, the shrinkage method used in our analysis ensured that sample variances did not significantly affect our associations. Yet, some of the issues associated with the data could not be completely eliminated. These were related to highly correlated drugs, PTs that represent both ADEs and indications, and lack of drug dosage and duration information. Second, we limited our analysis to drugs that act as substrates and inhibitors to seven CYP isoforms, thus limiting the number of drugs and subsequently the number of DDI-ADE associations examined. Third, the SS MedDRA PT was only one of the three narrow terms used for the NMS SMQ, and therefore represented only a small portion of our ADEs in the SMQ, which may partly explain our negative results. And, although the SMQs are validated and are equivalent to clinical events, the exploratory nature of our analysis limits our ability to provide clinical interpretation. Lastly, we only focused on a few of the substrates and inhibitors that showed maximum overlap for ADEs between and within CYP isoform substrates in our discussion. However, we have provided a curated list of the screened PK DDI-ADE associations that can be used to generate and test hypotheses based on researchers' drugs or ADEs of interest.

In summary, we utilized a translational approach to provide evidence for PK DDIs associated with ADEs by utilizing known CYP substrates and inhibitors and the FAERS post-marketing surveillance data. We found a substantial number of DDI-ADE associations, and were able to find clinical and experimental evidence for the association between the paclitaxel-clopidogrel interaction and peripheral neuropathy. Other known dose-related or unknown ADEs were also reported for the substrates but need to studied further in the context of their respective DDIs. Future studies that are not only experimental but also include clinical as well as population and electronic records based data are needed to validate our findings. Moreover, incorporating more defined MedDRA terms as well as the severity of ADEs could provide more stratified and detailed results.

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Table 1. PK DDI and ADE translational discovery approach

Stages/names	Input	Methods	Output
1 – PK data	1) FDA's substrate and inhibitor tables for clinical studies and drug labeling 2) Flockhart's drug interaction tables (substrates and inhibitors)	Compiling a list of CYP substrates and inhibitors using the input data sources	List of known substrates and inhibitors, categorized by CYP enzymes
2 – FAERS data processing	1) Drug, ADEs, and indications information from FAERS 2) MedDRA preferred terms (PT) and SMQ terms 3) DrugBank, RxNorm, and USAGI	1) Mapping drug names in FAERS to DrugBank, RxNorm, and USAGI 2) Defining ADEs using MedDRA PT terms and removing cases where indications matched ADEs 3) Mapping MedDRA PT terms to SMQ terms	Unique cases in FAERS with 1) Normalized drug names 2) ADE information a) MedDRA PT b) SMQ terms
3 – DPA	1) Stage 1 output 2) Stage 2 output	Analysis using omega (Ω) shrinkage observed-to-expected ratio	List of substrate-inhibitor-ADE sets with their respective Ω values that indicate the degree of disproportionality, categorized by their CYP metabolizing enzymes

ADE: adverse drug events, CYP – cytochrome P450, DPA: disproportionality analysis, FAERS: Food and Drug Administration's Adverse Events Reporting System, MedDRA: Medical Dictionary for Regulatory Activities, PK DDI: pharmacokinetic drug-drug interactions, SMQ: standardized MedDRA Queries

Table 2. Four-by-two contingency table for DDI signal evaluation

Drug combinations	ADE A	Not ADE A	Total
Both D_1 and D_2	n_{111}	n_{110}	$n_{11.}$
D_1 Not D_2	n_{101}	n_{100}	$n_{10.}$
D_2 Not D_1	n_{011}	n_{010}	$n_{01.}$
Neither D_1 nor D_2	n_{001}	n_{000}	$n_{00.}$

ADE: adverse drug event, DDI: drug-drug interactions
D1: drug 1, D2: drug 2, n indicates the number of reports in each case with the suffix indicating if the drug or ADE is involved (1=yes, 0 =no, . = not applicable).

Table 3. Number of substrates and inhibitors categorized by CYP isoforms using FDA and Flockhart's drug interaction tables.

CYP isoform	No. of substrates	No. of inhibitors
CYP1A2	18	6
CYP2B6	9	4
CYP2C8	6	4
CYP2C9	14	5
CYP2C19	13	4
CYP2D6	25	10
CYP3A	64	29
Total	**149**	**62**

CYP: cytochrome P450, FDA: Food and Drug Administration

Table 4. Number of ADEs associated with substrates for each of the CYP isoforms (Ω > 0 for all substrate-inhibitor pairs) in FAERS

CYP450 enzyme	No. of substrates	No. of substrate-inhibitor pairs	No. of ADEs
CYP1A2	7	172	34
CYP2B6	8	387	173
CYP2C19	6	414	71
CYP2C8	1	230	115
CYP2C9	9	552	145
CYP2D6	3	54	8
CYP3A	4	276	44
Total	**38**	**2,085**	**590**

ADR: adverse drug events, CYP: cytochrome P450, FAERS: Food and Drug Administration's Adverse Events Reporting System

Table 5. Comparison of omega (Ω) values for overlapping ADEs between paclitaxel (CYP2C8) and pethidine (CYP2B6) related DDIs using MedDRA Preferred Terms and SMQs in FAERS.

Substrates	**Paclitaxel Ω value**		**Pethidine Ω value**	
Inhibitors	**Clopidogrel**	**Gemfibrozil**	**Clopidogrel**	**Voriconazole**
Preferred terms				
Atelectasis	1.93	0.67	1.31	0.57
Cellulitis	0.10	0.22	1.19	1.64
Cholelithiasis	1.30	1.58	0.87	0.18
Colitis	1.05	0.89	0.61	1.16
Dehydration	0.99	1.66	0.80	0.15
Diarrhea	0.30	0.79	1.14	1.53
Febrile neutropenia	1.80	1.68	0.34	1.52
Fluid overload	0.36	**2.50**	1.19	1.74
Hyperglycemia	0.73	0.21	0.49	0.74
Hypotension	0.12	1.37	0.75	1.42
Hypoxia	0.16	0.40	0.04	1.80
Ileus	1.35	0.75	0.38	1.04
Lung infiltration	0.54	0.89	0.24	1.51
Lymphadenopathy	0.55	0.91	1.59	1.57
Mental status changes	0.13	0.70	**2.17**	0.29
Nausea	0.18	0.62	0.81	0.38
Neuropathy peripheral	0.86	0.85	0.96	0.37
Neutropenia	**1.99**	0.41	1.62	1.17
Pancytopenia	0.32	2.27	1.40	**1.88**
Pneumonia	0.97	0.64	1.34	1.33
Renal failure	0.39	0.38	1.38	0.71
Tachycardia	1.15	0.86	0.40	1.28
White blood cell count decreased	0.22	0.75	0.10	1.08
SMQs				
Hematopoietic cytopenia affecting more than one type of blood cell	0.75	1.69	1.02	2.05
Hematopoietic leukopenia	1.26	0.81	0.70	0.92
Neuroleptic malignant syndrome	<0	<0	<0	0.29

ADR: adverse drug events, DDIs: drug-drug interactions, FAERS: Food and Drug Administration's Adverse Events Reporting System, MedDRA: Medical Dictionary for Regulatory Activities, SMQ: standardized MedDRA queries.
Bold values indicate the highest Ω values observed with each DDI.

Table 6. Comparison of omega (Ω) values for overlapping ADEs between two CYP2C9 related DDIs using MedDRA Preferred Terms in FAERS.

CYP2C9 substrates	Piroxicam Ω value			Zafirlukast Ω value		
ADEs/ Inhibitors	**Amiodarone**	**Fluconazole**	**Paroxetine**	**Amiodarone**	**Fluconazole**	**Paroxetine**
Anxiety	2.06	0.17	0.51	1.48	1.17	0.64
Arthralgia	0.52	0.03	0.47	0.80	0.09	1.06
Cataract	1.54	**1.58**	1.71	1.26	0.90	0.76
Coronary artery disease	1.86	0.71	1.59	1.10	0.93	1.44
Depression	0.29	1.07	1.05	0.68	**1.77**	0.67
Gastro-esophageal reflux disease (GERD)	1.27	0.36	**1.85**	**1.75**	0.31	1.28
Intervertebral disc degeneration	**2.31**	0.87	1.47	1.43	1.09	**1.80**

ADEs: adverse drug events, DDI: drug-drug interactions, FAERS: Food and Drug Administration's Adverse Events Reporting System, MedDRA: Medical Dictionary for Regulatory Activities. Bold values indicate the highest Ω values observed with each DDI.

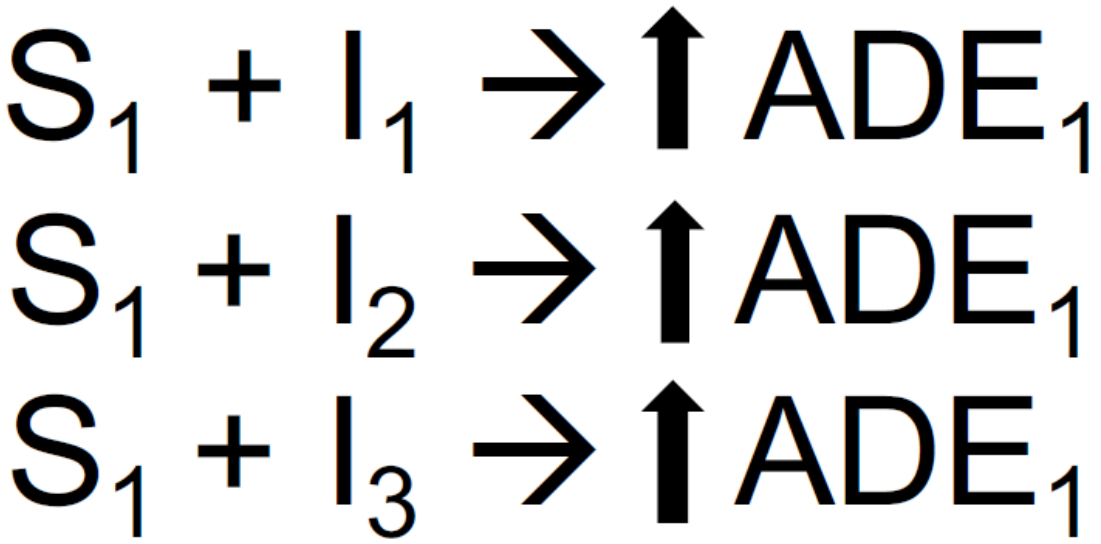

Fig 1. Equations depicting consistent association of a substrate with an ADE across multiple inhibitors of a CYP enzyme. S_1 indicates substrate #1, ADE_1 indicates ADE #1 and I_1, I_2, and I_3 indicate 3 different inhibitors numbered 1 to 3.