Systematic analysis of drug combinations that mitigate adverse drug reactions

J. Shim, H. Luo, P. Zhang, Y. Li

Seeking beneficial drug-drug combinations (DDCs) from real-world evidence is an emerging topic in phenotypic drug discovery. With sophisticated algorithms, the number of DDC hypotheses generated often reach to tens of thousands. However, due to limited resources, only a few, top-ranking hypotheses are selected for experimental validations. Often, researchers start from the topmost DDC pairs and work their way down until they find a pair with successful validation. While this is an established way of performing validations, there still exists room to improve. Here, we present a systematic approach to perform a secondary analysis on the DDCs to streamline the validation procedure. Specifically, we propose a method in which we search for additional patterns in terms of (1) chemical classes and (2) biological target interactions of the drug pair. Using 78,345 DDC hypotheses generated from the FDA Adverse Event Reporting System (FAERS) data in our prior study, we demonstrate how the proposed analysis can reveal additional biochemical and mechanical insights of drug interactions that can streamline experimental validation.

Introduction

Drug repurposing is a novel strategy in pharmacology to find a new usage for the existing drugs [1,3]. An application of this strategy is to find drug pairs, or beneficial drug-drug combinations (DDCs), in which the combination synergistically potentiates the therapeutic efficacy [2,3]. One example of aforementioned drug-drug interaction would be when an adverse drug reaction (ADR) caused by one drug is mitigated by the other drug. Most robust way to search for such beneficial DDCs is to apply sophisticated machine learning algorithms on large-scale clinical databases such as FDA Adverse Event Reporting System (FAERS). This approach usually results in myriad number of DDCs with order of magnitude at 5. Zhao et al., the first study to examine beneficial DDCs by mining through FAERS, has generated 19,133 combinations [21]. Our previous study by Li et al. also produced a considerable number of DDCs from FAERS, totaling in 78,345 combinations [3]. While all of the predicted combinations are essentially new hypotheses that can be experimentally verified, given the lengthy and costly nature of the experimental procedure, only a few, top-ranking pairs are tried for the validation. This conventional method of testing the top-performing pair does satisfy the task of validating algorithm's performance. However, a room for improvement nonetheless exists. Specifically, the DDCs generated from these algorithms are essentially a curated dataset that can be mined for embedded chemical or biological patterns. Performing a secondary analysis to understand these embedded patterns would allow researchers to enrich the understanding of DDCs. For instance, in addition to the DDCs ranked by the performance metric of the algorithm, we can generate the best DDC candidates for studying beneficial effects based on chemical classes of the drugs or biological target interactions.

To demonstrate the benefit of performing a secondary analysis, we have conducted a systematic analysis on 78,345 DDC hypotheses generated from our previous study using FAERS database. In particular, we have searched for drug class interaction patterns by further classifying the DDCs based on the WHO Anatomical Therapeutic Chemical (ATC) classification code. Additionally, biological targets and actions of DDCs are examined by referencing information listed in the DrugBank. With this approach, we have conducted three case studies to demonstrate the various level of information that can be retrieved from DDCs which can be used to tailor or streamline the experimental validation process.

Materials and Methods

Source of DDC hypotheses

We have generated 78,345 DDCs with ADR prediction algorithm from Li et al. to conduct secondary analyses [3]. The algorithm developed by Li et al. is consisted of three major steps: (1) identify and filter potential candidate triples of Drug A-ADR-Drug B; (2) compute propensity scores for individual drugs; and (3) determine the associations for each specific Drug A-ADR-Drug B triple. The algorithm output contains a predicted beneficial score for each triple in which lower score suggests higher mitigative potency of the Drug B for the ADR induced by Drug A. We have ranked the beneficial score of each triple and filtered for high statistical significance for the mitigative effect by Drug B which finalized our list to 77,502 DDCs.

Case 1: examination of prediction result ranked by the predicted beneficial score pattern

The DDC pairs were first ranked by predicted beneficial scores and then each drug in the pair were filtered to only include the pairs with identifiable (1) therapeutic target and action information registered in DrugBank [4] (2) therapeutic classes by WHO Anatomical Therapeutic Chemical (ATC) classification code (http://www.whocc.no/atcstructure_and_principles/) (Figure 1). As an example of conventional method to select drug pair to validate the performance of the algorithm, the best performing...
DDC pair, based on the predicted beneficial score, is selected for a case study.

**Case 2: examination of prediction result using therapeutic class interaction pattern**

We obtained ATC level 4 information for each drug in the DDC pair to examine whether there is any pattern for chemical class interactions (Figure 1). Using ATC level 4 classes of each drug, we computed the frequency of class combinations. The top 10 most frequent ATC level 4 class combinations for ADR mitigation were examined to investigate if (1) certain offending drug class has higher number of mitigating classes being paired with and (2) whether there is a favored mitigating drug within the same therapeutic class for a specific class combination category. In order to address these points, a case study has been conducted from the most frequently paired offending therapeutic class with a mitigating drug.

**Case 3: examination of prediction result using drug target interaction pattern**

To examine whether there is a direct interaction on the shared target from the predicted DDC pair, we have identified the shared target(s) and the associated action(s) using DrugBank reference (Figure 1). The targets were identified using molecular target, enzyme and transporter reference lists from DrugBank. Once target and action have been identified for all the DDC pairs, they were categorized them into a group with at least one shared target and another group with no shared target. Next, the action of the drug on the shared target has been categorized as positive, negative and the other to classify the type of interaction.

<table>
<thead>
<tr>
<th>Offender</th>
<th>ADR by the Offending Drug</th>
<th>Potential Mitigator</th>
<th>Predicted Beneficial Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone</td>
<td>PYREXIA</td>
<td>Proguanil</td>
<td>-0.355125324</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Pamidronate</td>
<td>-0.327538763</td>
</tr>
<tr>
<td>Niacin</td>
<td>FLUSHING</td>
<td>Adalimumab</td>
<td>-0.324978734</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Adalimumab</td>
<td>-0.318317057</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Exenatide</td>
<td>-0.31646666</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Adalimumab</td>
<td>-0.311627727</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Adalimumab</td>
<td>-0.28759145</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Infliximab</td>
<td>-0.281904513</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Omeprazole</td>
<td>-0.280770576</td>
</tr>
<tr>
<td>Progesterone</td>
<td>BREAST CANCER</td>
<td>Prednisone</td>
<td>-0.2647752</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Adalimumab</td>
<td>-0.26331541</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>MYOCARDIAL INFARCTION</td>
<td>Zolpidem</td>
<td>-0.260049212</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>CEREBROVASCULAR AR ACCIDENT</td>
<td>Adalimumab</td>
<td>-0.259385891</td>
</tr>
<tr>
<td>Progesterone</td>
<td>BREAST CANCER</td>
<td>Niacin</td>
<td>-0.258407649</td>
</tr>
</tbody>
</table>
by each drug of the DDC pair. Positive interactions include terms such as *activator*, *agonist*, *potentiator*, and *stimulator* while negative interaction includes terms like *antagonist*, *inhibitor*, and *suppressor*. Other group of interactions include such terms as *other*, *chaperone*, and *unknown*. After categorizing interaction of the shared target, DDCs were further divided into the drug pairs with *incoherent* (or opposing) interactions on the shared target and the drug pairs with *coherent* (or reinforcing) interactions. An example of an incoherent interaction would be when a DDC pair is composed of drug A that is an agonist (positive effector) on the shared target while drug B is an antagonist (negative effector). A coherent interaction could be when both drug A and B of DDC pair act as either agonist or antagonist on the shared target. For the case study, we examined the DDCs with incoherent action on the shared target. In particular, we examined whether the incoherent action on the shared target could be used as a potential hypothesis for the underlying mechanism of the mitigative effect.

**Result**

**Examining prediction results by the predicted beneficial score**

A total of 78,345 DDC pairs were initially generated, and after examining the beneficial scores from the DDC prediction algorithm by Ying et al., 77,502 pairs were identified as showing statistical significance for ADR reduction by its mitigative pair, and therefore, selected for the further analysis. Prior to matching drug pairs with the respective target and action information, drug names from FAERS were first converted to its matching generic names and then to the corresponding DrugBank ID. From 77,502 pairs, using DrugBank reference, generic name and the matching DrugBank IDs were retrieved for 62,695 pairs. Of those, 58,549 pairs had identifiable target for both drugs and 4,146 pairs had at least one drug with unidentified target (or the target information missing from the DrugBank reference).

Based on the predicted beneficial score, the DDC pairs were ranked in the descending order (Table 1) and the top most pair was chosen to be examined in a case study to confirm the validity of the predictions generated.

Table 2 Drug target and action information for the highest ranking DDC pair: atovaquone & proguanil.

<table>
<thead>
<tr>
<th>Atovaquone</th>
<th>Proguanil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>Cytochrome b</td>
<td>inhibitor</td>
</tr>
<tr>
<td>Dihydroorotate dehydrogenase (quinone), mitochondrial</td>
<td>inhibitor</td>
</tr>
<tr>
<td>Dihydroorotate dehydrogenase (quinone), mitochondrial</td>
<td>inhibitor</td>
</tr>
</tbody>
</table>

**Case Study 1: Atovaquone & Proguanil**

From the 58,549 DDC pairs with identified target and action for both offending drug and the potential mitigating drug, atovaquone and proguanil pair has been identified as having the strongest therapeutic potential with the predicted beneficial score of -0.36. Atovaquone and proguanil are both anti-malarial drug with different molecular targets (Table 2).

In support of this prediction result, we have found numerous studies reporting strong therapeutic benefits with reduced incidence of atovaquone associated side effect for this particular combination in the treatment of malaria [5-7]. While atovaquone is reported to have maculopapular rash, gastrointestinal disturbances, and fever (pyrexia) as common adverse events [8], the clinical studies using combination therapy reported having virtually no side effect [6] or minimal side effect including nausea and abdominal pain [5]. Furthermore, it has been found that atovaquone and proguanil combination therapy has a higher treatment efficacy for malaria than atovaquone alone [6]. This reduction in adverse events while increasing the potency for malaria treatment is thought to be caused by the synergistic effect of the two drugs on inducing the collapse of inner-mitochondria membrane potential of the malarial parasite [9]. This reinforced outcome is thought to take parts in two separate pathways as their targets do not participate in the same molecular process. Atovaquone selectively inhibits malarial cytochrome bc1 complex[10] while proguanil inhibits dihydrofolate reductase, an enzyme needed to produce pyrimidine [9]. It has been suggested that atovaquone destabilizes cytochrome bc1 complex leading to proton leakage from mitochondria and this leakage is reinforced by proguanil through unclear mechanism [9].

**Examining prediction results by the patterns related to chemical classes & biological target interactions**

**Therapeutic Chemical Class Interaction Analysis**

To investigate any favorable chemical class combinations, we have filtered 58,549 DDCs with identifiable chemical classes using WHO ATC classification code. Of those, 49,643 pairs had both drugs’ therapeutic chemical class identified. The 49,643 DDC pairs were then subjected to the further analysis to examine (1) if there is a favorable interaction between particular therapeutic chemical classes and (2) whether these pairings have support from previous work. Addressing the first topic, we have identified the therapeutic chemical classes of each drug in the DDC pairs and generated a histogram of the top 10 most frequent class-class combinations (Figure 2A). The highest number of ADR reducing, therapeutic class combination from the DDC list was antidepressant and TNF-α inhibitor (363 incidents of ADR reduced by this class combination). All the top 10 class combinations exhibited similar beneficial score distribution (Figure 2B).

A pattern that is immediately noticeable from looking at top 10 favorable therapeutic class interactions (Figure 2A) is that Selective Serotonin Reuptake Inhibitor (SSRI) appears to interact with many of other chemical classes. Intrigued by this pattern of therapeutic class pairing, we further examined class combinations where the SSRI class was the offending drug class.

A total of 154 different classes were predicted to be mitigative
of SSRI related adverse effects. To investigate the strength of these class interactions, for each of 154 interactions, a total number of SSRI drugs and the mitigating class drugs were counted. This step revealed that 113 out of 154 interactions had either one SSRI drug interacting with multiple mitigative class drugs or one mitigative drug with multiple SSRI drugs. Because we are interested in class-class combinations where numerous drugs from each class are predicted to cause beneficial effect, we focused on the remaining 41 class interactions and ruled out the other 113 interactions. The 41 interactions with SSRI as the offending class were ranked based on the number of SSRIIs and the mitigating class drugs (Table 3).

From the list of SSRI class interaction in Table 3, we selected the SSRI interaction with ‘Other antidepressants in ATC’ for the second case study. This combination was chosen because it had 4 or 5 drugs in each class with relatively small number of DDC specific ADR mitigation, which indicates specificity in ADR being mitigated.

Under SSRI and the other antidepressant class combination, 22 DDCs have been predicted to reduce SSRI related ADRs. Of the 22 DDCs, 14 were paired with bupropion (Figure 3). This favored pattern in SSRI pairing with bupropion appeared as a

Table 3 Predicted mitigative drug classes for SSRI class induced adverse reactions ranked by the number of interacting drugs.

<table>
<thead>
<tr>
<th>Offender Drug Class</th>
<th>Mitigator Drug Class</th>
<th>No. of ADR-drug pairs</th>
<th>No. of SSRI drugs</th>
<th>No. of Mitigating Class Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td>171</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td></td>
<td>242</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
<td>188</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td>194</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other antidepressants in ATC</td>
<td></td>
<td>22</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Other antiepileptics in ATC</td>
<td></td>
<td>106</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Benzo diazepine derivative anxiolytics</td>
<td></td>
<td>22</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Beta blocking agents</td>
<td></td>
<td>137</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*No of ADR-drug pair represents the number of unique drug-drug-adverse reaction combination

Figure 2 Top 10 Favorable Therapeutic Class Interaction found from 49,643 DDC combination & beneficial score distribution. (A) The ranking is based on the frequency of therapeutic chemical class interactions based on the level4 information of the WHO ATC chemical classification code. (B) The beneficial score distribution of each of top 10 class interactions are shown in boxplots. The first class represents the offending drug class and the class after <> represents the mitigating class.

Figure 3 The list of mitigative drugs under other antidepressant class for SSRI-related ADR. Five mitigative drugs are predicted to be beneficial in reducing SSRI related ADRs. Bupropion is reported as the most frequently paired mitigative drug.
Case Study 2: SSRI & Bupropion

We found a total of 14 adverse event mitigation events in drug combination with 4 drugs from SSRI class and bupropion, an Other antidepressants in ATC, from Li et al. SSRI is a class of drug used to treat major depressive disorder (MDD) and the common side effects associated are Gastrointestinal (GI) disturbances, anxiety, agitation, insomnia, sexual dysfunction, weight gain, and sleep disturbance [11]. We found supportive evidence from the literature showing the potency of this type of class combinations on reducing SSRI induced ADRs. The DDC list suggests that the combination therapy with bupropion would reduce several adverse events associated with SSRI while maintaining the potency of SSRI for MDD treatment. The adverse events relieved by this combination are outlined in Table 4.

In numerous previous studies, bupropion has been suggested as an option for combination therapy to mitigate the adverse events associated with SSRI. The major side effects reported to be reduced by bupropion include sexual dysfunction [12-13], weight gain [13], and SSRI-induced emotional detachment [14]. Additionally, there has been a strong clinical evidence in SSRI pairing with bupropion for the treatment of MDD related symptoms with minimal side effects. In previous studies, SSRI drugs, escitalopram, citalopram and sertraline have been recommended to be paired with bupropion with significantly improved remission rate of depression [15-17]. In a large clinical study for evaluation of combination therapy with citalopram and bupropion, it has been shown that this combination therapy can be used for patients with intolerance to citalopram, indicating this combination therapy can not only augment the therapeutic value of citalopram but makes treatment with citalopram tolerable [18]. While these previous studies do not specifically address the ADRs found to be associated in the prediction, they strongly suggest that the SSRI and bupropion combination have clinical importance in reducing SSRI-induced ADRs and augmenting potency of MDD treatment.

The mechanism behind the benefits of SSRI and bupropion pairing is unclear although it has been suggested that it may come from synergistic effect of two different antidepressant mechanism on serotonergic, dopaminergic and noradrenergic systems [16].

Target Action Analysis

From the 58,549 DDCs with identified targets, only 517 DDCs had at least one shared target. Among the 517 DDCs, there were a total of 6,921 shared target interactions found. Of all, 4,274 interactions were coherent, meaning both drug had similar type of interaction with the shared target. The other 2,013 interactions had shared target identified but the interaction information was either vague or unknown for one of the DDC. The rest, 634 target interactions, were composed of incoherent (opposing) act by the DDCs on the shared target. We have ranked these 634 interactions by the predicted beneficial score. The top 10 list from this group has been examined to see whether there is any support from previous studies on the DDCs with incoherent interaction on the shared target (Figure 4A). In particular, we chose to conduct case study on the association between D2 Dopamine Receptor & Diabetes Mellitus as this combination had the strongest predicted beneficial score.

Table 4 Bupropion mediated relief of SSRI related ADRs.

<table>
<thead>
<tr>
<th>SSRI &amp; Bupropion</th>
<th>ADR Mitigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>HOT FLUSH, JOINT STIFFNESS, APLASIA PURE RED CELL</td>
</tr>
<tr>
<td>Bupropion</td>
<td>AGGRESSION, HYPERKALEAemia, GASTRIC ULCER, FEELING JITTERY, NERVOUSNESS, COLD SWEAT</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>HYPOGLYCAemia, EPISTAXIS, DYSKINESIA</td>
</tr>
<tr>
<td>Sertraline</td>
<td>IRRITABILITY, FEELING JITTERY</td>
</tr>
</tbody>
</table>

Figure 4 Top 10 favorable therapeutic class interaction found from 49,643 DDC combination & beneficial score distribution. (A) The ranking is based on the frequency of therapeutic chemical class interactions based on the level4 information of the WHO ATC chemical classification code. (B) The beneficial score distribution of each of top 50 class interactions are shown in boxplots.
distribution (Figure 4B).

Case Study 3: Diabetes Mellitus as ADR & Dopamine D2 Receptor

In previous studies, dopamine D2 receptor has been identified as a potential diabetes therapeutic target. Specifically, in 2009, a dopamine D2 receptor agonist, bromocriptine, was approved as a therapeutic for type 2 diabetes [19]. This suggests that dopamine D2 receptor is important molecular target in the development and treatment of diabetes. Under the ADR-target category of D2 Dopamine Receptor & Diabetes Mellitus, there were total of 8 DDCs predicted to be beneficial (Table 5). The offenders -- olanzapine, quetiapine, and risperidone -- are all used as antipsychotics and have shown strong association with diabetes [20]. Olanzapine, in particular, has been reported to induce acute diabetes in dose dependent manner [20].

While the association with diabetes is an established phenomenon for the three offenders, the mechanism behind the development of diabetes still remains unclear. However, there has been a hypothesis involving dopamine D2 receptor. Specifically, it has been suggested that blocking dopamine D2 receptor can prevent normal activity of sympathetic-adrenal regulation there by leading to elevated sympathetic tone and metabolic dysregulation, mimicking symptoms of diabetes [20]. From examining our list of DDCs, we notice that olanzapine is a mixed agonist-antagonist, meaning under certain conditions the drug will behave like an agonist and in another like an antagonist. Interestingly, olanzapine is found to be beneficial when paired with a dopamine D2 antagonist (Table 4) indicating that olanzapine might have been acting as an agonist in those incidences. Therefore, this might introduce a new hypothesis that, perhaps, it is not just a blockage of dopamine D2 receptor but also interfering with normal dopamine D2 receptor activity/ regulation in general that can lead to diabetes.

Discussion

We have examined three case studies to exemplify different level of additional chemical and biological information that can be retrieved with the systematic secondary analysis. The first case study represents the conventional method of verifying the validity of drug combinations found through mining electronic medical records. Second and third case studies demonstrate that there are additional patterns researchers can find in their drug combinations to further explore experimental ideas. Specifically, for our second case study regarding chemical class combination patterns, we have examined SSRI as a class beneficially interacting with bupropion. There were four SSRIs -- escitalopram, citalopram, fluoxetine and sertraline -- predicted to be beneficial with bupropion. Interestingly, we found that only three of the four SSRIs -- escitalopram, citalopram and sertraline -- have already been recommended for a combination therapy with bupropion. This strongly suggests that the therapeutic potency of the fourth drug, fluoxetine, could also be augmented through combination with bupropion. The secondary analysis using chemical classes, which led to the identification of fluoxetine and bupropion as a strong experimental candidate, demonstrates two major benefits. First, researchers can examine whether there is pre-existing evidence for beneficial combination for the other members of the therapeutic chemical class with similar structure and target, which could be reassuring for the potency of the predicted interaction. Second, researchers can refer to the previous experiments and methods for how the other similar drugs have been verified so they can tailor their experimental design more efficiently.

In our third case study, we examined frequently paired ADR & the shared drug target and identified possible association between diabetes and dopamine D2 receptor. Specifically, we noticed that opposing action on dopamine D2 receptor by the DDC mitigates diabetes as ADR. Our offender drugs, four antipsychotics (Table 5), were either an antagonist paired with an agonist as the mitigative drug or a mixed agonist-antagonist paired with an antagonist. The DDC pairing with dopamine D2 antagonist as an offender and agonist as a mitigator has literature support, as the leading hypothesis of antipsychotic drug induced diabetes is the blockage of dopamine D2 receptor. However, the pairing with mixed agonist-antagonist and the antagonist as the mitigator presents possibility for a slightly modified hypothesis. Because previous work has demonstrated that blockage of dopamine D2 receptor is strongly associated with diabetes, it is highly likely that the mixed agonist-antagonist offenders here acted closer to agonist than an...
antagonist for them to be paired with an antagonist as mitigator. Therefore, another possible hypothesis could be interfering with homeostasis of dopamine D2 receptor in general increases the susceptibility of drug induced diabetes.

In addition to the three case studies, we have explored whether there is a correlation between structure similarity of DDCs with shared target (Figure 5). First, we extracted DDCs where both of drugs have identifiable SMILES (Simplified Molecular Input Line Entry System) from DrugBank [4] and this resulted in a total of 1,893 DDCs. Second, we classified these DDCs into two groups involving coherent and incoherent group. The coherent group indicates that drugs in DDC pairs share the same target, and regulates the target in the same direction, e.g. both inhibit or activates the target, while the incoherent group indicates that drugs in DDC pairs share the same target but regulate the target in the opposite direction, e.g. one inhibits the target and the other activates the target. This step led to 1,685 DDCs in coherent group and 208 in incoherent group. We further plot the histogram for both coherent group and incoherent group according to their predicted beneficial scores shown in Figure 5A.

Next, we generated Tanimoto coefficients between the offending and the mitigating drug of each DDC pair for both coherent and incoherent groups using SMILES and R package ‘rcdk’ [22]. The Tanimoto coefficient was used as a metric to indicate structural similarities between the offending and mitigating drug of each DDC pair.

To examine if there is any relationship between the drug structural similarities and the predicted score, we generated a scatter plot for Tanimoto coefficient versus predicted score (Figure 5B). From this additional analysis, we concluded that there is no obvious sign of structural differences between the two groups. Furthermore, we report that there is no obvious relationship between the structural similarities and the predicted scores in both groups.

This type of secondary analysis to identify possible target responsible for specific ADR presents an opportunity to explore an existing hypothesis, such as shown here, or generate a new, detailed hypothesis for mechanistic insights of toxicity development. Given experiments with clear hypothesis is easier to perform in a time and cost effective way, we present this analysis as a possible method for tailoring experimental validation process.

**Conclusion**

We have performed a systematic, secondary analysis on the 78,345 pairs of beneficial drug combinations generated by mining through the FAERS database. The purpose of this analysis is to explore additional pattern that could reveal insights into chemical and biological information about the beneficial drug combinations.

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**References**


Jaehee Shim Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA (jaehee.shim@icahn.mssm.edu). Ms. Shim is a 5th year PhD Candidate in the Department of Pharmacological Sciences at Icahn School of Medicine at Mount Sinai. Her thesis project aims to predict tyrosine kinase inhibitor induced cardiotoxicity using gene expression data. The work involved in her thesis project includes building a computational pipeline to integrate gene expression data with mathematical models descriptive of cellular signaling in cardiomyocytes such as structural remodeling and contractile dysfunction. Ms. Shim has participated in the summer internship with the Health Analytics Group at the IBM T.J. Watson Research Center in 2016.

Heng Luo IBM Research, Thomas J. Watson Research Center, Yorktown Heights, NY 10598 USA (heng.luo@ibm.com). Dr. Luo is a Postdoctoral Researcher in Drug Discovery Technologies Group at IBM Thomas J. Watson Research Center. His research interests and experiences include bioinformatics, machine learning, statistical analysis and their applications in drug safety evaluation, drug repositioning and precision medicine. He analyzes real-world evidence data, gene-expression data, structural data, chemo-informatics data and other knowledgebases to generate insights in the healthcare domain.

Ping Zhang Healthcare & Life Sciences Research, IBM Thomas J. Watson Research Center, Yorktown Heights, NY 10598 USA (pzhang@us.ibm.com). Dr. Zhang is a Research Staff Member at IBM. He received his PhD in Computer and Information Sciences from Temple University. His research focuses on machine learning, data mining, and their applications to biomedical informatics and computational medicine. Dr. Zhang is a distinguished speaker of Association for Computing Machinery (ACM), and a senior member of the Institute of Electrical and Electronics Engineers (IEEE). He serves on the editorial boards of BMC Medical Informatics and Decision Making, CPT: Pharmacometrics & Systems Pharmacology, and Journal of Healthcare Informatics Research.

Ying Li IBM Research, Thomas J. Watson Research Center, Yorktown Heights, NY 10598 USA (yiling@us.ibm.com). Dr. Li is a Research Staff Member in the IBM T.J. Watson Research Center. She graduated with a Ph.D. degree of Biomedical Informatics at Columbia University. Her research interests involve pharmacovigilance, drug repurposing and medication use related analysis using real world evidence and data mining techniques. She has published several articles in refereed journals and conferences, including Nature Biotechnology, Journal of the American Medical Informatics Association (JAMIA) and Drug Safety journals, and American Medical Informatics Association Annual Symposium (AMIA).