Construction of Drug Network Based on Side Effects and Its Application for Drug Repositioning

Hao Ye¹, Qi Liu², Jia Wei¹

1 R&D Information, AstraZeneca, Shanghai, China, 2 School of Life Sciences and Technology, Tongji University, Shanghai, China

Abstract

Drugs with similar side-effect profiles may share similar therapeutic properties through related mechanisms of action. In this study, a drug-drug network was constructed based on the similarities between their clinical side effects. The indications of a drug may be inferred by the enriched FDA-approved functions of its neighbouring drugs in the network. We systematically screened new indications for 1234 drugs with more than 2 network neighbours, 36.87% of the drugs achieved a performance score of Normalized Discounted Cumulative Gain in the top 5 positions (NDCG@5)\(\geq 0.7\), which means most of the known FDA-approved indications were well predicted at the top 5 positions. In particular, drugs for diabetes, obesity, laxatives and antimycobacterials had extremely high performance with more than 80% of them achieving NDCG@5\(\geq 0.7\).

Additionally, by manually checking the predicted 1858 drug-indication pairs with Expression Analysis Systematic Explorer (EASE) score\(\leq 10^{-7}\) (EASE score is a rigorously modified Fisher exact test p-value), we found that 80.73% of such pairs could be verified by preclinical/clinical studies or scientific literature. Furthermore, our method could be extended to predict drugs not covered in the network. We took 98 external drugs not covered in the network as the test sample set. Based on our similarity criteria using side effects, we identified 41 drugs with significant similarities to other drugs in the network. Among them, 36.59% of the drugs achieved NDCG@5\(\geq 0.7\). In all of the 106 drug-indication pairs with an EASE score\(\leq 0.05\), 50.94% of them are supported by FDA approval or preclinical/clinical studies. In summary, our method which is based on the indications enriched by network neighbours may provide new clues for drug repositioning using side effects.

Introduction

The inefficiency of pharmaceutical drug development with high expenditure but low productivity has been widely discussed [1,2,3,4]. Drug repositioning is considered to be a promising strategy to revitalize the slowing drug discovery pipeline due to shorter development timelines and lower risk of unexpected toxicity [5,6,7]. Traditionally, most of the successful examples mainly relied on serendipity or ‘happy accidents’ (eg, Viagra, Dapoxetine, Duloxetine) [6,8], which made repositioning very unpredictable. In 2006, Lamb et al [9] proposed the connectivity map based on the gene expression profiles of drugs for repositioning, which is the first computational method in this field. Then a group of investigators utilized structural features of compounds/proteins to predict new targets of drugs, such as molecular docking [10,11], QSAR modelling [12]. In addition, the association between diseases/drugs in genetic activity was suggested to facilitate repositioning, such as genome-wide association [13], pathway profiles [14,15], and transcriptional responses [16]. Furthermore, several integrative methods which combined chemical or genetic features were proposed to predict the drug targets or indications, for example, PREDICT [17], TMFS [11]. Obviously, most of these methods focus on the molecular mechanism of action (MOA) from a genotypic perspective. Nevertheless, the pre-clinical outcomes based on MOA often do not correlate well with therapeutic efficacy in drug development. It is estimated that of all the compounds effective in cell assays, only 30% of them could work in animals. Even worse, only 5% of them could work in humans [18].

The gap between MOA and the physiological responses of drugs may limit the usefulness of the methods mentioned above. Side effects are generated when the drugs bind to off-targets, which perturb unexpected metabolic or signaling pathways [19]. Therefore, side effects from clinical patients may be seen as valuable read-outs of drug effects on human bodies, which may also serve as a promising perspective for drug repositioning. Up to now, only a few of the repositioning efforts focus on physiological responses. Most of them are developed using the side effect data in SIDER [20], which was constructed by the Bork’ group in 2010. The latest version of SIDER contains 996 drugs and 4192 side effects. Lun proposed DReSeF [21], where the basic hypothesis is that if the side effects associated with a drug are also induced by many drugs treating a disease, then this drug should be evaluated as a candidate to treat that disease. Initially, they constructed side effect profiles of diseases based on drug-indication data and drugside effect data. The QSAR models were trained to build associations between structures and side effects. Then indications of the drug could be predicted by combining the side effect profiles of diseases with structure and side effect associations. Lun’s work pioneered an approach to drug repositioning using side effects and achieved good performance. Up to now, side effects are still the...
Network Based Drug Repositioning Using Side Effect Information

In this study, we intend to propose a network based method for drug repositioning by exploring the entire existing catalog of side effect data. Instead of directly building the relationship between side effects and diseases, we would like to construct drug-drug relationships through side effect similarities. Our basic hypothesis is that drugs with similar side-effect profiles may also share similar therapeutic properties [22]. A drug network could be constructed based on the similarities of side effects. In this way, the indications of a drug may be predicted by the functional distribution of its neighbouring drugs. Since we have already investigated chemical structures [23] and pathway profiles [14,15] for drug repositioning, side effect based repositioning could enhance our computational repositioning platform and provide complementary evidence.

Materials and Methods

Drug side effects

In this study, side effects were extracted from Meyler’s Side Effects of Drugs 15th edition [24]. Additional drug sides effects, especially for the drugs launched after 2006, were collected from Side Effects of Drug Annuals (2007–2012) [25] and the FDA drug approval package (see Table 1). Specifically, each electronic book was converted from PDF to text format by Acrobat professional v10.1. Then, a Java program was implemented to parse the drug information and side effects. Considering the side effects in Meyler’s Side Effects of Drugs 15th edition and Side Effects of Drugs Annuals (2007–2012) were organised using MedDRA vocabularies version 15.1, the preferred items (PT level) in MedDRA were utilized as the standard side effect vocabulary. The side effect data from other resources were mapped to MedDRA preferred items, avoiding the semantic redundancy. For example “respiratory diseases” and “respiration diseases” were identified as two different side effects in the raw data, and both of them were mapped to the same preferred item “respiratory disease” in MedDRA.

External test samples

As described in Table 1, SIDER is a frequently cited resource for drug side effects. Herein, 98 drugs in SIDER version 2 which were not covered by the drug network were used as external test samples (see the 98 drugs in Table S1). Also, the side effects in SIDER were mapped to preferred items in MedDRA version 15.1.

Drug indication

FDA-approved indications were obtained from Citeline Pipeline, Thomson Reuters Partnering and GenoGo (see details in Table 2). Next, each indication was modified to a MeSH heading. Finally, we obtained 2183 drugs with 6495 clinical side effects and 994 4th level MeSH items.

Drug network construction with side effects (see Figure 1)

Step 1: Build the side effect fingerprint. Herein, each side effect was treated as a feature vector. If a drug displays side effect i, then it would be tagged “1” in the element i, otherwise, it would be marked “0”. After that a 0-1 binary vector was defined as the side effect fingerprint for the drug. For the 2183 drugs with recorded clinical side effect data, each would be assigned a 6495-dimension vector.

Step 2: Calculate the similarity between drugs. The Jaccard index was used to evaluate the similarities of side effect fingerprints. In a given drug pair (labelled A and B), the Jaccard index for the binary vectors could be calculated as the formula I.

\[
J(A,B) = \frac{c}{a + b - c}
\]

In this formula, a, b represent the number of side effects for drugs A and B, respectively. c represents the number of side effects shared by drug A and B.

Step 3: Evaluate the side effect similarities between drugs. The difference in the quantity of side effects associated with drugs may lead to similarity bias. It’s necessary to evaluate whether the similarities between two drugs are randomly generated. As shown in Figure 1, the random side effect fingerprint sets of drug A were generated by randomly selecting the same number of side effects from the side effects pool 10000 times. For each random side effect fingerprint of drug A, the \(J_{\text{random}}(A, B)\) similarity was calculated according to formula I. Then, the random Jaccard index set \(S_d\), drug B = \(\{J_{\text{random}}(A, B)\}_{d}\) was calculated. Finally, the drug pairs that \(J(\text{drug A, drug B})\) > \(J_{\text{random}}(A, B)\) were obtained. The \(\zeta\) score calculated by formula II was used to test whether the similarities between drug A and drug B were significantly larger than the random distribution. (\(\zeta\) score \(\geq 2.576\) was set as the threshold).

Table 1. Drug side effects resources.

| Source | Description |
|--------|-------------|
| Meyler’s Side Effects of Drugs (15th edition) | The International Encyclopaedia of Adverse Drug Reactions, a publication for a history spanning more than 60 years. It has been published every four years since 1980. It is the most comprehensive and authoritative resource of drug side effects, which contains >3,400 drugs and >12,600 side effects. |
| Side Effects of Drugs Annuals (2007–2012) | The Side Effects of Drugs Annual was first published in 1977. It has been continually published since then as a yearly update to the encyclopedia Meyler’s Side Effects of Drugs. |
| Drugs@FDA Database | Drugs@FDA includes most of the drug products approved by the FDA since 1939. Most patient information, labels, approval letters, reviews, approval packages and other information for drug products approved since 1998 are available. |
| SIDER | Contains information on 996 marketed drugs and corresponding 4192 recorded adverse drug reactions. The information is extracted from public documents and package inserts. |

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### Table 2. Drug indication resources.

| Source                   | Description                                                                 |
|--------------------------|-----------------------------------------------------------------------------|
| Pipeline                 | Developed by Citeline. Reputed to have collected information on drugs developed for any disease anywhere in the world since 1980, including their approval dates, companies and related clinical trials. |
| Thomson Reuters Partnering| The database was formally called IDdb and acquired by Thomson Reuters. The drug pipeline information is integrated from a variety of sources, such as company websites, and over 200 global conferences. |
| GeneGO                   | GeneGO is a comprehensive biological database, covering a wide range of data, including pathways, drug information, biomarkers etc. Each drug indication is mapped to a MeSH item. |

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$Z_{score} = \frac{J(drugA, drugB) - mean(S(drugA, drugB))}{std(S(drugA, drugB))}$  

(II)

$NDCG@p = Z \sum_{i=1}^{p} \frac{2^{rel_i} - 1}{\log_2(i+1)}$  

(III)

Z is the normalization constant.

i is the rank position of indication m.

rel_i is the relevance value of indication m. If indication m is the FDA approved indication of drug A, rel_i is set to 1, otherwise, rel_i is set to 0.

p is the maximum position.

For example if the FDA approved indications of drug A are ranked at 2, 3 & 8, respectively, while the ideal rank position of drug A’s FDA-approved indications should be 1, 2 & 3, then,

$Z = \frac{1}{\sum_{i=1}^{3} \frac{1}{\log_2(i+1)}} = 0.4693$

In the top 5 results,

$NDCG@5 = Z \left( \frac{1}{\log_2(2+1)} + \frac{1}{\log_2(3+1)} \right) = 0.5307$

### Results

**Cutoff selection criteria and drug-drug network construction**

As mentioned in Methods, we investigated variation trends in the percentage of covered drugs and co-indicated drug-drug pairs according to different Jaccard indexes. As shown in Figure 2, the percentage of co-indicated drug-drug pairs is positively correlated with the Jaccard index at four MeSH hierarchy levels. This evidence also suits our hypothesis that drugs with similar side effects would display similar functions. From Figure 2, it is obvious that the percentage of co-indicated pairs dramatically increases from 26.27% to 62.35% in the inflection area at the Jaccard index [0.2, 0.35] at the fourth level of MeSH hierarchy. Herein, Jaccard index = 0.275 was defined as the cutoff threshold. Then a drug-drug network based on side effect similarities was constructed, which contains 17400 drug-drug pairs, covering 1647 drugs. 1234 drugs with no less than 2 neighbors were used as our test samples. These drugs can be mapped to 81 ATC therapeutic categories including 3337 FDA approved drug-indication pairs, covering 584 indications. On average, 36.87% of the drugs achieved NDCG@5>=0.7, which means the known FDA-approved indications were well predicted. For details, the top 10 categories with NDCG@5>=0.7 were listed in Table 4 (see full list.
Network Based Drug Repositioning Using Side Effect

Step 1: Build Side Effect fingerprint

Side Effect fingerprint randomization

Random 1

Random 2

Random n

Step 2: Calculate the Similarity (Jaccard Index)

J(drug 1, drug 2)

J(random 1, drug 2)

J(random 2, drug 2)

J(random n, drug 2)

Test: J(drug 1, drug 2) > ? J(random, drug 2)
J(drug 1, drug 3) > ? J(random, drug 3)
J(drug 1, drug n) > ? J(random, drug n)

Step 3: Evaluate the Similarity (compare with the random set)

Drug pairs

J(drug 1, drug 2)

J(random, drug 2)

J(drug 1, drug 3)

J(random, drug 3)

J(drug 1, drug n)

J(random, drug n)

Step 4: Cutoff optimization

Drug network

FDA approved indication of drug i

Sub-network of drug i

New indication
Table 3. The 2×2 contingency table of drug A and indication i.

| Indication i | Drug A’s neighbours n \(-\)1 | Other indications N \(-\)n | The background network r | d \(-\)r |
|--------------|-------------------------------|---------------------------|--------------------------|---------|

\(n\) : The number of drug A’s neighbors which are approved for indication i \((n \geq 2)\);  
\(N\) : The number of drug A’s neighbors;  
\(r\) : the number of drugs in the network which are approved for indication i;  
\(d\) : The number of drugs in the network.

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Table 4. Top 10 ATC therapeutic categories with NDCG@5 \(\geq 0.7\).

| ATC code | Therapeutic category | NO. drugs | Percentage of drugs with NDCG@5 \(\geq 0.7\) |
|----------|----------------------|------------|------------------------------------------|
| A10      | Drugs used in diabetes | 33         | 84.85%                                   |
| A08      | Antiobesity preparations, excluding diet products | 12         | 83.33%                                   |
| A06      | Laxatives             | 6          | 83.33%                                   |
| J04      | Antimycobacterials    | 6          | 83.33%                                   |
| G02      | Other gynecologicals  | 11         | 72.73%                                   |
| C09      | Agents acting on the renin-angiotensin system | 43         | 72.09%                                   |
| J05      | Antivirals for systemic use | 37         | 70.27%                                   |
| C03      | Diuretics             | 38         | 68.42%                                   |
| B05      | Blood substitutes and perfusion solutions | 3          | 66.67%                                   |
| R07      | Other respiratory system products | 3          | 66.67%                                   |

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The drugs for diabetes, obesity, laxatives and antimycobacterials were best predicted with more than 80% of them achieving NDCG@5 \(\geq 0.7\). The drugs for cardiovascular disease (diuretics and agents acting on the renin-angiotensin system) were also well predicted with more than 70% of them achieving NDCG@5 \(\geq 0.7\).

Besides that, we also investigated the prediction performance in a different indication range (number of drugs approved for the indication) (see Table 5). Totally, 32.77% FDA approved drug-indication pairs could be predicted in the top 5 results, covering 202 (34.59%) indications. It seems that the indications with more drug approvals are likely to be predicted in the top 5 results. Good
performance was generated in the indications with 30~40 and 46~55 approved drugs. The top 5 drug indication pairs in these groups achieved 40.69% and 61.33% of the corresponding FDA approved drug indication pairs respectively. In addition, for indications with 15 or more FDA drug approvals, more than 62.75% of them were ranked with at least one drug-indication pair at the top 5 positions.

Herein, only the FDA approved drug-indication pairs are considered a positive set. The prediction performance may be underestimated due to the fact that drug-indications have not yet been approved though they may well be capable of treating disease. For example, the drug-indications being tested in the clinical studies through phase I, II and III, were also classified as false positive. We manually checked the 1858 drug-indication pairs through preclinical/clinical studies or scientific literature (see Table S3). We found that 80.73% of them could be verified by preclinical/clinical studies or scientific literature (see Table S3). We further investigated three drugs to understand their predicted results.

**Dynastat**

Dynastat (also called Parecoxib) is a COX-2 selective inhibitor developed by Pfizer. It was initially approved for pain management by the European Union in 2002. Dynastat relieves pain through modulating prostaglandins levels. It exerts the effect by inhibiting COX-2, which is responsible for converting arachidonic acid to prostaglandin G2 and prostaglandin H2. Prostaglandins also play an important role in the pathogenesis of rheumatoid arthritis (RA) [29]. Prostaglandins were found at elevated levels in rheumatoid synovial fluid, and the bone-resorption activity produced by rheumatoid synovial tissues was shown to be mediated in part by prostaglandin E2 [30], which is one of the downstream products of prostaglandin H2 in the arachidonic acid metabolism pathway. In our predicted results, the neighbours of Dynastat are significantly enriched in pain relief (EASE score = 1.76×10^{-14}) and rheumatoid arthritis (EASE score = 1.03×10^{-21}) management. As shown in Figure 3, Dynastat displays a similar side effect profile to 33 RA drugs in addition to the pain drugs. Up to now, a group of COX-2 inhibitors were verified as promising drugs in the treatment of RA. For example, Celecoxib, Rofecoxib and Valdecoxib have already been approved in RA treatment. Considering that Parecoxib is a water-soluble prodrug that can be rapidly hydrolyzed into Valdecoxib [31], it may also be effective in the treatment of RA.

**Tasmar**

Tolcapone (brand name Tasmar) developed by Roche, was approved as an effective adjunctive treatment with Levodopa for Parkinson’s disease in 1997 [32]. As a catechol-o-methyltransferase (COMT) inhibitor, Tasmar could improve the pharmacokinetic profile of Levodopa in two ways. First, it could directly inhibit the metabolic path from Levodopa to 3-O-methyl-dopa, which may finally increase the Levodopa half-life. Second, it may facilitate the transport of Levodopa to the brain by reducing 3-O-methyl-dopa, which may compete with Levodopa in brain barrier penetration [33]. The mechanism of actions also may explain why Tolcapone shares similar side effects with only 4 drugs for Parkinson therapy (EASE score = 0.39). We found that the indication of Tolcapone’s neighbours was significantly enriched in anti-depression functions (15 drugs were approved for depression treatment, EASE score = 5.09×10^{-15}). See Figure 4. A group of pharmaco-genetics studies showed that COMT variations are correlated with the effective management of depression [34,35,36,37,38,39]. Besides that, Elin et al’s study [40] proved that the Met-variants of COMT Val158Met are risk

### Table 5. Prediction performance of the 1234 drugs in different indication range (number of network drugs approved for an indication).

| NO. drugs per indication | NO. indications approved by FDA | Top 5 covered indications (percentage) | NO. drug-indication pairs approved by FDA | Top 5 covered drug-indication pairs (percentage) |
|--------------------------|---------------------------------|---------------------------------------|------------------------------------------|-----------------------------------------------|
| less than 5              | 196                             | 11 (5.61%)                            | 430                                      | 18 (4.19%)                                    |
| 6~10                     | 130                             | 26 (20.00%)                           | 556                                      | 66 (11.87%)                                   |
| 11~15                    | 66                              | 27 (40.91%)                           | 508                                      | 92 (18.11%)                                   |
| 16~20                    | 66                              | 32 (62.75%)                           | 560                                      | 87 (15.54%)                                   |
| 21~25                    | 38                              | 26 (68.42%)                           | 566                                      | 124 (21.91%)                                  |
| 26~30                    | 20                              | 16 (80.00%)                           | 389                                      | 99 (25.45%)                                   |
| 31~35                    | 19                              | 17 (89.47%)                           | 412                                      | 185 (44.90%)                                  |
| 36~40                    | 14                              | 13 (92.86%)                           | 376                                      | 153 (40.69%)                                  |
| 41~45                    | 8                               | 7 (87.50%)                            | 224                                      | 58 (25.89%)                                   |
| 46~50                    | 5                               | 5 (100.00%)                           | 163                                      | 106 (65.03%)                                  |
| 51~55                    | 8                               | 8 (100.00%)                           | 297                                      | 183 (61.62%)                                  |
| 56~60                    | 4                               | 4 (100.00%)                           | 150                                      | 92 (61.33%)                                   |
| more than 60             | 10                              | 10 (100.00%)                          | 706                                      | 486 (68.84%)                                  |
| Total                    | 584                             | 202 (34.59%)                          | 5337                                     | 1749 (32.77%)                                  |

### Table 6. Predicted results with evidence supported at an EASE score≤10^{-5}.

| Drug-indication pairs | Number | Percentage |
|-----------------------|--------|------------|
| FDA-approved          | 1336   | 71.91%     |
| Clinical              | 132    | 7.10%      |
| Preclinical           | 32     | 1.72%      |
| Unknown               | 358    | 19.27%     |

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variants for depression in the Swedish population. All of the available evidence indicates that COMT inhibitors may have an effect on depression. In fact, the application of COMT inhibitors in depression treatment was approved for a US patent in 2005 (US 20050137162 A1). In animal studies, an increase of SAMe in the central nervous system was detected after the administration of Tolcapone [41]. SAMe is a naturally occurring compound with putative antidepressant properties [42]. This effect, coupled with antidepressant properties exhibited in the rat model of chronic mild stress-induced anhedonia [43], suggests that Tolcapone may have significant antidepressant properties. Moreover, in an open study on 21 adults with major depressive disorders, the group treated with Tolcapone showed significant improvement over the placebo group (17-item Hamilton Rating Scale for Depression 19.4$\pm$2.9 vs 10.7$\pm$5.5; Clinical Global Impressions Severity 3.9$\pm$0.6 vs 2.4$\pm$1.1; Beck Depression Inventory 21.6$\pm$8.1 vs 12.3$\pm$8.6) [44]. The preliminary results suggest that Tolcapone may be a promising anti-depressant.

Adamon

Tramadol hydrochloride (brand name Adamon) is a centrally acting synthetic analgesic used to treat moderately severe pain, which was first approved in 1977 as a product of the German pharmaceutical company Grunenthal GmbH. It is supposed to have an analgesic effect on pain based on two complementary mechanisms of action derived from its affinity for the mu opioid receptor and its blockade of norepinephrine and serotonin reuptake [45,46]. Herein, two systems involved in pain relief are activated by Tramadol; namely, the opioid and the descending monoaminergic pain modulating pathways. In our predicted results, it shares similar side effect profiles with 22 pain management drugs (general pain: EASE score = 0.021; postoperative pain: EASE score = 0.0063). As shown in Figure 5, Tramadol is also connected to 13 anti-depression drugs (EASE score = 9.06$\times$10$^{-5}$). Desmeules’s study [47] suggested that the analgesic action of Tramadol is mainly related to the central monoaminergic mechanism rather than opioid receptor pathways. Antidepressants usually act by inhibiting norepinephrine-serotonin reuptake, which is similar to Tramadol’s effect of blocking monoaminergic reuptake [48]. In addition, opioid systems are also influenced in the pathophysiology of depression [49]. All the evidence suggests

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Figure 3. Sub-network of Dynastat. Each node represents a drug. Drugs approved for pain management are marked in yellow. Drugs approved for rheumatoid arthritis therapy are marked in purple. doi:10.1371/journal.pone.0087864.g003

Figure 4. Sub-network of Tasmar. Each node represents a drug. Drugs approved for the treatment of Parkinson’s disease are marked in orange. Drugs approved for rheumatoid arthritis therapy are marked in blue. doi:10.1371/journal.pone.0087864.g004
that Tramadol may have an effect on depression. In fact, a group of preclinical studies based on several depressive mice models showed the efficacy of Tramadol in depression management, such as the forced swimming test and the tail suspension test [48,50,51]. In 2008, the application of Tramadol in depression treatment was patented by European Union (EP20080011241). More promisingly, according to the pipeline of e-Therapeutics, the indication of Tramadol on depression has already been moved to Phase IIb clinical studies http://www.etherapeutics.co.uk/Information/pipeline.html.

External data evaluation

After we tested the predicted results of all drugs in the network, external drugs with side effect data were also tested. 98 drugs exclusively covered in SIDER were used as inputs to our system to calculate similarities with the drugs in the network one by one. As described in the Methods, we calculated similarities between 98 SIDER drugs with the background 2183 drugs. As shown in Table 7, 84.69% of SIDER drugs showed similarities to the network drugs with Jaccard index ≥ 0.275. Herein, the Jaccard index = 0.225 in the inflection area [0.2, 0.35] was set as the threshold. Next, 61 drugs with more than 2 neighbours were inputted to evaluate the method. Finally, the indications of 41 drugs could be predicted since they have more than 2 neighbouring drugs approved for the same indication. Among the top 5 predicted results, 36.59% of the drugs reached a performance score NDCG@5 ≥ 0.7. In addition, by selecting the

Table 7. The similarity of 98 SIDER drugs in test sample set with the drugs in the network.

| Similarity (Jaccard index) | Drugs with more than 2 neighbours (Percentage) |
|---------------------------|-----------------------------------------------|
| (0.0, 0.15)               | 5 (5.10%)                                      |
| (0.15, 0.2)               | 21 (21.43%)                                    |
| (0.2, 0.225)              | 11 (11.22%)                                    |
| (0.225, 0.25)             | 25 (25.51%)                                    |
| (0.25, 0.275)             | 21 (21.43%)                                    |
| More than 0.275           | 15 (15.31%)                                    |

Table 8. Predicted drug-indication pairs of SIDER drugs.

| Drug-indication pairs | Number | Percentage |
|-----------------------|--------|------------|
| FDA-approved          | 37     | 34.91%     |
| Clinical              | 10     | 9.43%      |
| Preclinical           | 7      | 6.60%      |
| Unknown               | 52     | 49.06%     |

Figure 5. Sub-network of Adamon. Each node represents a drug. Drugs approved for the treatment of Parkinson's disease are marked in orange. Drugs approved for pain treatment are marked in blue. doi:10.1371/journal.pone.0087864.g005
top 5 predicted results of 41 drugs with an EASE score ≤ 0.05, 106 drug-indication pairs were generated. (See details in Table S4). During the manual check, we found that 30.94% of them were FDA approved or could be verified by clinical trials or scientific literature (See Table 8).

Discussion

In this study, we integrated drug side effect data from several different resources. With these data, we built a drug network and screened new indications of drugs based on their network neighbours. Our method performed well at predicting their FDA approved indications in the top 5 positions. In addition to screening new indications of FDA approved drugs, our method could also be extended to candidate drugs with clinical side effect data. Since approved drugs sharing similar side effect profiles with query candidates could be identified, the indications of candidates could be inferred by their neighbours. Especially for drugs which failed in the late clinical stages, the comprehensive side effect data should have been generated in early clinical studies. These side effects can be used as inputs to our repositioning platform so that new indications for these drugs can be predicted.

Our drug repositioning platform has its own limitations. Due to the differences between side effect data resources, during an external data test using 98 drugs exclusively covered by SIDER, we found 38.16% of these SIDER drugs have low side effect similarities with the drugs in the network. Our method is not applicable to these SIDER drugs. Since very few side effect databases are available, many efforts are still needed to build or integrate these resources. For example, clinical case reports or other adverse event reporting systems may supply additional information on drug side effects. Up to now, only the direct neighbours in our network were considered to evaluate the indications in the study. We could quantify the influences of each neighbouring drug in the indication enrichment process according to their side effect similarities. Besides that, considering the fact that side effects vary in severity and frequency of occurrence, the current Jaccard index may not correctly mimic side effect similarities between the drugs. For example, the severity of a given side effect might be tagged as “serious” or “mild”, while its frequency of occurrence might be described as “common” or “rare”. Actually, these two side effect parameters are also related to the number of clinical patient samples and drug doses in treatment. Further meta-analysis should be carried out to modify the side effect data in order to take account of information regarding the severity and frequency of these side effects. This could certainly improve the accuracy of the predictions.

Drug repositioning is a complicated process. It is impossible that any one computational method alone would be accurate enough to provide promising results. A package of methods from different perspectives could be integrated to make predictions more precise. In our study, we also compared our results to Lun’s [21] predicted results. In his study, 14040 drug-indication pairs are proposed. 14.57% of them overlapped with our results (747 drug-indications with EASE score ≤ 0.05, see details in Table S5). In particular, five of the drugs (Ziprasidone, Quetiapine, Oxcarbazepine, Clozapine, Sildenafil) mentioned in Lun’s paper were able to be used in the treatment of obsessive-compulsive disorder. The associations were also predicted by our method with a low EASE score ≤ 6.35 × 10^{-3}. The overlapping results from different methods, which may integrate comprehensive features in drug repositioning at the chemical levels, the MOA levels, and the phenotypic levels could provide promising predictions as well as cross validations.

Supporting Information

Table S1 The 98 drugs exclusively covered in SIDER.

Table S2 Performance of drugs in 81 ATC therapeutic categories.

Table S3 The predicted 1858 drug-indication pairs with an EASE score ≤ 10^{-3}.

Table S4 The predicted 106 drug-indication pairs in external data evaluation using SIDER.

Table S5 The 747 drug-indication pairs overlapped with Lun’s paper.

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Author Contributions

Conceived and designed the experiments: HY JW. Performed the experiments: HY. Analyzed the data: HY. Contributed reagents/materials/analysis tools: HY QL. Wrote the paper: HY.

References

1. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, et al. (2010) How to improve R&D productivity: the pharmaceutical industry’s grand challenge. Nat Rev Drug Discov 9: 203–214.
2. David E, Tramoni T, Zemmell R (2009) Pharmaceutical R&D: the road to positive returns. Nat Rev Drug Discov 8: 609–610.
3. Berggren R, Möller M, Mose R, Poda P, Simenata K (2012) Outlook for the next 5 years in drug innovation. Nat Rev Drug Discov 11:435–436.
4. Kola I, Landis J (2004) Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3: 711–715.
5. Ashburn TT, Thor KB (2004) Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 3: 673–683.
6. Wu Z, Wang Y, Chen L (2013) Network based drug repositioning. Mol Biosyst 9:1268–1281.
7. Opreat TI, Mestre J (2012) Drug repurposing: far beyond new targets for old drugs. AAPS J 14: 759–763.
8. Liu X, Zhu F, Ma XJ, Shi Z, Yang SY, et al. (2013) Predicting targeted polypharmacology for drug repositioning and multi-target drug discovery. Curr Med Chem 20: 1646–1661.
9. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, et al. (2006) The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science 313: 1929–1935.
10. Luo H, Chen J, Shi L, Mikalov M, Zhu H, et al. (2011) DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical-protein interactome. Nucleic Acids Res 39: W492–498.
11. Dakhamaumarthy S, Issa NT, Asselfina S, Seshasayee A, Peters OJ, et al. (2012) Predicting new indications for approved drugs using a proteoschemometric method. J Med Chem 55: 6832–6848.
12. Cheng F, Zhou Y, Li J, Li W, Liu G, et al. (2012) Prediction of chemical-protein interactions: multi-target-QSAR versus computational chemogenomic methods. Mol Biosyst 8: 2373–2384.
13. Saneu P, Agarwal P, Barnes MK, Pastinen T, Richards JB, et al. (2012) Use of genome-wide association studies for drug repositioning. Nat Biotechnol 30: 317–320.
14. Ye H, Tang K, Yang L, Cao Z, Li Y (2012) Study of drug function based on similarity of pathway fingerprint. Protein Cell 3: 132–139.
15. Ye H, Yang L, Yang L, Cao Z, Tang K, Li Y (2012) A pathway profile-based method for drug repositioning. Chin Sci Bull 57: 2106–2112.
16. Iorio F, Bosotti R, Scacheri E, Belcastro V, Mithaokar P, et al. (2010) Discovery of drug mode of action and drug repositioning from transcriptional responses. Proc Natl Acad Sci U S A 107: 14621–14626.
17. Gottlieb A, Stein GY, Koppin E, Sharan R (2011) PREDICT: a method for inferring novel drug indications with application to personalized medicine. Mol Syst Biol 7: 496.
18. Pammolli F, Magazzini L, Riccaboni M (2011) The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 10: 428–430.
19. Paolini GV, Shapland RH, van Hoorn WP, Mason JS, Hopkins AL (2006) Global mapping of pharmacological space. Nat Biotechnol 24: 805–815.
20. Kuhn M, Campillos M, Letunic I, Jensen LJ, Bork P (2010) A side effect resource to capture phenotypic effects of drugs. Mol Syst Biol 6: 343.
21. Yang L, Agarwal P (2011) Systematic drug repositioning based on clinical side-effects. PLoS One 6: e20925.
22. Duran-Frigola M, Aloy P (2012) Recycling side-effects into clinical markers for drug repositioning. Genome Med 4: 3.
23. Ye H, Tang K, Li Y (2012) Drug-Drug Network Based on Similarity of Molecular Fingerprint. Journal of East China University of Science and Technology 3: 301–306.
24. Aronson JK (2007) Meyler’s Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition).
25. Aronson JK (2006) Meyler’s Side Effects of Drugs Annual: A worldwide yearly survey of new data in adverse drug reactions and interactions. Volume 29–34.
26. Hosack DA, Dennis G, Sherman BT, Lane HC, Lempicki RA (2005) Identifying biological themes within lists of genes with EASE. Genome Biol 6: R70.
27. Huang da W, Sherman BT, Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 4: 44–57.
28. Jarvelin K, Keckalainen J (2002) Cumulated gained-based evaluation of IR techniques. ACM Transactions on Information Systems 20: 422–446.
29. Sundy JS (2001) COX-2 inhibitors in rheumatoid arthritis. Curr Rheumatol Rep 3: 86–91.
30. Robinson DR, Tashjian AH, Levine L (1975) Prostaglandin-stimulated bone resorption by rheumatoid synovia. A possible mechanism for bone destruction in rheumatoid arthritis. J Clin Invest 54: 1116–1138.
31. Bingham CO (2002) Development and clinical application of COX-2-selective inhibitors for the treatment of osteoarthritis and rheumatoid arthritis. Cleve Clin J Med 69: S5–12.
32. Truong JJ (2009) Tolcapone: review of its pharmacology and use as an antidepressant therapy in patients with Parkinson’s disease. Clin Interv Aging 4: 109–113.
33. Borges N (2005) Tolcapone in Parkinson’s disease: liver toxicity and clinical efficacy. Expert Opin Drug Saf 4: 69–73.
34. Seregi A, Rujescu D, Tadic A, Muller MJ, Kohnen R, et al. (2005) The catechol-O-methyltransferase Val108/158Met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression. Pharmacogenomics J 5: 49–53.
35. Arias B, Serretti A, Lorenzi C, Gasto C, Catalan R, et al. (2006) Analysis of COMT gene (Val 158 Met polymorphism) in the clinical response to SSRI in depressive patients of European origin. J Affect Disord 90: 251–256.
36. Benedetti F, Colombo C, Pirovano A, Marino E, Smeraldi E (2009) The catechol-O-methyltransferase Val108/158Met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. Psychopharmacology (Berl) 203: 155–160.
37. Yoshida K, Higuchi H, Takahashi H, Kamata M, Sato K, et al. (2008) Influence of the tyrosine hydroxylase val119met polymorphism and catechol-O-methyltransferase val158met polymorphism on the antidepressant effect of milnacipran. Hum Psychopharmacol 23: 121–128.
38. Benedetti F, Dallapiazza S, Colombo C, Lorenzi C, Pirovano A, et al. (2010) Effect of catechol-O-methyltransferase Val108/158Met polymorphism on antidepressant efficacy of fluvoxamine. Eur Psychiatry 25: 476–478.
39. Sprok D, Arns M, Barnett KJ, Cooper NJ, Gordon E (2011) An investigation of EFG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: a pilot study. J Affect Disord 128: 41–48.
40. Aberg E, Fardin-Louada A, Sjoholm LK, Forsell Y, Lapinlahti C (2011) The functional Val158Met polymorphism in catechol-O-methyltransferase (COMT) is associated with depression and motivation in men from a Swedish population-based study. J Affect Disord 139: 158–166.
41. Prada DM, Börglum A, Napolitano A, Zurcher G (1994) Improved therapy of Parkinson’s disease by tolcapone, a central and peripheral COMT inhibitor with an S-adenosyl-L-methionine sparing effect. Clin Neuropharmacol 17: S26–S37.
42. Bressa GM (1994) S-adenosyl-L-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neuro Scand Suppl 154: 7–14.
43. Moreau JL, Börglum A, Jenck F, Martin JR (1998) Tolcapone: a potential new antidepressant detected in a novel animal model of depression. Behav Pharmacol 5: 344–350.
44. Tayal V, Kalra BS, Khwaja S (2000) Evaluation of antidepressant activity of tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. Br J Pharmacol 130: 147–151.
45. Desmeules JA, Piguet V, Collart L, Dayer P (1996) Contribution of monoaminergic modulation to the antidepressant effect of tramadol. Br J Clin Pharmacol 41: 7–12.
46. Tzvetkova M, Chavda S, Bhuvanesh Kumar K, Bryant H, MacGregor A, et al. (2008) Evaluation of antidepressant activity of tramadol in mice. Indian J Pharmacol 40: 129–130.
47. Berrocoso E, Sánchez-Blázquez P, Garzon J, Mico JA (2009) Opiates as antidepressants. Curr Pharm Des 15: 1612–1622.
48. Chowta MN, Manjunath M, Gopalakrishna HN, Gokul P (2011) Evaluation of role of noradrenergic system in the antidepressant activity of tramadol using tail suspension test in Albino mice. J Pharmacol Pharmacother 2: 281–282.
49. Rojas-Correales MO, Gilbert-Rahola J, Mico JA (1996) Tramadol induces antidepressant-type effects in mice. Life Sci 63: PI175–180.