DDInter: an online drug-drug interaction database towards improving clinical decision-making and patient safety

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1. Comparison with other web-based tools

Several excellent public medicine databases or web servers have slightly touched upon drug-drug interactions, including DrugBank, SuperDRUG2, SuperCYPsPred, etc. Detailed comparison of these tools has been summarized in Table S1.

**Table S1.** Comparison of the main features of DDInter with other web-based drug interaction tools. Symbols used for function evaluations with ‘√’ for present, ‘-’ for absent, and ‘+’ for a broader coverage (more ‘+’ indicate better support)

| Features                        | DDInter | DrugBank 5.0 | SuperCYPsPred | SuperDRUG2 |
|---------------------------------|---------|--------------|---------------|------------|
| Data volume                     | 0.24M   | 0.36M        | Unavailable    | Unavailable|
| Type coverage                   | +++     | +++          | +             | +++        |
| Data browsing                   | √       | -            | -             | -          |
| Data retrieval                  | √       | √            | √             | -          |
| Interaction checker             | √       | √            | √             | √          |
| Network visual analytics        | √       | -            | -             | -          |
| Severity classification         | √       | √            | -             | √          |
| Mechanism description           | √       | √            | -             | -          |
| Management methods              | √       | -            | -             | -          |
| Alternative medications         | √       | -            | -             | -          |
| Metabolism profile              | √       | -            | √             | -          |
| Downloadability                 | √       | √            | -             | -          |

**URL links:**

DDInter: [http://ddinter.scbdd.com/](http://ddinter.scbdd.com/)

DrugBank 5.0: [www.drugbank.ca](http://www.drugbank.ca)

SuperCYPsPred: [http://insilico-cyp.charite.de/SuperCYPsPred/](http://insilico-cyp.charite.de/SuperCYPsPred/)

SuperDRUG2: [http://cheminfo.charite.de/superdrug2](http://cheminfo.charite.de/superdrug2)

Particularly, DrugBank and SuperDRUG2 are web-enabled databases containing comprehensive molecular information about drugs. The latest release of DrugBank (version 5.0, updated in 2018) contains about 0.36M drug-drug interactions, which are manually sourced from FDA/Health Canada drug labels as well as primary literature. SuperDRUGS2 extracted the drug-drug interaction data mainly from DrugBank and additionally extracted information from package inserts, labels of pharmaceutical products and scientific literature through semi-automated text-mining, however, the data volume has not been revealed in the original literature or website. It should be noted that Drugbank employs drug and target/enzyme categories to generate drug-drug interactions, which may influence the data reliability. And this may explain why the data volume of DrugBank could reach up to 0.36M. Further, the annotations of these tools are not as comprehensive as DDInter. The lack of management methods, alternatives, metabolism profiles, and visualization annotations makes them difficult to give practical guidance to rational medication. For SuperCYPsPred, the DDI matrix is based on a manually curated dataset from literature (known interactions with reference) as well as prediction based on computational models.
(unknown interactions). It merely focuses on metabolism interactions, which constitute part of drug interactions. In comparison, DDInter is a high-quality, easy-to-use database that offers the most comprehensive functions including data browsing, retrieval, interaction checker, and network visual analytics to support clinical rational administration in ways that no other tools currently can. About 0.24M DDI associations connecting 1833 approved drugs are extracted from literature and product labels and curated by a registered pharmacist team. It provides professional and comprehensive annotation of each drug-drug pair, which is one of the most important highlights of our database. In summary, DDInter caters for both clinicians as well as bioinformaticians by providing friendly and efficient service for drug-drug interactions.

2. Criteria for mechanism annotation

2.1 Absorption

Absorption-related drug interactions are commonly associated with various mechanisms, with most cases hindering and very few promoting. First, decreased absorption may be secondary to chelation with a cation such as calcium or iron. Second, absorption may be decreased when the dissolution of the medication is highly dependent on gastric pH. Third, intestinal absorption may be influenced by inhibition or induction of the p-glycoprotein efflux transporter in the intestinal epithelium

- Most quinolones antibiotics could bind to the iron cation to form an insoluble and unabsorbable mental chelation complex in the gastrointestinal tract, leading to reduced intestinal permeability.
- The absorption of itraconazole is pH-dependent and may be impaired when gastric pH is increased after antacid administration such as proton pump inhibitor omeprazole.
- The macrolides may potentiate digoxin toxicity. The inhibition of the P-gp transporter in the intestine is the mechanism of this interaction, as digoxin is a p-glycoprotein substrate and the macrolides may inhibit this transporter.

2.2 Distribution

The distribution of medications into tissues is mediated by drug influx and efflux transporters and influenced by protein binding as only the free fraction will be able to penetrate across tissue membranes. Distribution-related drug interactions include competing for the plasma protein binding sites, changing the free-drug fraction, or influencing the distribution in some tissues and organs, etc.

- Methotrexate leads to hematological toxicity when coadministered with acetylsalicylic acid. This interaction occurs due to decreased clearance of methotrexate through competition with acetylsalicylic acid, resulting in methotrexate being displaced from its plasma protein binding site.
- Coadministration with drugs that reduce catecholamine uptake or deplete catecholamine stores may interfere with iobenguane I-131 uptake into neuroendocrine tumors such as pheochromocytoma and paraganglioma that express high levels of norepinephrine transporter on their cell surfaces.

2.3 Metabolism

Metabolic interactions are mostly due to CYP450 isoenzymes and are responsible for up to 40% of DDIs found in patients. Medications interacting with the CYP450 system can be classified as substrates, inhibitors, or
inducers.

- The co-administration of zidovudine with valproic acid causes increased oral bioavailability of zidovudine, due to reduced metabolism of zidovudine by glucuronidation. This interaction may increase the risk of adverse effects, including severe anemia and hematologic toxicity.
- Rifampin, due to its enzyme-inducing activities, may increase the metabolism of lamotrigine, reducing the AUC by up to 40%. This can result in decreased efficacy in preventing and controlling seizures.

2.4 Excretion

As the main excretion organ, most excretion-related interactions occur in the kidney, including affecting the PH of renal tubule fluid, inhibiting the tubular secretion, changing the kidney blood flow, etc.

- Probenecid is a uricosuric and renal tubular blocking agent that inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by any route the antibiotic is given. Probenecid is indicated to be given as an adjuvant to therapy to penicillin to enhance their plasma levels, and concomitant use has been associated with increased penicillin-related adverse reactions.
- Diuretics may increase serum lithium concentration. Diuretics affect filtration rates and affect electrolyte exchange in the nephron. By reducing sodium reabsorption thiazide diuretics can increase the reabsorption of lithium and result in increased serum lithium concentrations.

2.5 Synergy

The synergistic effect occurs when the overall effect of the drug combination is greater than additive. The synergistic effect can be beneficial or adverse, which is decided by the pharmacological characteristics of drug combinations.

- The additive effects between benzodiazepines and opiates can lead to respiratory depression and possibly cause coma and death. The risk of respiratory depression, coma and death is important to note. This interaction occurs due to the co-location of GABA and opiate receptors in the central nervous system, and cross-reactivity and common pathways of intracellular transduction for these agents.
- Following furosemide injection, there was a rapid and reversible decrease in the endocochlear potential and eighth nerve action potential with a more gradual decrease of the endolymph potassium concentration, leading to transient or permanent ototoxicity. As aminoglycoside antibiotics have the potential to cause ototoxicity, furosemide may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function.

2.6 Antagonism

The antagonistic effect occurs when the overall effect of the drug combination is less than additive. Sometimes antagonistic interactions are used to alleviate the harmful effects of certain medications clinically, while they may also offset the pharmacological effects of the drugs taken together.

- The concomitant administration of an opioid antagonist with an opioid can result in the mitigation of both classes of medications’ therapeutic effects for the patient. While the pharmacological effect of the opioid antagonist to treat or manage opiate abuse or overdose can be inhibited, at the same time the legitimate pharmacological effect of any opioids administered for the genuine management of pain can also be decreased.
Some beta-blockers, such as propranolol, may antagonize the bronchodilatory, hypotensive, and tachycardic effects of isoproterenol. The mechanism is blockade of beta-adrenergic receptors, which leads to bronchoconstriction, vasodilation, and increased heart rate. Beta-blockers have been used successfully to treat catecholamine or isoproterenol-induced tachyarrhythmias.

### 2.7 Others and Unknown

The expanded descriptions of some interactions were ambiguous, which made it difficult work to identify the concrete categories. Therefore, these interactions were annotated with ‘Others’. In addition, the DDIs collected from the article published in *Sci Transl Med* were lack of mechanism descriptions, and thus these DDIs were annotated with ‘Unknown’.

### 3. Criteria for severity annotation

Categories of severity were accepted as suggested by DRUGDEX and other similar resources:

- **Major**: The interactions are life-threatening and/or require medical treatment or intervention to minimize or prevent severe adverse effects.
- **Moderate**: The interactions may result in exacerbation of the disease of the patient and/or change in therapy.
- **Minor**: The interactions would limit the clinical effects. The manifestations may include an increase in frequency or severity of adverse effects, but usually they do not require changes in therapy.
- **Unknown**: The DDIs collected from the article published in *Sci Transl Med* were lack of mechanism descriptions, and thus the severity classifications of these DDIs were annotated with ‘Unknown’.

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