

Title: Translational high-dimensional drug Interaction discovery and validation using health record databases and pharmacokinetics models

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#### **Conflict of Interest**

The authors have no conflicts of interest to report.

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## Abstract

Polypharmacy increases the risk of drug-drug interactions (DDI's). Combining epidemiological studies with pharmacokinetic modeling, we detected and evaluated high-dimensional DDI's among thirty frequent drugs. Multi-drug combinations that increased risk of myopathy were identified in the FDA Adverse Event Reporting System (FAERS) and electronic medical record (EMR) databases by a mixture drug-count response model. CYP450 inhibition was estimated among the 30 drugs in the presence of 1 to 4 inhibitors using in vitro in vivo extrapolation. Twenty-eight 3-way and 43 4-way DDI's had significant myopathy risk in both databases and predicted increases in the area under the concentration time curve ratio (AUCR) >2-fold. The HD-DDI of omeprazole, fluconazole and clonidine was associated with a 6.41-fold (FAERS) and 18.46-fold (EMR) increase risk of myopathy (LFDR<0.005); the AUCR of omeprazole in this combination was 9.35. The combination of health record informatics and pharmacokinetic modeling is a powerful translational approach to detect high-dimensional DDI's.

## Introduction

Drug-drug interactions (DDIs) are a common cause of adverse drug events (ADE) (1-3). In the United States alone, each year an estimated 195,000 hospitalizations and 74,000 emergency room visits are the result of DDIs. National Health and Nutrition Examination Survey data published in 2010 (4) showed that the number of patients using two or more prescription drugs increased from 25.4% to 31.2% in ten years. In particular, more than 64% of elderly individuals took three or more prescription drugs, and 37% took five or more prescription drugs (4). In the FDA Adverse Event Reporting System (FAERS) data, 35% of reports include three or more prescription drugs, and 20% reports have five or more prescription drugs.

In order to evaluate clinical effects and molecular mechanisms of DDIs, clinical pharmacokinetic (PK) studies, pharmaco-epidemiologic studies, and *in vitro* PK experiments have been routinely utilized.

One salient example is that of breast cancer hormonal therapy, tamoxifen. The formation of its active metabolite, endoxifen, was inhibited by concomitant selective serotonin reuptake inhibitor paroxetine in a clinical pharmacokinetics study (5). *In vitro* metabolism studies revealed that this is due to paroxetine's strong inhibition of the tamoxifen bio-transformation to endoxifen via the CYP2D6 pathway (6). In a follow-up pharmacogenetic study, breast cancer patients with CYP2D6 loss function variants have a higher risk of disease relapse and a lower incidence of hot flush (7). The clinical consequence of treating breast cancer and depression using tamoxifen and SSRIs was reviewed (8), and a call made for further investigation. Another example is the sedation agent midazolam. Co-administration of midazolam and ergosterol synthesis inhibitor ketoconazole has been identified to reduced subjects' cognitive function (9). In clinical PK and *in vitro* experiments, midazolam metabolism was inhibited by ketoconazole through the CYP3A pathway (10, 11), leading to increased midazolam exposure (12).

These examples clearly demonstrate that the translational significance of drug interaction studies relies on both clinical and molecular pharmacology evidence. As described by Hennessy and Flockhart (13), an integrated informatics, epidemiology, and pharmacology approach has the potential

to accelerate the translational drug interaction studies. Pioneered by Tatonetti *et al.* (14), FAERS and electronic medical records were utilized to generate and validate drug-ADE and drug-drug-ADE associations. In a follow-up study, Lorberbaum *et al.* demonstrated that patients co-administrated ceftriaxone and lansoprazole were 1.4 times as likely to have a prolong QT prolongation than the administrated single drug in both EMR and FAERS data. Further validation showed that ceftriaxone/lansoprazole drug interaction was due to hERG channel blocker in a patch-clamp experiment system (15). Duke *et al.* proposed a text mining strategy for DDI molecular pharmacology evidence discovery from the public literature (16), which discovered 13,197 potential DDIs. In the follow-up *in vitro* study, Han *et al.* validated the loratadine-simvastatin myotoxicity interaction, and its increased myopathy risk in both EMR and FAERS databases (17). Similarly, Schelleman *et al.* examined the increased risk of hypoglycaemia with co-administration of fibrates and statins in sulfonylurea users in a pharmaco-epidemiology study (18). This DDI was further evaluated in an *in vitro in vivo* extrapolation (IVIVE) pharmacokinetic model.

High dimensional drug interactions (HDDIs), i.e. DDIs with three or more drugs, have not yet been broadly investigated. There are a few examples of clinical PK studies, *in vitro* PK experiments, and IVIVE PK models that evaluate interactions among 3 or more drugs. Co-administration of gemfibrozil and itraconazole were shown to increase repaglinide plasma exposure to a greater extent than either one alone (19). Zhang *et al.* found an additive PK model, including mechanism-based and competitive components, best described the *in vitro* inhibition of midazolam metabolism by erythromycin, diltiazem and their metabolites (20). Through IVIVE, this model was confirmed *in vivo* in mice (21). On the other hand, to our knowledge, there are no studies of three way drug interactions using pharmaco-epidemiology studies. Proportional reporting ratio (PRR) (22), the reporting odds ratio (ROR) (23), the information component (IC) (24), and the empirical Bayes geometric mean (EBGM) (25) have been proposed for detection of drug-ADE signals. However, these methods are focused on ADE detection for

single drugs, not drug combination. To overcome this limitation, we have recently developed a new method, a mixture drug-count response model (MDCM). This model focuses on detecting high dimensional drug interactions, and characterizes the drug-count response relationship between the number of co-administered drugs and an ADE. We have successfully demonstrated its statistical and computational performance in a recent publication (26).

In this paper, we will use this newly developed MDCM to detect HDDIs that lead to increased risk of myopathy in two independent databases: Indiana Network of Patient Care - CDM (INPC-CDM) electronic medical record and FAERS. Using *in vitro* cytochrome P450 (CYP) inhibition data and mechanistic static *in vitro in vivo* DDI predictions, we evaluate the potential pharmacological mechanisms of these HDDIs.

## Results

### Drug Selections

As our MDCM is computationally expensive, we limited this analysis to top 30 drugs. After normalizing drug names by their DrugBank IDs, 1,238 and 1,716 FDA approved drugs were identified in the INPC-CDM and FAERS datasets. Of these, after selecting drugs 268 and 172 drugs in INPC-CDM and FAERS, respectively, had a relative frequency  $\geq 0.5\%$ , with 119 drugs overlapping both databases. Among these 119 drugs, 95 have reported myopathy risk according to SIDER (<http://sideeffects.embl.de/>). We curated the *in vitro* pharmacokinetic data for these 119 drugs to determine their potential to interact via CYP450 inhibition. Nine drugs had reported fraction metabolism ( $f_m$ ) by human CYP450 enzymes. These drugs were evaluated as substrates for the prediction of area under the concentration-time curve ratio in the presence to absence of inhibitor (AUCR). Published competitive inhibition ( $k_i$ ) values for at least one CYP450 enzyme were available for 64 of the drugs. The top 23 drugs with inhibition ranked by  $\frac{f_u \times C_{max}}{k_i}$  were selected as inhibitors (Figure 1).

## **INPC-CDM and FAERS Show Strikingly Different Drug-Count Myopathy Response Mixture Models**

Under the MDCM, each drug combination has a probability of being assigned to either a drug-count myopathy response model or a constant myopathy risk model. The drug-count response model and constant model share the same myopathy risk when subjects take only one drug. The drug-count myopathy response model captures the overall trend of the nonlinear relationship between the number of co-administered drugs and myopathy risk. It also characterizes a constant myopathy risk and the maximum myopathy risk as the number of co-administered drugs increases. Strikingly, the drug-count response model demonstrated very different trends between drug combinations and myopathy risk in INPC-CDM and FAERS databases. INPC-CDM had constant myopathy risk of 0.42, and maximum risk of 0.74; while FAERS data shows constant risk of 0.07 and a maximum risk of 1.0 (Figure 2). In the INPC-CDM, the maximum myopathy risk occurs when the four drugs are co-administered. However, in the FAERS, the myopathy risk continues to increase beyond 5-drug combinations.

## **Overlapping Drug Combinations in INPC-CDM and FAERS**

The drug-count-response mixture model generates a local false discovery rate (LFDR) statistic that allows us to differentiate drug combinations that are more likely to follow the drug-response myopathy risk model than the constant risk model. Figure 3 shows the percentage of overlapping drug combinations that are shared between two databases, with a LFDR of 0.05. We see strong and consistent evidence of increased myopathy risk with an overlap of 37-40% of 2-way to 5-way drug combinations shown to increase myopathy risk in both databases.

## **The Overall Trend of High Dimensional Drug Interactions in Pharmacokinetics Predicted by IVIVE**

One common mechanism of drug-drug interaction occurs through inhibition of drug metabolism. In order to assess whether the potential DDIs identified by pharmaco-epidemiology evidence are due to pharmacokinetic drug interactions, we used IVIVE to evaluate the change in drug exposure between a drug administered alone and co-administered with 2-, 3-, or more drugs. In the IVIVE prediction, CYP substrates and CYP inhibitors are differentially defined. Among our 30 selected drugs, nine are CYP substrates with curated  $f_m$ ,  $f_e$ , and  $f_u$  data from the literature. We also obtained the  $k_i$ ,  $f_u$ , and  $C_{max}$  for 23 drugs identified as CYP inhibitors. These data were combined through IVIVE to predict the area under the concentration time curve ratio (AUCR) for 156 two-way, 1302 three-way, 6971 four-way, and 26901 five-way drug interaction combinations (Figure 4). When we look at all the AUCR data under different dimensions of drug interactions, their medians, 75<sup>th</sup> percentiles, and the maximum AUCRs all reach a maximum plateau with the co-administration of 3 drugs.

### **Sensitivity Analyses of Significant Three-way Drug Interactions**

Among the 9 substrates and 23 inhibitors, 28 three-way drug interactions have a predicted AUCR >2 and a LFDR from the MDCM model < 0.05. We hypothesized that among these drugs, the risk of myopathy would increase as the number of co-occurring drugs increased. Therefore, for each 3-drug combination we evaluated myopathy risk between individuals taking 1 drug vs any 2-drug combination, and between 2-drug and 3-drug combinations. One drug-triplet showed a strong increasing trend in myopathy risk: omeprazole, clonidine, and fluconazole (Figure 5) after adjusting for the number of additional co-medications, age, and gender. In the FAERS data set, taking any two of these three drugs together increased the risk of myopathy by 1.88-fold compared to taking any of the drugs alone ( $p = 0.012$ ). Taking the 3-drug combination of omeprazole, clonidine and fluconazole increased the risk of myopathy by 5.01-fold compared to the 2-drug combinations ( $p = 0.000012$ ). In the INPC-CDM, taking any two of these drugs concurrently increased the risk of myopathy by 1.75-fold ( $p=7.8E-13$ ) and taking all three

together increased the risk by 4.18-fold ( $p=0.0069$ ) compared to taking one drug and two drugs, respectively. Similar comparisons of 2- and 3-drug combinations to 1- and 2 drug combinations for the other 27 drug triplets examined did not reveal significantly increased myopathy risk in both data sets for other drug combinations (Table S1).

The AUCRs of omeprazole due to the inhibition by clonidine and fluconazole alone or together were estimated from literature data using mechanistic static interaction models (27). Omeprazole is a racemic mixture of R- and S-omeprazole. While both enantiomers are metabolized by CYP2C19 and CYP3A (Figure 6), the  $f_m$ 's for each pathway are slightly different (Table S2). Fluconazole is a well-known CYP2C19 and CYP3A inhibitor with a median  $k_i$  value of 5.075  $\mu\text{M}$  and 13.25  $\mu\text{M}$ , respectively (28-30).

The  $k_i$  of clonidine for CYP3A is 0.15  $\mu\text{M}$  (31). Incorporating these values into the IVIVE model (Equation 4), predicts AUCRs of R- and S-omeprazole of 1.45 and 1.35, respectively, after the clonidine inhibition, and 5.06 and 5.17 after fluconazole inhibition. Following co-administration of the 3 drugs, the AUCRs of R- and S-omeprazole are predicted to be 9.35 and 8.51, respectively. Alternatively, the  $f_m$  of omeprazole can also be estimated from pharmacogenetics PK study. Venkatakrishnan *et al.* calculated the  $f_m$  of omeprazole from AUCR of CYP2C19 extensive metabolizer and poor metabolizer (32, 33) ( $f_m = 0.87$  for CYP2C19). Using this  $f_m$ , the AUCR estimated from IVIVE is predicted to be 1.14 after the clonidine inhibition; 5.99 after fluconazole inhibition; and 7.69 after inhibition by both drugs.

## Discussion

Using the MDCM, we mined the high dimensional drug interactions among 30 common drugs in two independent health record databases. We identified a number of high-dimensional drug interactions that have increased risk of myopathy in both databases. This model further reveals interesting differences in the drug-count response relationship in the two databases. In the FAERS, the maximum



myopathy risk goes to almost 1.0 as the dimension of drug combinations increases. Thus, a patient would be expected to experience a myopathy event if he/she takes a large number of drugs. On the other hand, the maximum myopathy risk in the INPC-CDM data is 0.72. However, because it was estimated from a case-control study, this number cannot be simply interpreted as a population maximum myopathy risk. Our 1:10 case control design has a higher myopathy case frequency (0.09) than the INPC-CDM population myopathy risk (0.067) reported previously (16). Hence, we anticipate that the population maximum HDDI myopathy risk in the INPC-CDM data is less than 0.72. While we observe that the maximum myopathy risk is higher in the FAERS database than in the INPC-CDM database, it is extremely striking that the frequency in FAERS approaches one. Although the maximum myopathy risk in the INPC-CDM data is lower than that of FAERS, it is still an extremely common ADE.

Among the statistically significant three-way drug interactions identified from MDCM and validated by two databases, more stringent sequential comparisons are further conducted between 1-drug vs 2-drug and 2-drug vs 3-drugs. We further demonstrated that omeprazole, clonidine, and fluconazole, exhibited statistically significantly increased myopathy risk from single drug to three-drug combination in both databases.

In parallel to our MDCM model, we evaluated the potential CYP PK interactions among the 30 drugs. In the IVIVE high dimensional drug interaction prediction, one drug acts as the substrate and the other drugs are assumed to be reversible inhibitors of CYP enzymes. Substrate AUCR changes were predicted based the curated *in vitro* PK data. The maximum predicted AUCR was reached with three-drug combinations. In contrast, the maximum HDDI myopathy risk observed in the two medical record databases did not occur until five drugs were co-administered. This suggests that additional mechanisms are responsible for the increased risk of myopathy observed with HDDIs. For instance, we have

previously shown that the increased risk myopathy with co-administration of loratadine and simvastatin is due to a pharmacodynamic mechanism in the muscle cell (17). We have also shown that the increased risk of myopathy observed when chloroquine is co-administered with simvastatin is the result of increased lysosomal OATP1B1 protein degradation (34).

As the risk of myopathy consistently increased among 2-way and 3-way combinations of omeprazole, clonidine, and fluconazole, we closely examined the predicted AUCR using IVIVE for these combinations. Compared to the 1.5-5 fold increase in AUCR of R- and S-omeprazole when inhibited by only one drug, either clonidine or fluconazole, the co-administration of both drugs with omeprazole led to an AUCR of 8.5-9.4. As  $f_m$  is a critical component of predicting the extent of interaction, we evaluated the interaction using both *in vitro* data and data from clinical pharmacogenetic study of CYP2C19 to determine omeprazole's  $f_m$ . We estimated  $f_{mCYP2C19}$  (0.68) from *in vitro* data mining (35); Roman *et al.* estimated omeprazole clearance is decreased by 50% in CYP2C19 heterozygous patients ( $f_{mCYP2C19} = 0.5$ ) (36); Venkatakrishnan *et al.* estimated  $f_{mCYP2C19}$  (0.87) from AUCR of CYP2C19 PMs (32, 33). The different  $f_{mCYP2C19}$  estimation results AUCR of omeprazole inhibit by clonidine and fluconazole range from 7.55-11.74. Although the mechanism of omeprazole induced myopathy has not yet been understood, various hypotheses have been proposed such as the induction of auto-immune antibodies (37, 38), and the irreversible inhibition of potassium-hydrogen ATPase in the skeletal muscles (39).

Recently, Sansone *et al.* surveyed the Italian National Network of Pharmacovigilance Database and found that omeprazole was more frequently involved in reports of myopathy than any other non-statin drug (40). From these evidences, omeprazole is the primary candidate that induced myopathy. In addition, there were sixteen case reports in the literature (41, 42)) and summarized in a case series that associate the use of omeprazole with myopathy (38). Among these sixteen cases, two were

identified as Asians, but the race were not reported among the other cases. Similarly, in our database, the race data were incomplete and sometimes inaccurate. Hence, the race effect of omeprazole induces myopathy remains unknown.

One limitation of the MDCM model is its large computational expense. Because of this, only a limited number of drugs (i.e. 30) could be screened for high-dimensional drug interactions. Thus, screening steps are required to reduce the number of drugs. More research is needed to increase the computational efficiency of MDCM. Future research will also apply the MDCM model to evaluate the drug-count response patterns for other ADEs.

Although the mechanistic static model is a well-accepted screening tool for pharmacokinetic drug interactions, it may over- or under-estimate the extent of interaction. Of note, our model only included reversible inhibition and did not consider gut wall metabolism effects of inhibitors. Thus, we may have under-estimated the AUCR for orally administered drugs. While mechanistic static models have been established to predict the effect of mechanism based inhibitors and CYP inducers (43, 44), these models have not been validated with respect to high-dimensional interactions among drugs that inhibit the same enzyme. Additionally, interactions in other pathways, such as drug transporters, could be included using more mechanistic and time-dependent modeling techniques. In addition, we utilized  $C_{max}$  data from the literature without respect to the doses of drugs observed in the clinical records.

This study demonstrates the power to elucidate clinically significant high-dimensional drug interactions from clinical records. Using two unique data sets, ADE case reports from the FAERS and structured electronic medical record data from the INPC-CDM, we observed increasing trends in myopathy risk with higher medication burden. As a large number of DDIs are the result of PK interactions at the level of CYP

enzymes, we also estimated the increased exposure of 9 substrate drugs in the presence of 2, 3, or more inhibitors. Although we demonstrated that decreased clearance of drugs due to CYP inhibition is one source of the increased myopathy risk among polypharmacy patients, this mechanism is unable to fully explain the increased risk of myopathy observed in subjects taking 4 or more medications. As our computational efficiency expands to allow for the evaluation of greater number of drugs using our MDCM model, additional pharmacokinetic and pharmacodynamic mechanisms of interaction will need to be considered to further account for the increased risk of ADEs observed in polypharmacy patients.

## Materials and Methods

### Indiana Network of Patient Care (INPC) Electronic Medical Record

INPC-CDM data was derived from INPC patients between 2004 and 2015, following CDM Version 5.0 guideline (<http://omop.org/CDM>). The INPC-CDM consists of structured data detailing medical conditions, medications, and lab tests of patients. Using this data set, we have identified myopathy patients, as defined in our previous paper (Duke *et al.*, Table S6 (16)). The myopathy case definition contains both severe symptoms, such as rhabdomyolysis, and mild symptoms, such as muscle weakness. The myopathy cases include the first myopathy event recorded for a patient and cases in which no other myopathy event occurred within the past 6 months. For each case, ten controls were selected from records within the same time-frame (anchor time-matched) and matching demographic criteria. These controls did not have any myopathy events recorded in the INPC-CDM data set. Under each anchor time in both cases and matched controls, a one-month drug exposure window was generated. Drugs were coded as present if their prescription time periods overlapped with the drug exposure window. Drug names were normalized to their DrugBank IDs. The INPC-CDM data set has 450,673 cases and 4,506,730 controls. This case/control design for the myopathy using the INPC-CDM database was similar to that used in our previous publications (17, 26, 44).

## FDA Adverse Event Reporting System (FAERS)

Unlike INPC-CDM, FAERS is a case reporting system, not a longitudinal database. In FAERS, myopathy cases were similarly identified using the same terms we used in the INPC-CDM (Table S1). There were 136,791 myopathy cases, and 3,969,842 controls identified in the FAERS. The drug names were mapped to their DrugBank IDs.

## Drug Selection Criteria and Data Curation

- Only FDA-approved drugs included
  - Selected by frequency >0.5% in both INPC and FAERS databases
- Myopathy risk identified in SIDER
- Limited to 30 drugs due to computational expense of MDCM

Pharmacokinetic parameters required for *in vitro in vivo* extrapolation of AUCR ( $C_{max}$ ,  $f_u$ ,  $f_m$ ,  $K_m$ ,  $V_{max}$ ,  $K_i$ ) were curated from Goodman and Gilman (45) or published literature identified in PubMed.  $C_{max}$  obtained from literature review (45) was used as the inhibitor concentration  $[I]$ . This conservative approach to estimate maximal inhibition has been used by others (46). If a pharmacokinetics parameter was reported in multiple sources, the sample mean was used.

The  $f_m$  data was curated from several different types of published studies. Most of the  $f_m$  data were estimated from substrate depletion studies in human liver microsomes, in which the substrate is incubated with or without CYP-selective inhibitors (47). The percentage inhibition caused by the CYP-selective inhibitor reflects the  $f_m$  of drug for this CYP. The  $f_m$  can also be estimated through *in vivo* pharmacokinetic studies comparing the AUC or clearance of a substrate in the presence and absence of

a CYP-selective inhibitor (48) or in a pharmacogenetic PK study where it can be calculated from the fold-change in exposure of a victim drug in extensive metabolizers compared to poor metabolizers (26, 27).

### A Mixture Drug-Count-Response Model for the High-Dimensional Drug Effect on Myopathy

In 2015, our group developed a mixture drug-count-response model (MDCM) for identifying high-dimensional drug interaction-induced ADEs (26). In the MDCM,  $i$  is denoted as the number of drugs for  $i$ -way drug combinations;  $j$  is the  $j$ th  $i$ -way drug combinations;  $n_{ij}$  is the total number of patients taking  $j$ th  $i$ -way drug combination; and  $y_{ij}$  is the number of cases among those  $n_{ij}$  patients. The parameter  $\pi$  represents the proportion of drug combinations that follow the drug-count-response model. The probability distribution of  $y_{ij}$  is defined as the following mixture model

$$P(y_{ij}) = (1 - \pi) \text{Bin}(n_{ij}, y_{ij}, P_{const}) + \pi \text{Bin}(n_{ij}, y_{ij}, P_{count}) \quad (\text{Eq. 1})$$

where  $P_{const}$  and  $P_{count}$  represent a constant ADE risk probability and a drug-count-response ADE risk probability respectively:

$$P_{const} = \frac{c \times \exp(\beta_0)}{1 + \exp(\beta_0)}, P_{count} = \frac{c \times \exp(\beta_0 + \beta_1(i-1))}{1 + \exp(\beta_0 + \beta_1(i-1))}$$

After applying MDCM to both FAERS and INPC-CDM data, a local false discovery rate (LFDR) is calculated for each drug combination. A LFDR demonstrates the significance of a drug combination that follows the drug-count-response model. Then, all the drug combinations are ranked based on the LFDR accordingly.

$$LFDR = \frac{(1-\pi)\text{Bin}(n_{ij}, y_{ij}, P_{const})}{(1-\pi)\text{Bin}(n_{ij}, y_{ij}, P_{const}) + \pi\text{Bin}(n_{ij}, y_{ij}, P_{count})} \quad (\text{Eq. 2})$$

This MDCM allows different drug combinations to share the same risk probabilities, either a constant risk or a drug-count-response risk. This strategy overcomes the small sample size in each high dimensional drug combination. In this paper, we evaluate the dimension of the drugs taken from single drug to 5 co-administered drugs.

## Sensitivity Data Analysis

Overlapping and mutually validated significant (LFDR < 0.05) high dimensional drug combinations between FAERS and INPC-CDM data were further evaluated. In the follow-up sensitivity analyses, a sequential logistic regression was conducted to compare myopathy risk between any two adjacent dimensions of drug combinations, for example 1-way vs 2-way, 2-way vs 3-way, etc. The logistic regression model included the demographic, and the number of other co-medications as covariates to adjust for the confounding effects.

## High Dimensional Drug Interaction *in Vitro* to *in Vivo* Extrapolation (IVIVE)

A substrate's clearance ( $Cl_{total}$ ) is composed of hepatic clearance ( $Cl_H$ ) and renal clearance ( $Cl_R$ ),  $Cl_{total} = Cl_H + Cl_R$ . The ratio of area of under the concentration-time curve in the presence and absence of inhibitor (AUCR) is defined in (Eq 3), where  $Cl_H'$  is the hepatic clearance of the substrate drug after inhibition (49).

$$AUCR = \frac{AUC'}{AUC} = \frac{Cl_{total}}{Cl_{total}'} = \frac{Cl_H + Cl_R}{Cl_H' + Cl_R} \quad (\text{Eq. 3})$$

Let the fraction of the renal clearance ( $f_e$ ) =  $\frac{Cl_R}{Cl_H + Cl_R}$ , and  $Cl_R = Cl_H \left( \frac{f_e}{1 - f_e} \right)$ , and the AUCR can be further defined as

$$AUCR = \frac{1}{(1 - f_e) \frac{Cl_H'}{Cl_H} + f_e}$$

For high clearance drugs in which  $Cl_{int}$  approaches hepatic blood flow,  $Cl_H$  is limited by hepatic blood flow rate, and significant hepatic inhibition is unlikely. For the low clearance drugs,  $\frac{Cl_H'}{Cl_H} = \frac{f_u Cl_{int}'}{f_u Cl_{int}} =$

$$\frac{Cl_{int}'}{Cl_{int}} = \sum f m_i \frac{Cl_{int,i}'}{Cl_{int,i}}$$

where  $n$  is the number of metabolism routes.

When there is only one inhibitor and one metabolizing enzyme, Ito *et al.* (27, 49) showed that the change in clearance in the presence of a DDI can be predicted as  $\frac{Cl_{int,i}'}{Cl_{int,i}} = \frac{1}{1 + \frac{[I]}{K_i}}$ , where  $[I]$  is fraction unbound concentration of the inhibitor and  $K_i$  is the competitive inhibition constant. If there are inhibitors on the same enzyme, the inhibitors' effects are assumed to fit an additive model (50). The AUCR for inhibition of a single enzyme then becomes

$$AUCR = \frac{Cl_{int,i}'}{Cl_{int,i}} = \frac{1}{1 + \left( \sum_{j=1}^J \frac{[I_j]}{K_{ij}} \right)}$$

When considering multiple inhibitors and multiple enzyme pathways, the AUCR is predicted by equation 4 (46):

$$AUCR = \frac{1}{(1-f_e) \sum_{i=1}^n f m_i \times \frac{1}{1 + \left( \sum_{j=1}^J \frac{[I_j]}{K_{ij}} \right)} + f_e} \quad (\text{Eq. 4})$$

We used this method to predict the AUCR for each substrate drug in the presence of 1- to 4- inhibitors..

## Study Highlights

### What is the current knowledge on the topic?

High dimensional drug interactions are occasionally investigated in vitro, but rarely done in pharmaco-epidemiology studies.

### What question did this study address?

For the first time, this paper discovers and validates high dimensional drug interaction induced myopathy using two independent health record databases. This paper further investigates their pharmacokinetics mechanisms through the in vitro in vivo extrapolation.

### What does this study add to our knowledge?



Using the mixture drug-count-response model (MDCM), for the first time, this paper estimates the maximum high dimensional drug interaction induced myopathy risks. In particular, the maximum myopathy risk reaches 1.0 in the FAERS.

#### **How might this change clinical pharmacology or translational science?**

Using both IVIVE high dimensional drug interaction AUCR prediction and MDCM based data mining from two databases, we demonstrate the significantly increased myopathy risk among (omeprazole, clonidine, fluconazole), and via inhibition of CYP3A and CYP2C19 enzymes.

#### **Author Contributions**

L.L., C.C., and S.K.Q. wrote the manuscript; L.L. designed the research; C.C. performed the research; C.C. and S.K.Q. analyzed the data; C.C., P.Z., X.W., L.W., S.L., X.N., and S.K.Q. contributed new reagents/analytical tools.

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## Figure Legends

Figure 1: Drugs selection flow chart

Figure 2: Mixture dose-count model curve for both INPC and FAERS data. Red dash line is the constant risk estimated; Blue dash line is maximum risk estimated; Green dash line is drug count response risk estimated.

Figure 3: Overlapped drug combination between INPC and FAERS dataset with LFDR < 0.05

Figure 4: Simulated AUCR of 2-way to 5-way drugs combination. Only AUCR  $\geq 1.25$  are reported here.

Figure 5: Group-wise odds ratio analysis; OMZ is omeprazole or esomeprazole; CLN is clonidine; FLU is fluconazole

Figure 6: Hepatic metabolism and drug interactions between omeprazole, clonidine, and fluconazole.

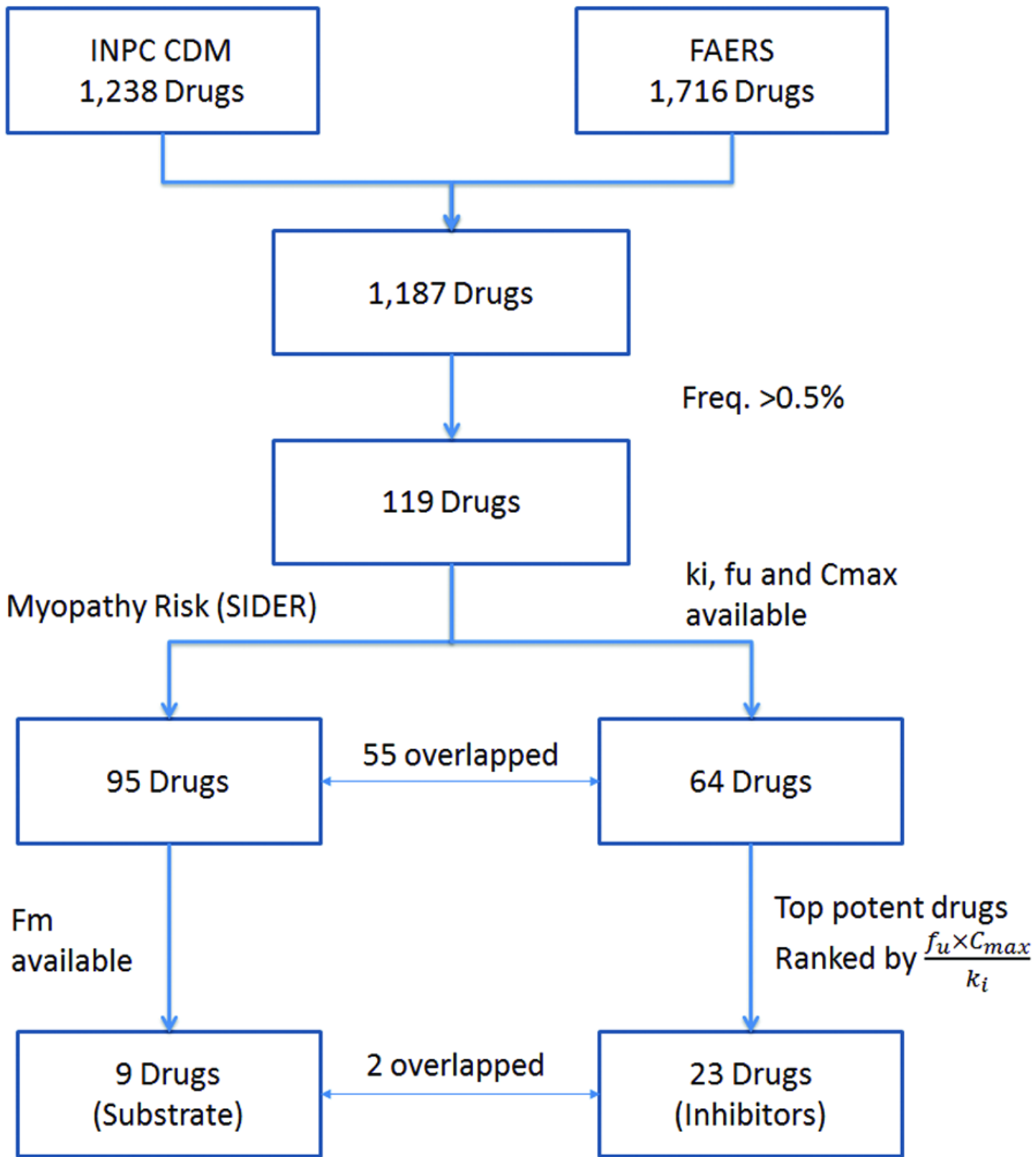
## Tables

Table 1: Top 28 3-way drugs interaction combination. G12 and G23 means the p-value of odds ratio compared taken 1 of 3 drugs vs 2 of 3 drugs, and taken 2 of 3 drugs and 3 of 3 drugs. a. Combine analysis: treated omeprazole and esomeprazole as same drug.

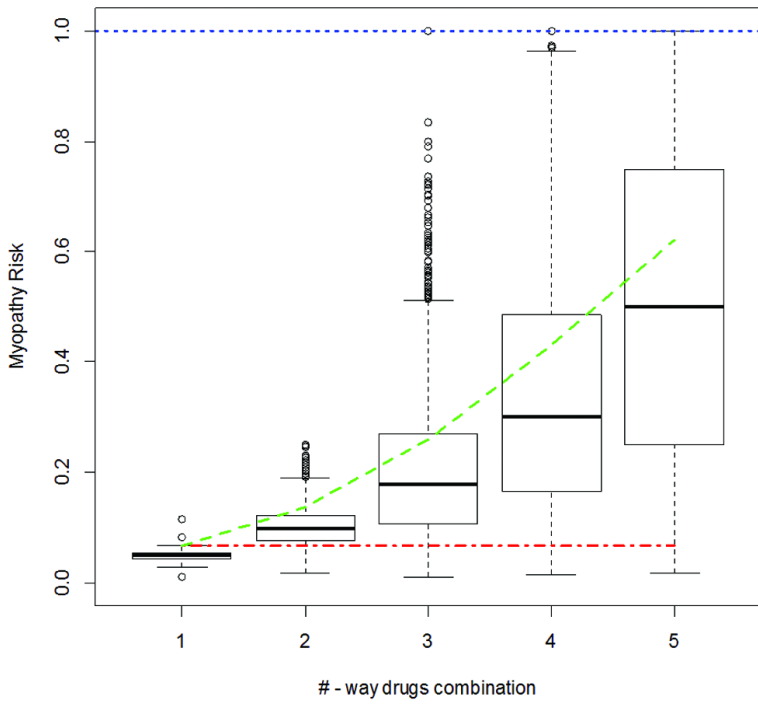
## Supplemental Material

Table S1: Phenotype definition

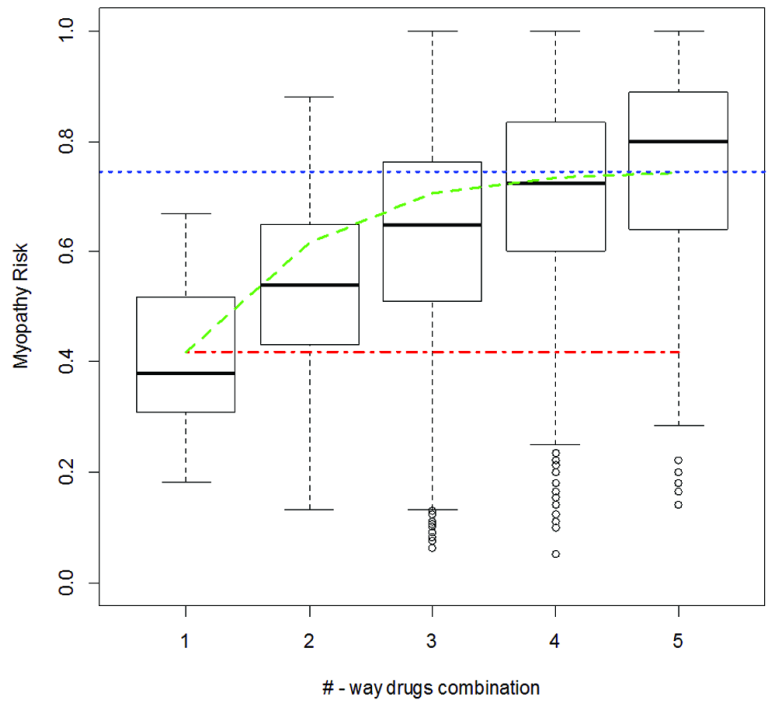
Table S2:  $f_m$  and  $f_e$



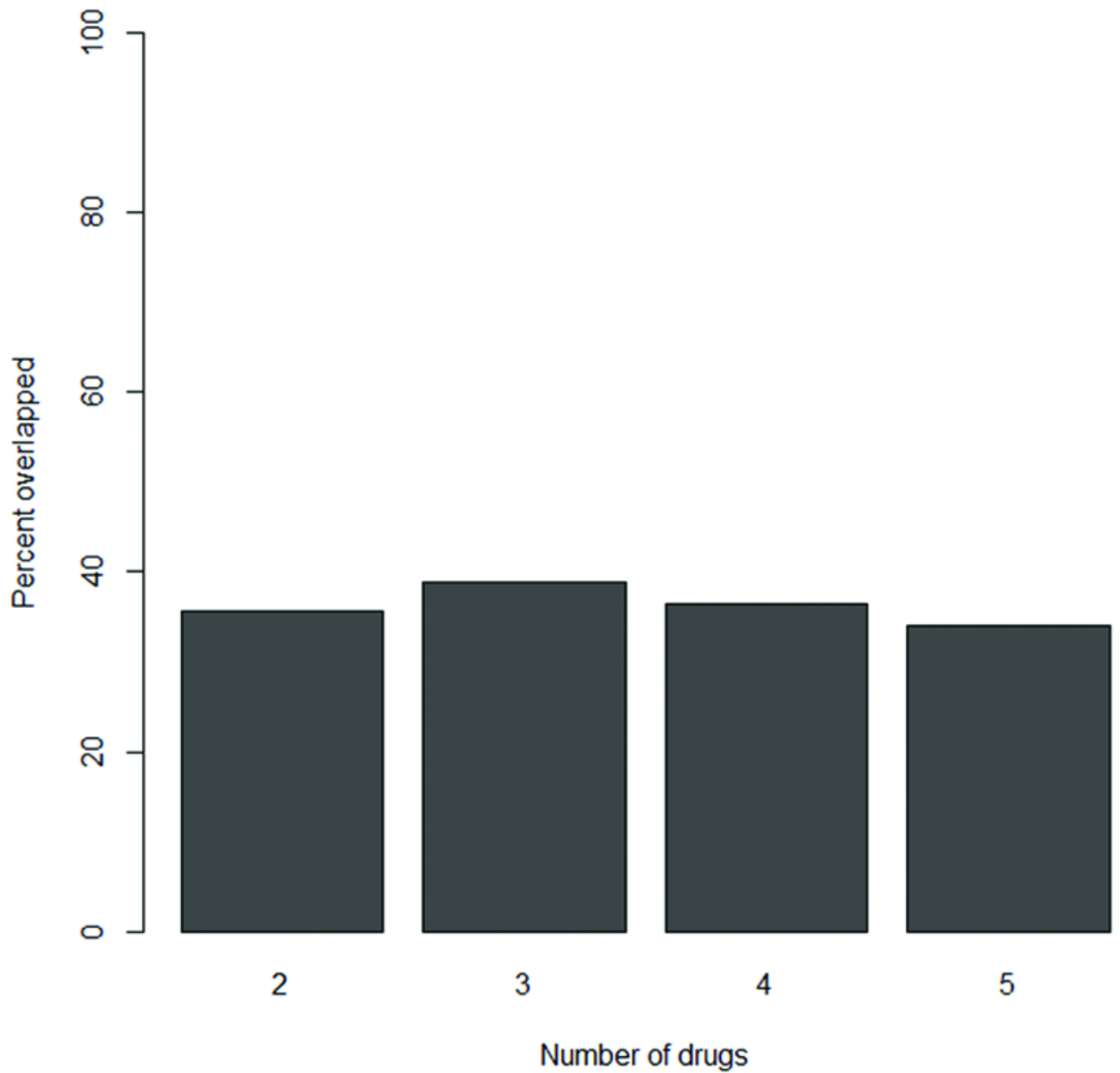
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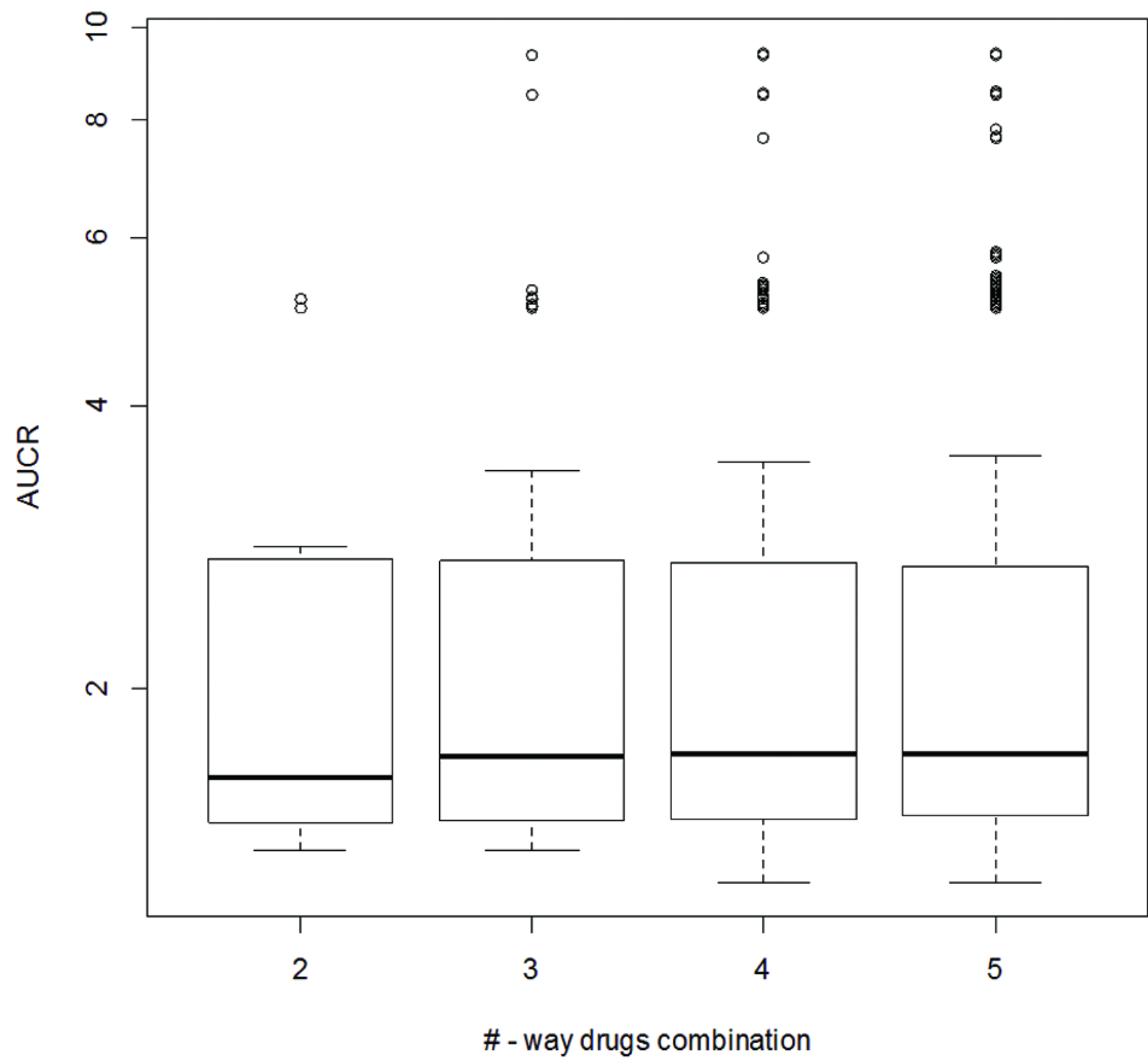
**INPC**



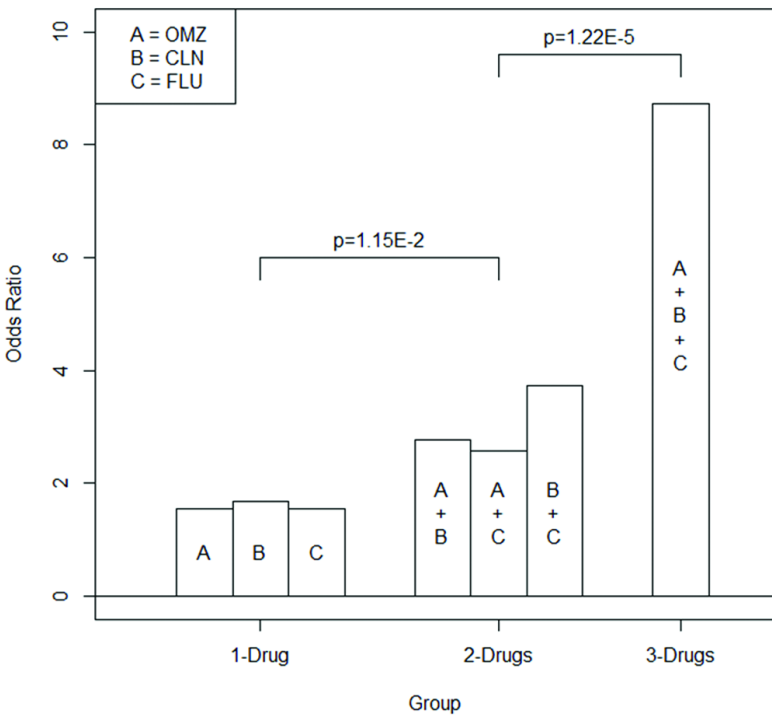




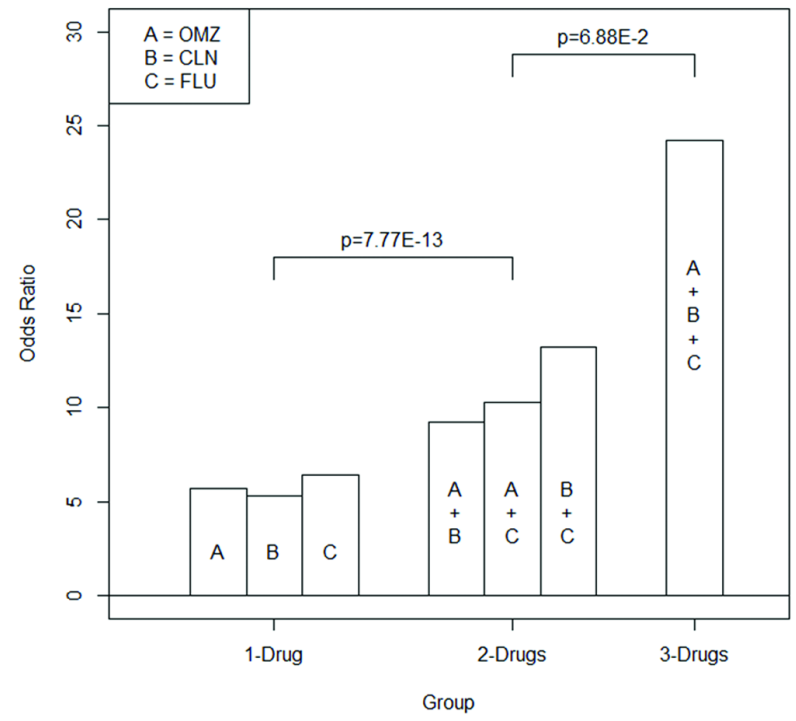
<b>Overlapped</b>	<b>109</b>	<b>1044</b>	<b>1482</b>	<b>444</b>
<b>Union</b>	<b>306</b>	<b>2686</b>	<b>4068</b>	<b>1302</b>



### FAERS



### INPC



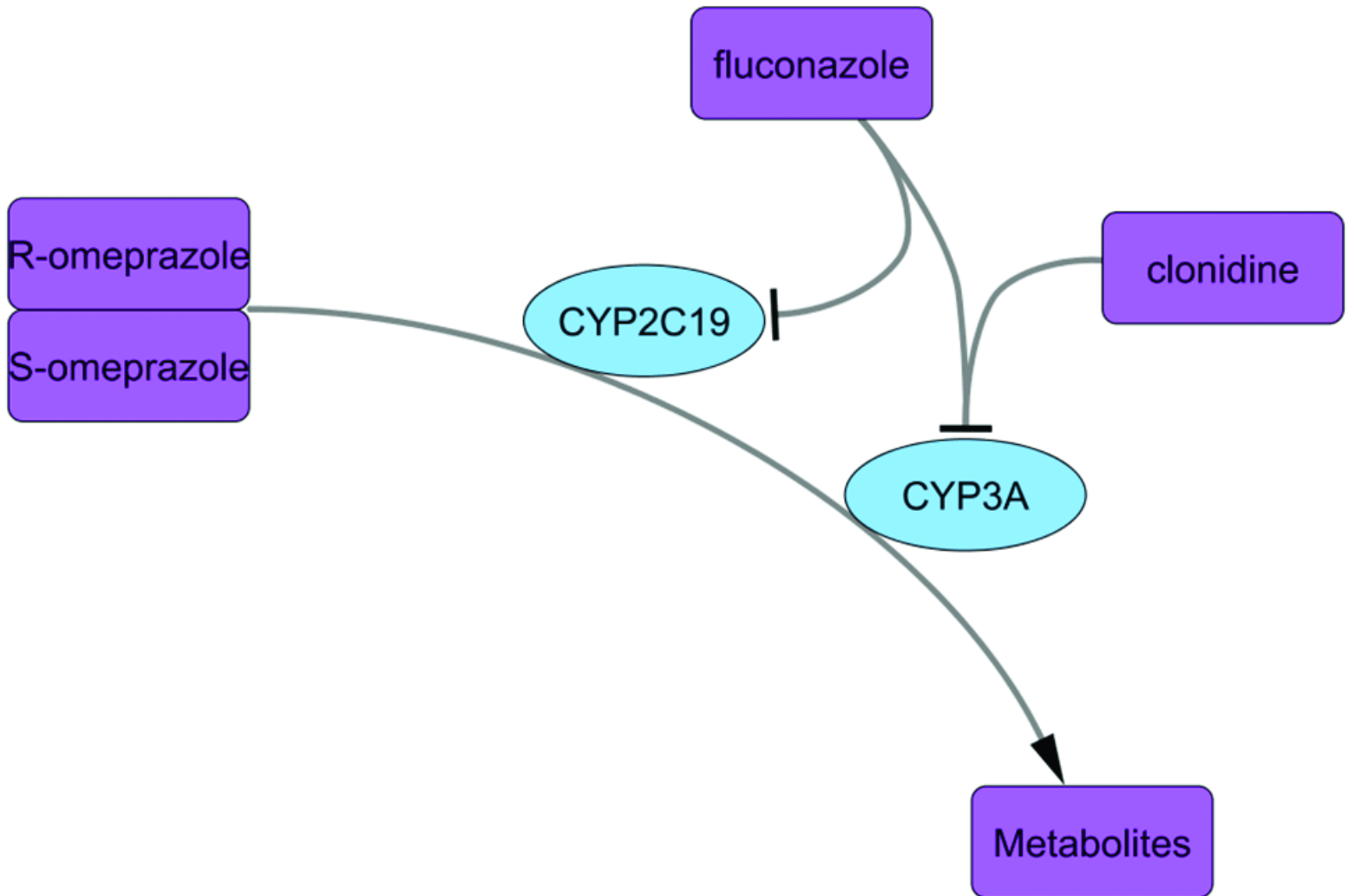


Table 1: Top 28 3-way drugs interaction combination. G12 and G23 means the p-value of odds ratio compared taken 1 of 3 drugs vs 2 of 3 drugs, and taken 2 of 3 drugs and 3 of 3 drugs. a. Combine analysis: treated omeprazole and esomeprazole as same drug.

Drugs			LFDR		AUCR			INPC-CDM					FAERS				
Substrate	Inhibitor 1	Inhibitor 2	INPC	FAERS	AUCR	AUCR1	AUCR2	OR	Total	Case	G12	G23	OR	Total	Case	G12	G23
omeprazole	fluconazole	clonidine	5.67E-03	2.68E-03	9.35	5.06	1.45	18.46	37	24	2.64E-12	4.18E-01	6.41	105	19	1.38E-01	2.00E-01
esomeprazole	fluconazole	clonidine	1.40E-04	7.14E-12	8.51	5.17	1.35	36.67	28	22	1.34E-04	4.35E-02	13.04	100	31	1.09E-01	7.64E-06
a- omeprazole/ esomeprazole	clonidine	fluconazole						24.21			7.77E-13	6.88E-02	8.73			1.15E-02	1.22E-05
esomeprazole	fluconazole	acetaminophen	4.22E-14	5.38E-04	5.20	5.17	1.01	18.77	279	182	5.13E-05	5.06E-02	5.20	922	140	3.75E-07	9.67E-02
esomeprazole	fluconazole	trazodone	6.57E-04	2.78E-06	5.19	5.17	1.01	17.31	71	45	3.83E-24	8.04E-01	10.45	68	18	1.22E-01	1.04E-01
esomeprazole	fluconazole	fentanyl	7.06E-08	2.28E-15	5.18	5.17	1.01	39.09	54	43	2.88E-24	4.96E-01	8.09	303	66	6.21E-18	2.30E-01
esomeprazole	fluconazole	metoclopramide	3.40E-06	1.29E-09	5.17	5.17	1.00	36.67	42	33	1.20E-09	9.91E-02	6.46	368	67	1.66E-01	9.00E-01
esomeprazole	fluconazole	tramadol	1.76E-02	3.69E-10	5.17	5.17	1.00	15.88	44	27	4.70E-03	4.40E-01	8.69	165	38	1.42E-01	2.76E-02
esomeprazole	fluconazole	levofloxacin	9.02E-03	1.41E-23	5.17	5.17	1.00	16.88	43	27	1.29E-16	6.44E-01	9.15	363	87	7.19E-01	8.97E-01
esomeprazole	fluconazole	ciprofloxacin	1.06E-03	4.06E-14	5.17	5.17	1.00	18.42	54	35	1.68E-05	1.00E-01	7.02	411	80	4.42E-04	2.95E-01
omeprazole	fluconazole	acetaminophen	1.25E-21	4.09E-13	5.10	5.06	1.02	18.67	450	293	3.78E-48	4.57E-02	5.67	1109	181	1.28E-01	4.15E-01
omeprazole	fluconazole	trazodone	4.12E-04	6.72E-16	5.08	5.06	1.01	18.26	65	42	4.48E-52	7.03E-01	12.74	141	43	4.50E-01	6.23E-04
omeprazole	fluconazole	fentanyl	1.07E-05	3.97E-16	5.08	5.06	1.01	27.69	49	36	4.33E-49	5.47E-01	7.85	343	73	1.21E-03	7.31E-01
omeprazole	fluconazole	paroxetine	1.69E-02	1.88E-06	5.06	5.06	1.00	18.00	28	18	1.00E-04	1.70E-01	7.38	148	30	1.94E-03	9.55E-01
omeprazole	fluconazole	diclofenac	2.42E-02	2.04E-03	5.06	5.06	1.00	17.78	25	16	8.62E-08	2.30E-01	6.61	97	18	3.57E-01	7.10E-03
omeprazole	fluconazole	levofloxacin	2.09E-03	1.93E-37	5.06	5.06	1.00	17.50	55	35	6.35E-25	4.23E-01	9.94	502	128	6.16E-02	5.28E-07
loratadine	fluconazole	tramadol	2.11E-03	1.37E-03	3.13	2.65	1.06	22.00	32	22	4.50E-09	6.91E-01	7.52	68	14	8.59E-01	5.49E-01
loratadine	clonidine	metoclopramide	2.70E-02	2.40E-02	2.86	2.84	1.00	26.67	11	8	1.74E-05	6.80E-01	7.81	33	7	3.91E-04	8.40E-01
loratadine	clonidine	levofloxacin	1.27E-03	4.50E-03	2.84	2.84	1.00	N/A	10	10	7.61E-05	6.96E-01	8.06	46	10	4.58E-01	7.91E-01
loratadine	fluconazole	fentanyl	2.32E-02	2.64E-04	2.68	2.65	1.02	35.00	9	7	3.63E-16	6.77E-01	7.46	88	18	1.61E-05	6.22E-01
loratadine	fluconazole	acetaminophen	2.57E-19	1.31E-04	2.67	2.65	1.04	39.34	148	118	3.97E-86	3.21E-03	5.86	262	44	1.19E-03	3.68E-01
loratadine	fluconazole	metoclopramide	2.50E-03	1.17E-04	2.67	2.65	1.00	100.00	11	10	1.49E-07	2.06E-01	8.88	64	15	1.28E-01	4.15E-01
loratadine	fluconazole	levofloxacin	2.14E-04	1.02E-09	2.65	2.65	1.00	80.00	18	16	9.40E-07	6.35E-02	10.24	115	30	4.97E-02	1.16E-01
venlafaxine	tramadol	clonidine	5.74E-03	2.47E-07	2.30	2.03	1.06	36.67	14	11	5.97E-08	1.18E-01	11.38	71	20	6.26E-03	5.49E-03
venlafaxine	tramadol	fentanyl	1.83E-05	2.69E-29	2.06	2.03	1.03	73.34	25	22	1.30E-22	4.55E-02	15.96	203	72	9.58E-21	1.33E-09
venlafaxine	tramadol	trazodone	6.48E-06	7.86E-13	2.06	2.03	1.03	18.00	112	72	2.39E-25	2.05E-01	7.72	281	59	1.64E-05	1.97E-03
venlafaxine	tramadol	metoclopramide	7.86E-04	8.81E-16	2.05	2.03	1.02	28.57	27	20	3.39E-16	3.34E-01	12.16	149	44	1.56E-09	4.52E-05
venlafaxine	tramadol	ciprofloxacin	1.60E-02	3.45E-12	2.05	2.03	1.00	16.92	35	22	1.30E-20	5.76E-01	14.51	90	30	8.54E-05	5.01E-02
venlafaxine	tramadol	acetaminophen	7.15E-17	1.05E-14	2.05	2.03	1.00	17.87	390	250	1.52E-59	1.07E-01	6.10	766	133	2.09E-16	1.04E-04