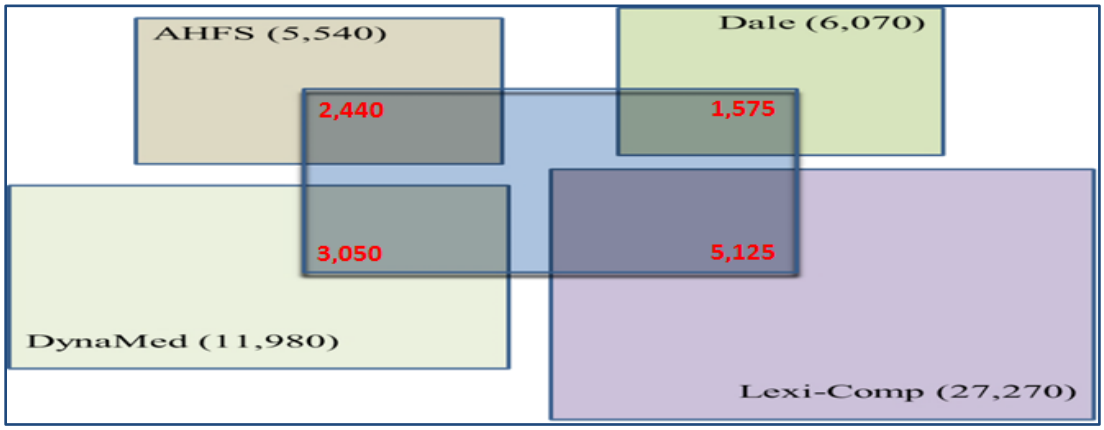
Contents

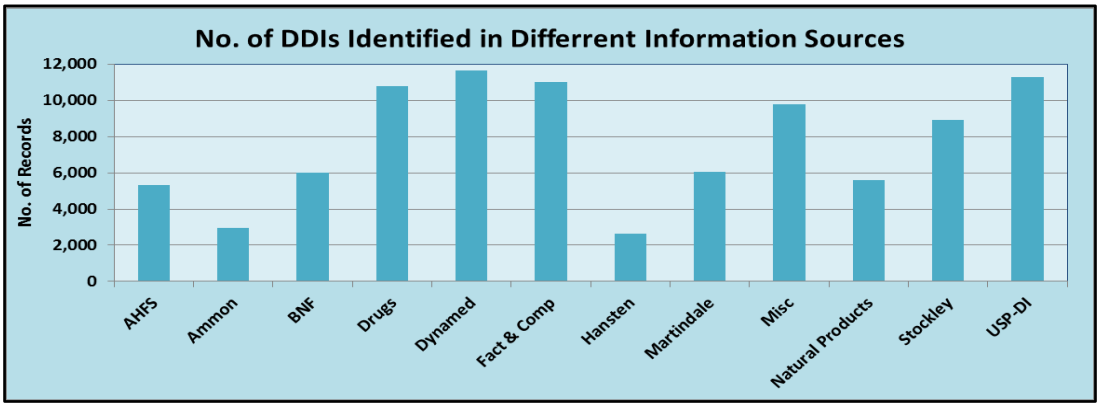
Background

For decades, the identification of drug-drug interactions (*DDIs*) and drug-herb interactions (*DHIs*) continued to be a mundane task for clinical practitioners and other workers in the healthcare sector. This may be attributed to several factors that may be summarized as follows:

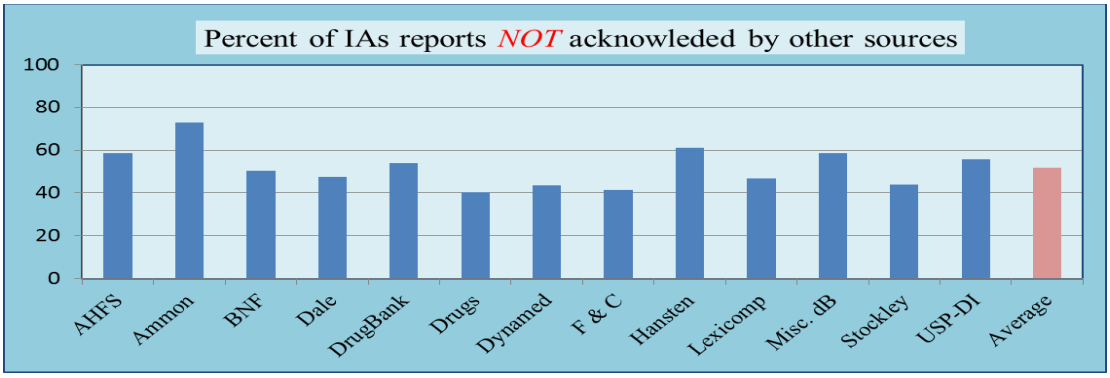
1. *DDI-Explorer DDIs* database comprises of about 200,000 interaction reports that have been identified in thirteen reputed drug information sources. In addition to the above mentioned information databases, other sources include the *British National Formulary, Ivan Stockley Drug Interaction, Philip Hansten, the Canadian DrugBank, Drugs Facts and Comparisons, the Natural Products* database and others. The diagram provided hereunder represents the number of interaction recognized in different information sources.



2. *DDI-Explorer DDIs* database comprises of about 200,000 interaction reports that have been identified in thirteen reputed drug information sources. In addition to the above mentioned information databases, other sources include the *British National Formulary, Ivan Stockley Drug Interaction, Philip Hansten, the Canadian DrugBank, Drugs Facts and Comparisons, the Natural Products* database and others. The diagram provided hereunder represents the number of interaction recognized in different information sources.



3. Most drug information databases emphasize the *evidence-based* characteristic of information provided by them. This is hardly the case with regard to the drug interaction part of these databases. The below diagram depicts the percentage size of different *DDIs* data that is not referenced or acknowledged by any of the major information databases.



4. Lack of comprehensive reporting on all drugs and their related uses across different countries. This is evident by the fact that the United States and Canadian databases cover about 1,650 out of 3,060 drugs that are globally acknowledged
5. In countless instances, the description of interactions (*IAs*) is too general, which renders the information provided of little use to general practitioners in the field.
6. Difficulties encountered in efficiently accessing relevant information due to the fact that interactions are often reported for classes and/or groups of drugs. The size of this type of reporting applies to an average of 29% of information provided by individual *DDIs* databases.
7. Synonyms for drug names are inadequately accounted for in all databases, further complicating the above mentioned problems. We have noted that the number of synonyms for a single drug or herb have reached approximately 5 and 12 names, respectively.
8. Difficulties are encountered when making queries on *DDIs* or *DHIs* using branded or commercial product names, over the counter drugs (*OTCs*) and/or nutritional supplements.
9. One of the alarming deficiencies in reporting *DDIs* by many databases is the inter-version inconsistency. This is exemplified by dropping clinically significant interactions that have been reported in previous versions of such databases.

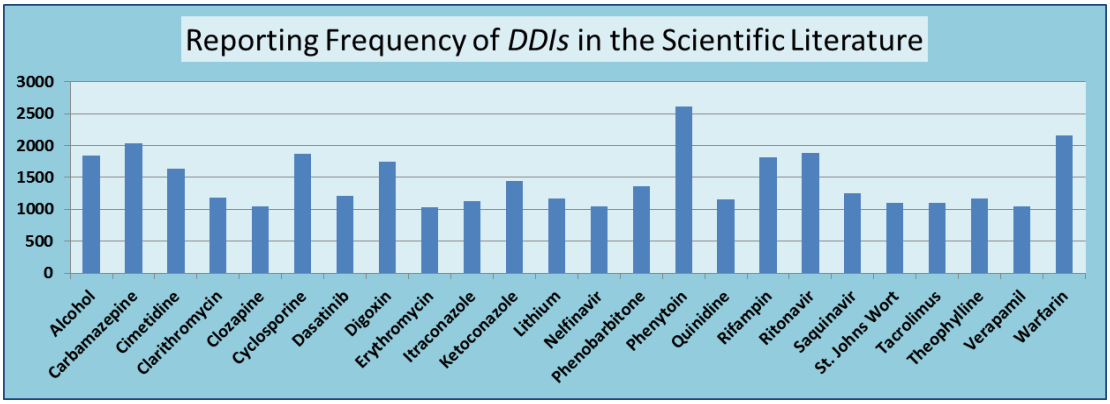
DDI-Explorer is a ground-breaking multifaceted tool that identifies drug interactions for a single drug substances or combinations of drugs or drug products. Identification of likely *DDIs* is a definitive prerequisite to minimize potentially life-threatening prescribing errors.

One of the most prominent benefits of using ***DDI-Explorer*** is its ability to reference the source of any data item accessed or reported through it; this means that information provided by the system is remarkably evidence-based. The core database of *DDI-Explorer* consists of the following:

- Approximately 57,000 names of generic drugs or herbs and more than 150,000 names of branded drug products - the interrelation between all these items is accurately defined and documented.
- Data dictionaries that consist of names of generic and branded products for almost any given drug name provided by Martindale: The Extra Pharmacopoeia, the USP-DI and the Japanese Pharmacopoeia.
- Extensive documentation of all known liver enzymes and transporters (8,650 records), up-to-date definition of ATC-Classification system (5,780 records), listing of all known drug induced

effects (7,260 records) and listing of all known targets of drugs (4,630 records). These are subject to continuous updates.

- ***DDI-Explorer*** database includes close to 5,600 *DHIs* reported by several herbal information sources such as Natural Medicines, E-Commission and other official European and Chinese herbal textbooks. In addition, names of herbal branded products and nutritional supplements in the *EU* and the *USA* represent a fundamental part of ***DDI-Explorer*** database.
- Lexicomp and DrugBank have not been presented in the above diagram due to the unrealistically staggering size of *DDIs* reported by them. By no means could this be regarded advantageous since the vast majority of their interaction reports is purely theoretical and are provided without verification versus other sources or clinical significance evaluation.
- The below diagram represent two dozen of drugs with the highest reporting interaction frequencies in the scientific literature. Again, Lexicomp and DrugBank were not included in this presentation since they are bound to distort the entire profile due to the exaggerated size of their computer-generated drug interactions text.

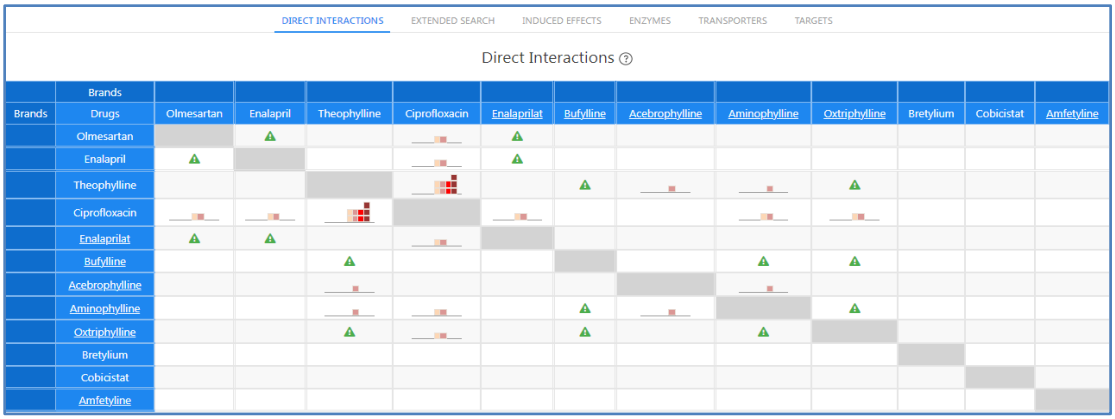


The DDI-Explorer

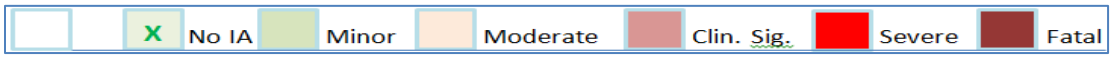
Unlike other systems, ***DDI-Explorer*** has evolved as a search engine that attempts to resolve most of the prevailing shortcomings other drug information sources. In its present status, the system offers more than one search modality for detecting potential *DDIs* in combination therapies. These include the following:

Directly Reported IAs (one-to-one search)

This represents reported interactions in the scientific literature for any pair of drugs on single drug–to–single drug basis. User may submit to the system any number of drug entities whose interactions are to be assessed. Upon proceeding with the query, the system will generate a multiple styles of output with a default table on the directly accessible interaction as shown the below table.



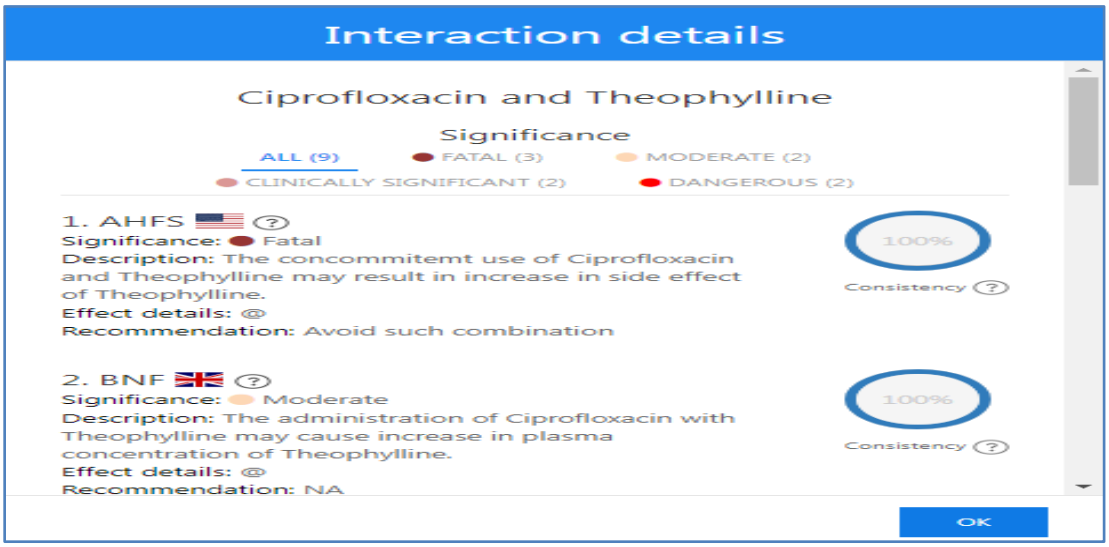
Cells represent the interacting drugs will contain the reporting frequency for every specific interaction, represented by small squares with varying color tones. The below bar describes the color tones used by the system. Also, the number of squares in each cell represents a true estimate of the documentation level for any reported interaction.



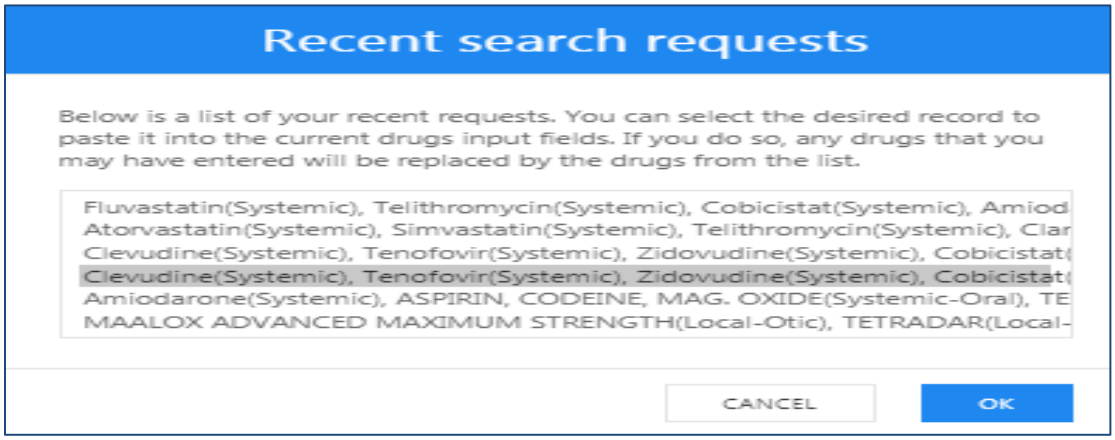
The blank square in the above diagram signifies that no clinical significance rating has been provided by the original source of the reported interaction.

For the above example, six drug entities were submitted for evaluation. However, system's output showed a dozen of drugs elements some of which are underlined. These underlined entities represent pro or co-drugs of the submitted drug names as well as metabolites or precursors of the drugs to be evaluated. This feature has been added to the system since separate DDIs for drugs and their prodrugs. A typical example for such situation is the case of Theophylline and Aminophylline. The ***DDI-Explorer*** accounts for about 300 such cases.

As shown below, more details on the description and source(s) of interactions presented in the above matrix are provided upon clicking on any cell of the matrix

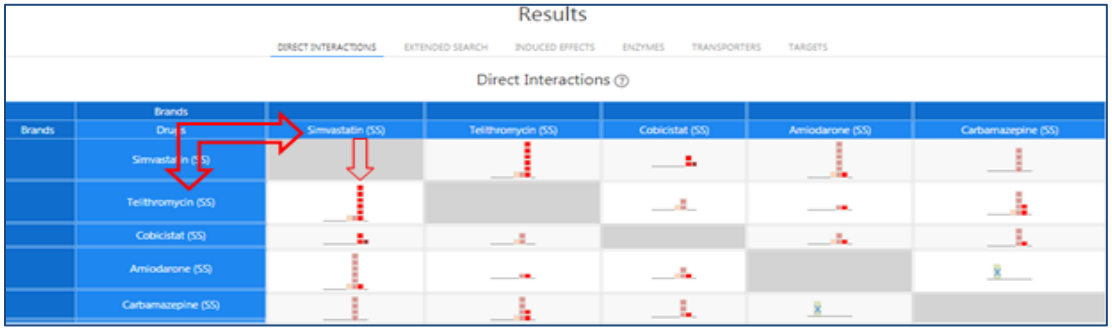


As shown hereunder, users may go back to recently queried prescriptions.

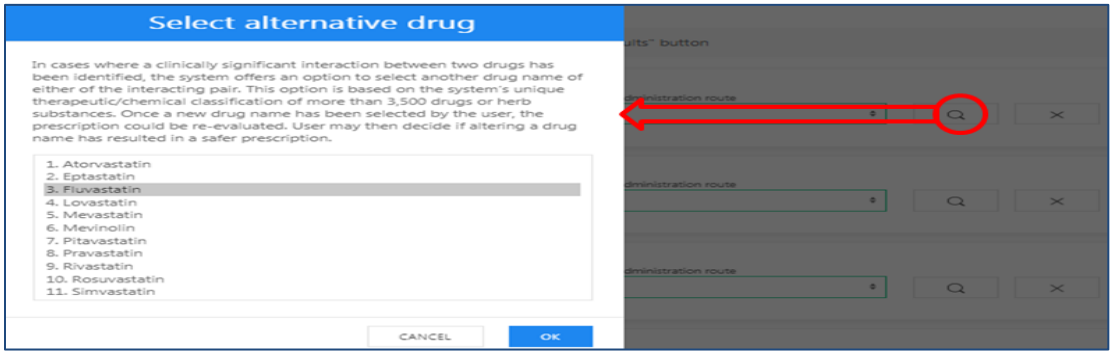


Therapy Modification Assistant

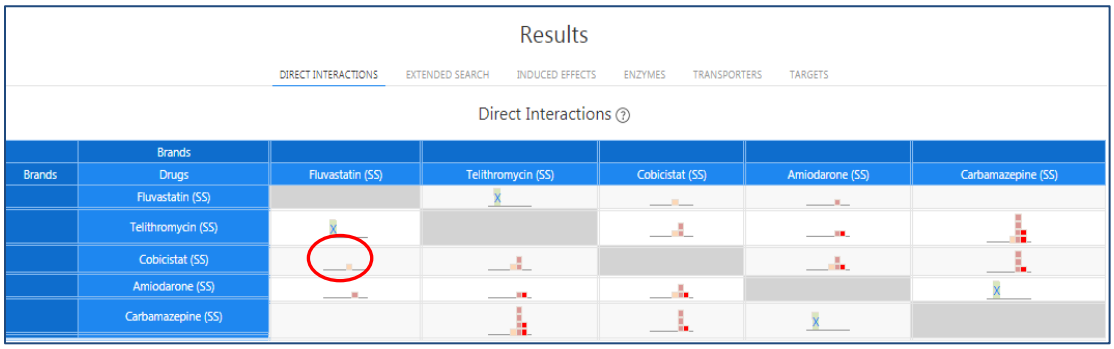
The ***DDI-Explorer*** can assist users modify a potentially unsafe therapeutic regimen. The below diagram depicts a situation whereby *Simvastatin* is co-administered with *Telitromycin.* This has resulted in a serious interaction between the two drugs (see the RED pointers in the below diagram) as provided by eight credible information sources.



As demonstrated below, upon clicking the search icon (marked with RED circle), the system will generate a list of all members of *HMG-CoA* Reductase class, from which user may select an alternative drug.



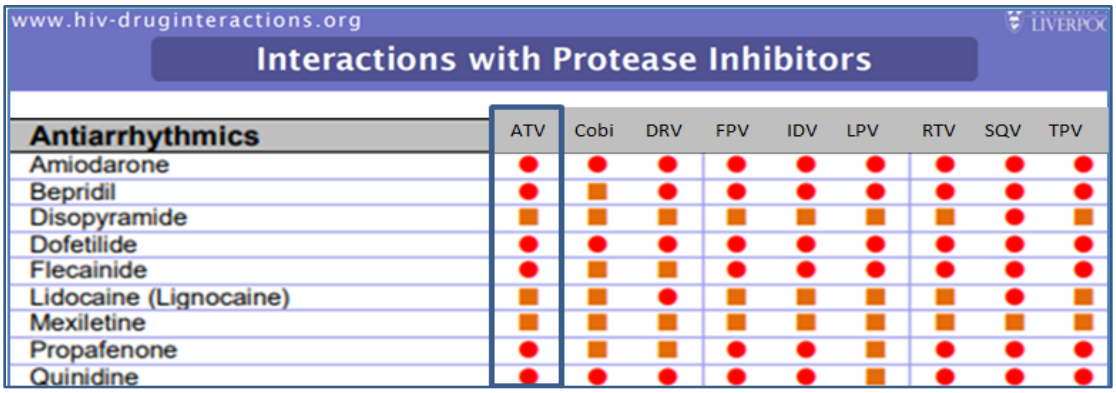
Replacing *Simvastatin* with *Fluvastatin* has resulted in a less interactive situation between the regimen's constituents.

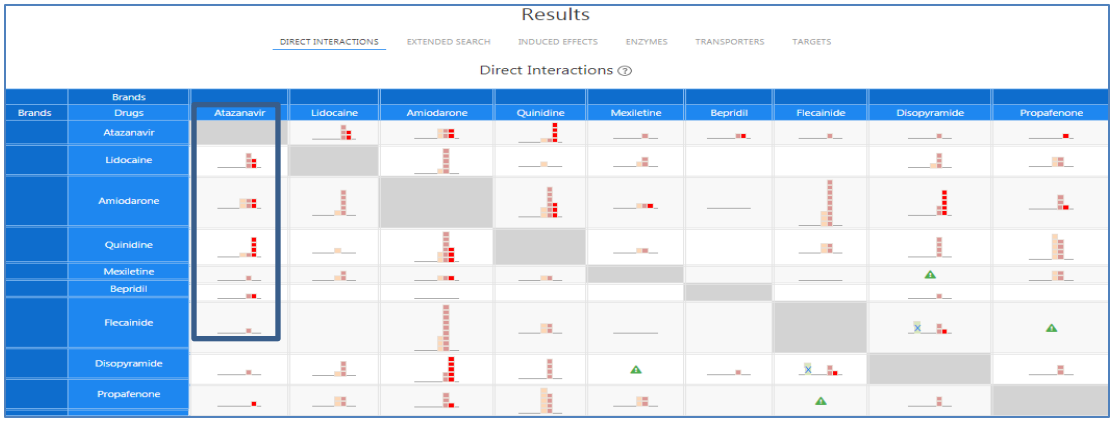


More advanced "Intelligent Suggestions" will be introduced in the future versions of the ***DDI-Explorer*** on the basis of drugs kinetic and dynamic characteristics.

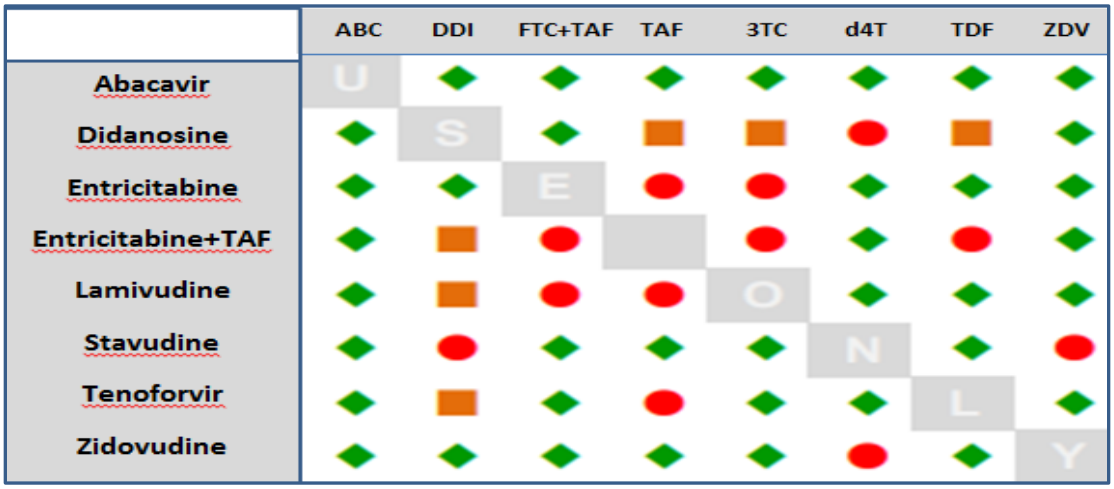
Performance Assessment of the *DDI-Explorer*

Although its contents is confined to recommendation on the use of *HIV* drugs, the drug interactions chart provided by *Liverpool Drug Interaction Group* represents one on the most credible information sources on the interactions of HIV drugs. The efficiency of the ***DDI-Explorer*** has been tested with a hypothetical combination of drugs comprising most of the known antiarrhythmic agents versus *Atazanavir* (*ATV*). The two snapshots provided hereunder represent information offered by the *HIV-Chart* and the "Direct Interactions" output offered by the ***DDI-Explorer***.





In addition to the fact that all interactions provided by the chart have been recognized by the ***DDI-Explorer***, information offered by the latter is far more detailed and comprehensive in comparison to that provided by *Liverpool HIV-Chart*. The vast difference between the two outputs is self-explanatory. Another example derived from this chart is provided below depicts interactions among eight protease inhibitors.



As demonstrated in the above two diagrams, *Abacavir* and *Zidovudine* do not appear interactive in the *HIV-Chart*, whereas two dozens of interaction reports provided by the ***DDI-Explorer***. These are ascertained by different information sources.

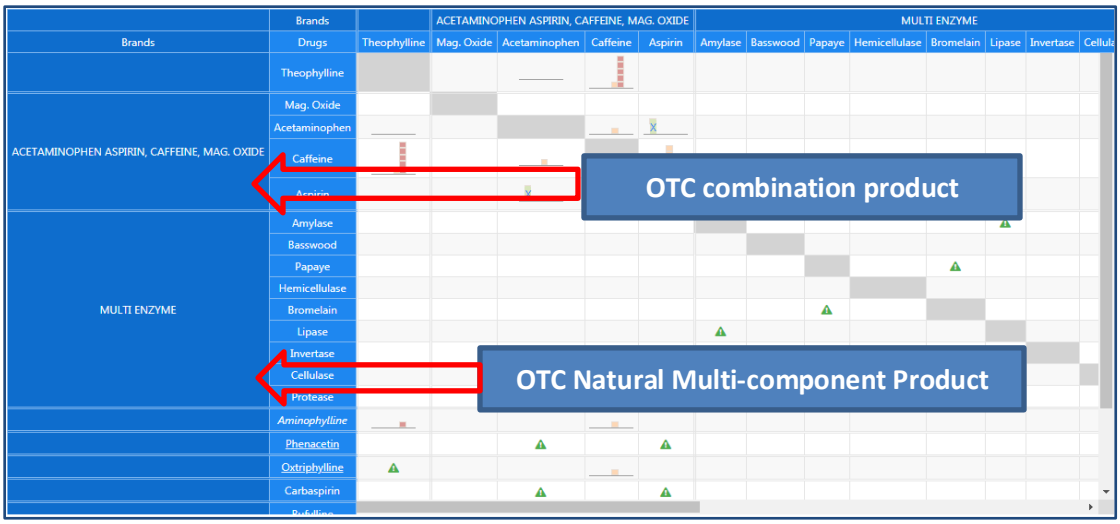
Prodrugs, Co-drugs, Active Metabolites and Precursors

These pairs of drug entities are either inadequately or independently reported in the literature, thus resulting in incomplete interaction profiles for drugs being queried. Some common examples include Primidone/Phenobarbitone, *Acyclovir/Valcyclovir*, *Aminophylline/Theophylline*, *Phenytoin/Fosphenytoin*. Only few pairs, out of about 280 cases, are recognized in some information sources. In some occasions, many precursors or co-drugs exist for a drug entity.

In the above matrix, the queried drug (*Theophylline*) exists as prodrug or co-drugs. These are marked by RED in the above diagram. Accordingly, all interaction of these system-retrieved entries will be displayed by the system. It is interesting to note that Primidone and Phenobarbitone (its active metabolite) are independently reported, in the global *DDIs* database, 960 and 1,365 times respectively.

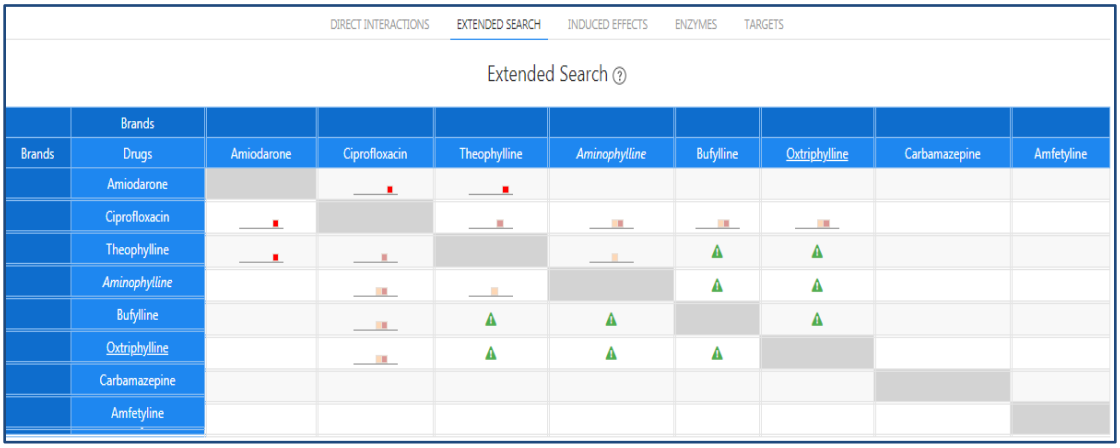
OTC Combinations, Multiple-Ingredients Products & Herbal Preparations

To date, the evaluation of *DDIs* for *OTC* multiple ingredient and natural products continues to pose a problematic issue for healthcare professionals. This applies to many therapeutic agents, including *HIV* combination products. A case in point is the provision of information for such products by the Liverpool chart. As demonstrated hereunder, this problem is efficiently dealt with by the ***DDI-Explorer***:



Extended Search Modality (one-to-many search)

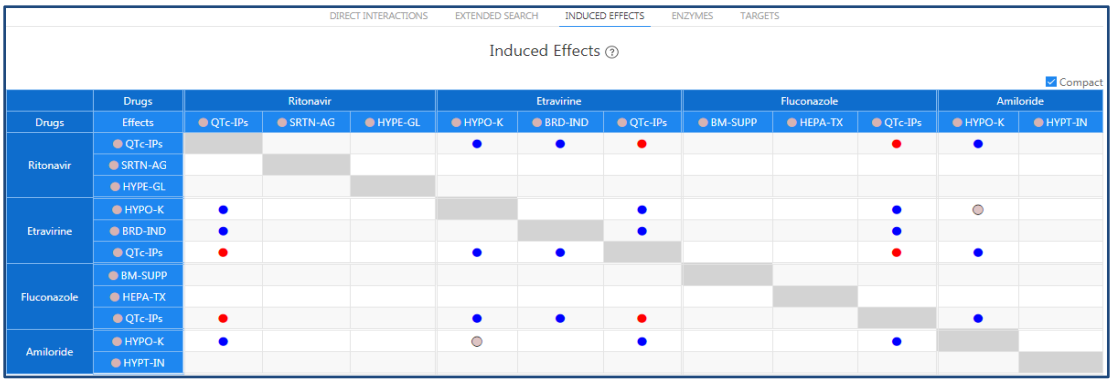
Rationale behind this search modality is substantiated by the fact that close to 25% of reported *DDIs* are provided within monograph for a therapeutic class or group of drugs. This renders direct access for relevant information rather difficult since it has not been adequately catered for by most soft drug information source or textbooks. In this regard, the extended search modality provided by the ***DDI-Explorer*** offers users ready access to interaction information for single drugs in cases wherever such information is reported under the monographs of their corresponding *class* or *category*.



Induced Drug Effects

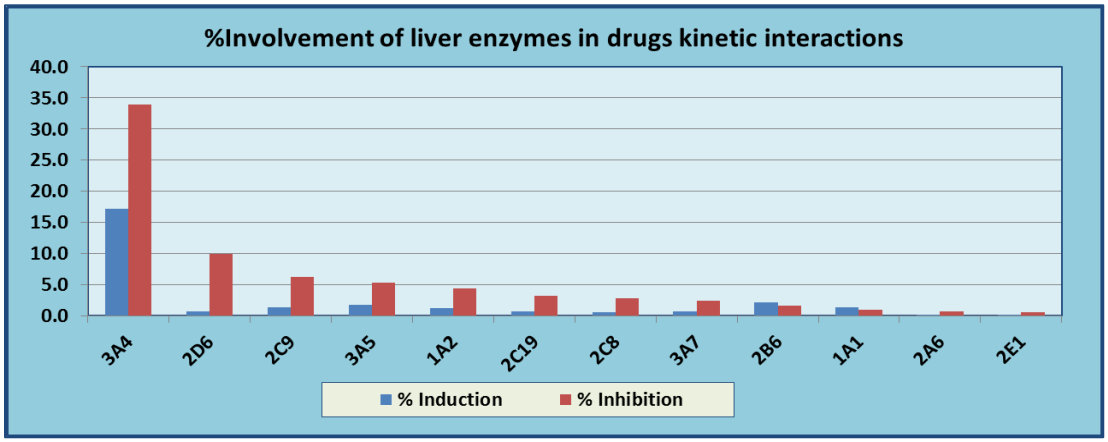
This display provided below covers *DDIs* caused by induced drugs effects, with special emphasis on anti-cholinergics and QTc-interval prolongators in accordance with their clinical significance rating by the Food and Drug Administration (FDA) and/or other regulatory agencies. The **RED**

marking in the display signifies additive QTc prolongation. Such effect is accentuated by the presence of other drugs having bradycardia, hypokalemic, negative inotropic effect. The **BLUE** marking in the table provided hereunder represent a case-in-point.

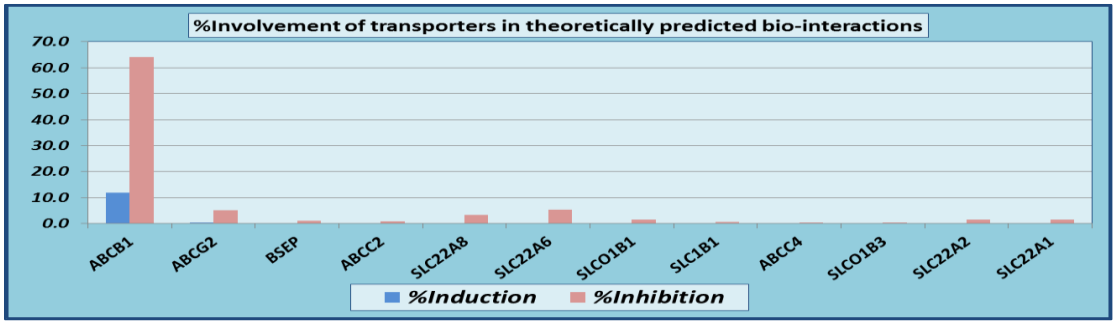


Kinetic (Enzymatic) Interactions

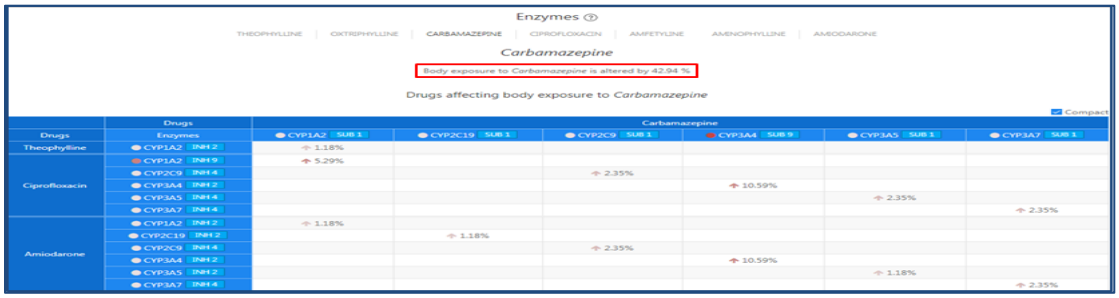
Different liver enzymes, including the cytochrome P450 class, are involved in the majority of documented kinetic DDIs. Although approximately sixty enzymes have been defined over the past decades, only a dozen of them account for more than 99.0% of kinetic interactions. The percentage involvement of liver enzymes is depicted in the diagram provided hereunder. It is worth noting that 50.0% of these interactions are caused by Cytochrome P450 3A4 alone.

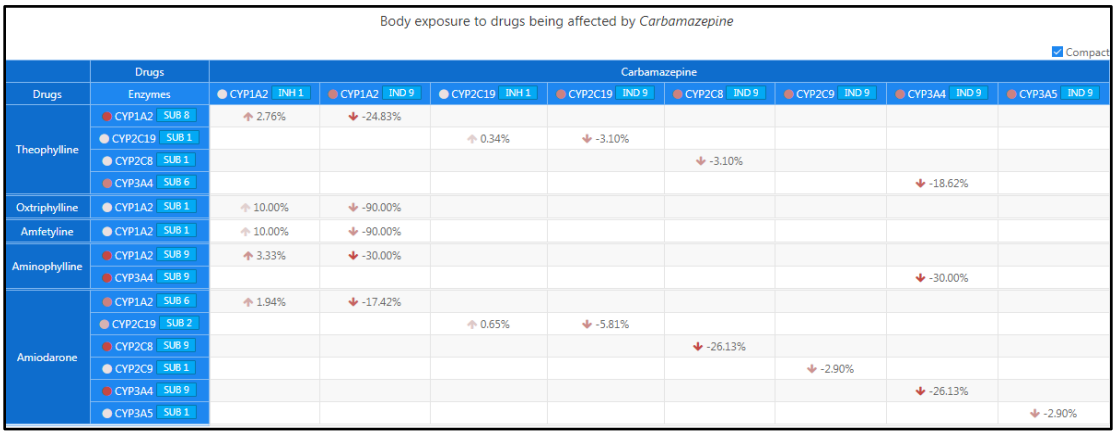


Likewise, despite the fact that close to 100 carrier proteins or transporters have been defined consequent to the elucidation of the human genome, only few of these accounts for 88.0% in the distribution and extrusion of drugs at the cellular level. The below diagram provides an exact picture for the involvement of these transporters in the disposition and/or translocation of drugs.

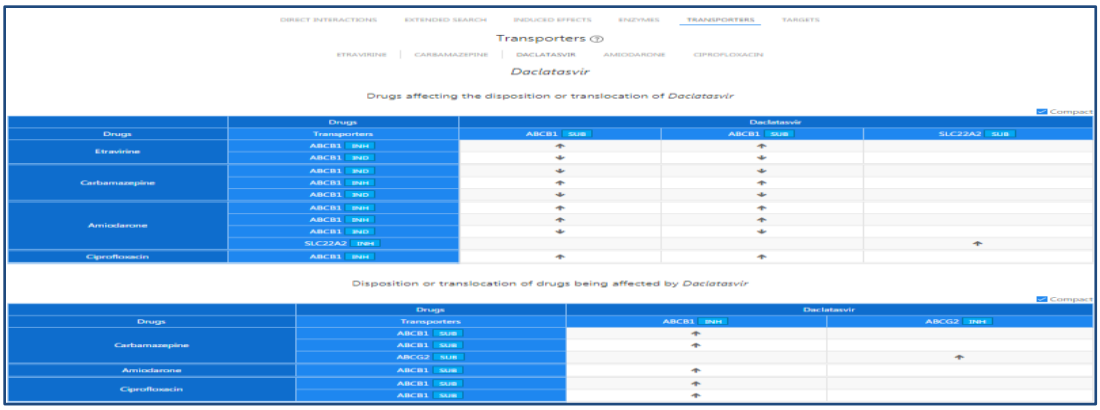


The ***DDI-Explorer*** offers information pertaining to the involvement of liver enzymes and transporters in novel fashion. The provision of such information by the Explorer represents a true departure from the too generalized, and often insufficient, provision of such information in most drug information databases. One the one hand, the overall effect of the concurrently administered drugs on body exposure to a specific drug is uniquely presented (marked with **RED** in the below diagram). On the other hand, the effect of a specific drug on the body exposure to other concurrently administered drugs is provided in a similar manner. As demonstrated below, such effects are expressed in percentage alteration of exposure in either on the above fashions.





The above tables are replicated for drug transporters interactions without quantification for the interactive effects caused by the involvement of these transporters. Interpretation of such theoretically predicted bio-interactions remains within the authority of highly qualified healthcare professionals.

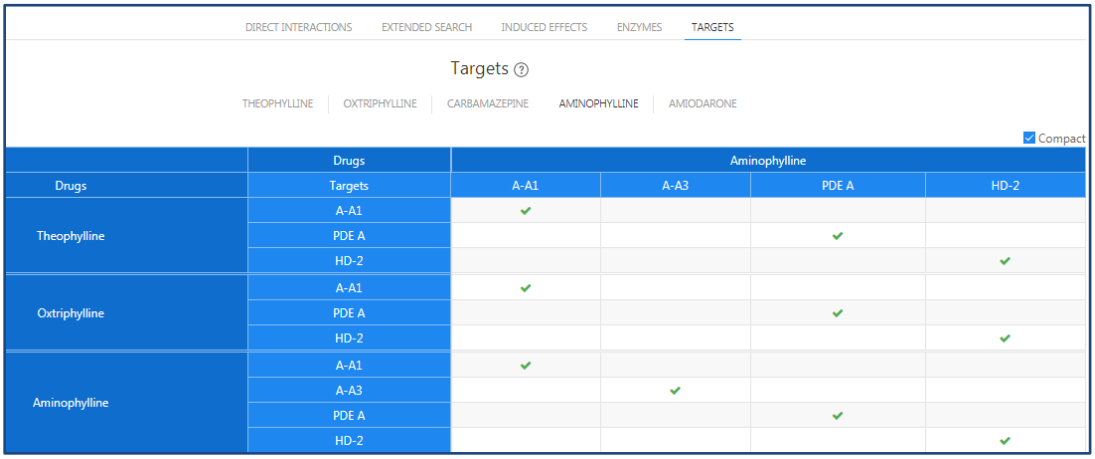


Not reporting percentage alteration values in the transporters' tables is related to the fact that no clinical significance rating has been to date defined for them by the international guidance.

It is appreciated that, unlike dynamic *DDIs*, the involvement of enzymes in the interactions of drugs is invariably enzyme-drug specific. Notwithstanding, some of information sources continues to report these interactions in a grossly generalized manner. Examples to this effect could be found in some renowned *Flockhart Drug Interaction Table and the Canadian DrugBank* where some enzymes cause in inhibition or induction of an entire group of drugs (fluoroquinolones) or that groups of drugs (barbiturates and estrogens) are substrate for a single enzyme.

Dynamic Interactions Matrix

This module is intended for the provision of more insight into the underlying causes for an interaction, and also predicts interactions that are not reported in clinical literature.

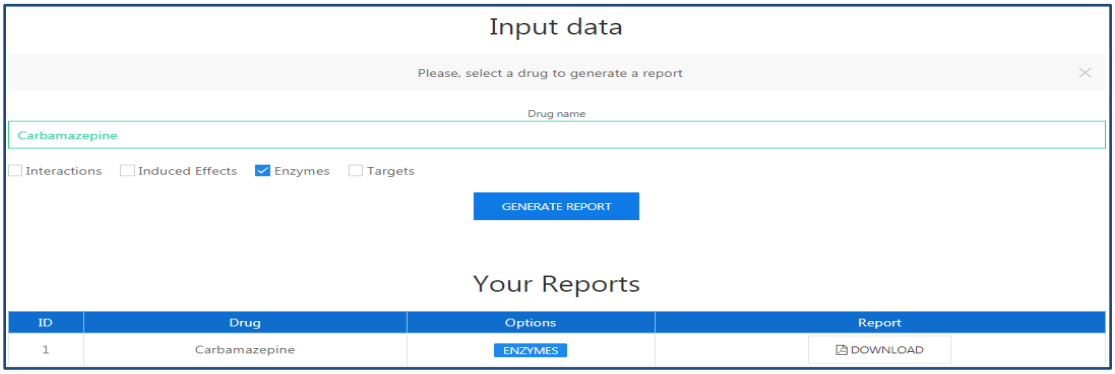


Drugs	Drugs	Aminophylline			
Drugs	Targets	A-A1	A-A3	PDE A	HD-2
Theophylline	A-A1	✔			
	PDE A			✔	
	HD-2				✔
Oxtriphylline	A-A1	✔			
	PDE A			✔	
	HD-2				✔
Aminophylline	A-A1	✔			
	A-A3		✔		
	PDE A			✔	
	HD-2				✔

The ***DDI-Explorer*** is equipped with a help utility that explain to users the specifics of option offered by the system as demonstrated hereunder:

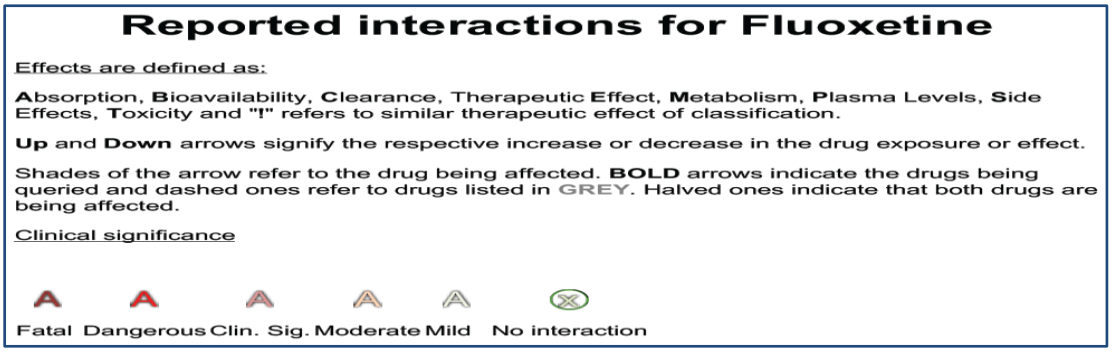
Single Drug Interactions Report

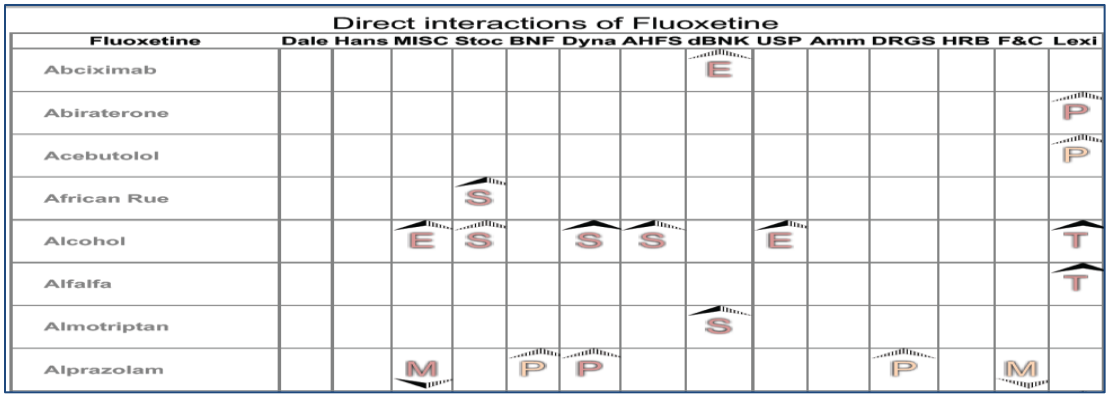
The Single Drug Interactions (***SDIs***) module represents a unique feature of the ***DDI-Explorer*** offering an unprecedented opportunity to establish a comprehensive overview of the interactive aspects for any drug. User may submit the name of the drug to be queried and select any report of interest. The system will generate the request downloadable reports. This option is described in the below data entry screen:



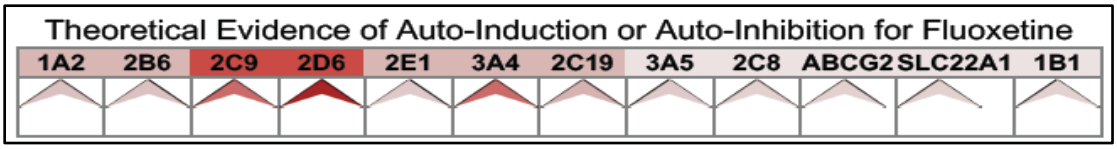
This report consists of four sections with a size amounting to about ***100*** **pages** for *Fluoxetine*. These sections may be described as follows:

1. *DDIs* that are reported by any of the fourteen major drug information sources that comprise the ***DDI-Explorer*** database.

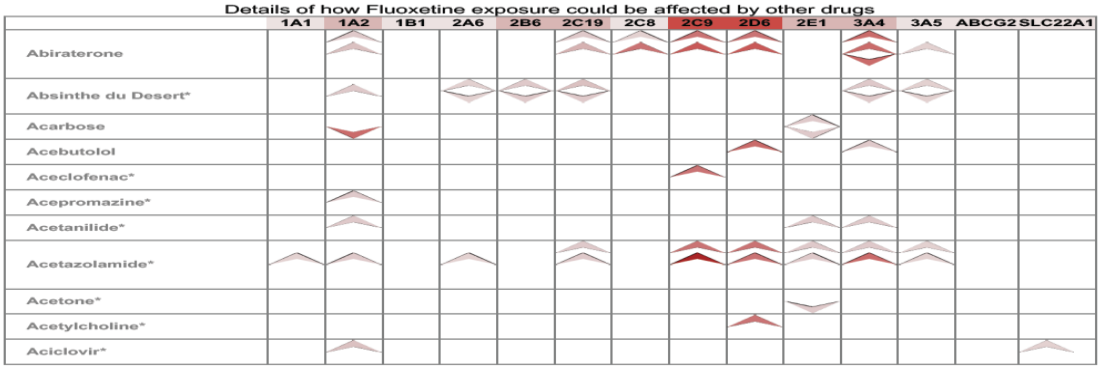




2. The second and third sections of the ***SDI*** report offers a comprehensive picture regarding the involvement of liver enzymes or transporters in it interactions with concurrently administered drugs. In addition, the report provides information on the likelihood of auto-inhibition and/or auto-induction for any specific drug. In the case for *Fluoxetine*, as shown hereunder the report shows an ample tendency for the drug to inhibit its own metabolic pathways. This is manifested by an increase of body exposure (upward arrows) caused the inhibition process. The auto-inhibition property applies to *Amiodarone*, which may account for the relative long biological half-lives of these two drug substances.



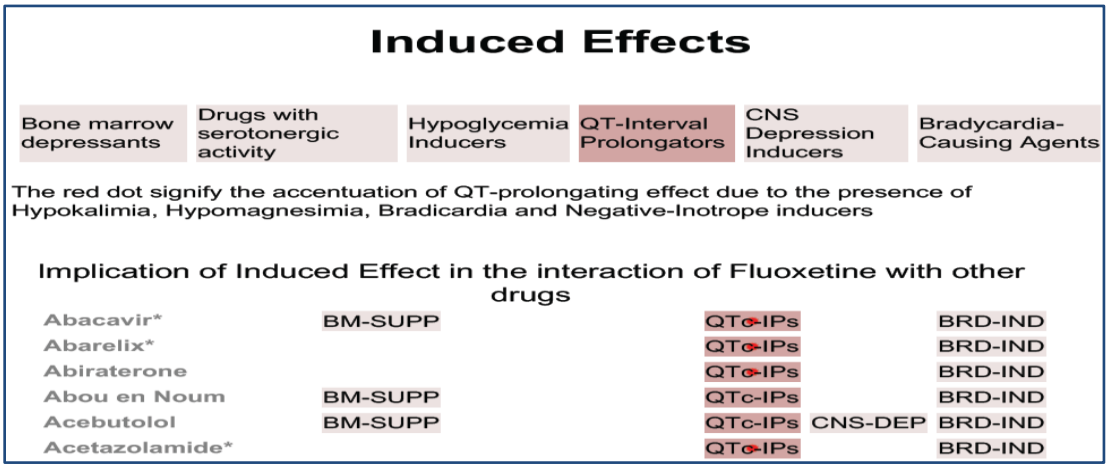
Contrary to the above mentioned the ***DDI-Explorer*** offers ample evidence of the known auto-induction characteristic of ***Carbamazepine*** as shown below:



It worth mentioning that entries in the above table marked with an asterisk (*****) have never been reported to interact with ***Carbamazepine*** in any of the fourteen databases upon that is recognized by the DDI-Explorer. For example, unlike Abiraterone, the disposition of Acetazolamide appears

to be profoundly affected by many cytochrome P450 isoenzymes. Nonetheless, its interactive profile with ***Carbamazepine*** has not been reported by any database. (The validity of the marking the entries in the above table will be verified later).

3. The fourth section of the SDI provides complete view of the likely interactions with other drugs having similar induced effects to the drug being queried



Deficiencies & shortcomings in reporting DDIs

The lack of information overlaps mention above represent one aspect of shortcomings in the reporting of DDIs in the scientific literature and drug information databases. It is unfortunate that the tremendous advancement in the domain of information technologies has not helped in resolving such shortcoming. On the contrary, it may be readily demonstrated, it has worsened the integrity of reporting of DDIs. Some examples to this effect are provided hereunder:

The British National Formulary

BNF-66

ACE Inhibitors + Antibacterials
Plasma concentration of active metabolite of imidapril reduced by rifampicin (reduced antihypertensive effect); quinapril tablets reduce absorption of tetracyclines (quinapril tablets contain magnesium carbonate); possible increased risk of hyperkalaemia when ACE inhibitors given with trimethoprim

Although a similar text has been provided in *BNF-67,* as demonstrated below, this was not the case in a more recent version of the BNF

BNF-69

ACE inhibitors+Antibacterials

Plasma concentration of eplerenone increased by clarithromycin and telithromycin— avoid concomitant use; plasma concentration of eplerenone increased by erythromycin (reduce dose of eplerenone); plasma concentration of eplerenone reduced by rifampicin—avoid concomitant use; avoidance of diuretics advised by manufacturer of lymecycline; increased risk of otoxicity when loop diuretics given with aminoglycosides, polymyxins or vancomycin; acetazolamide antagonises effects of methenamine; possible increased risk of hyper-kalaemia when spironolactone given with trimetho-prim; increased risk of hyperkalaemia when eplerenone given with trimethoprim

ACE inhibitors+Antifungals

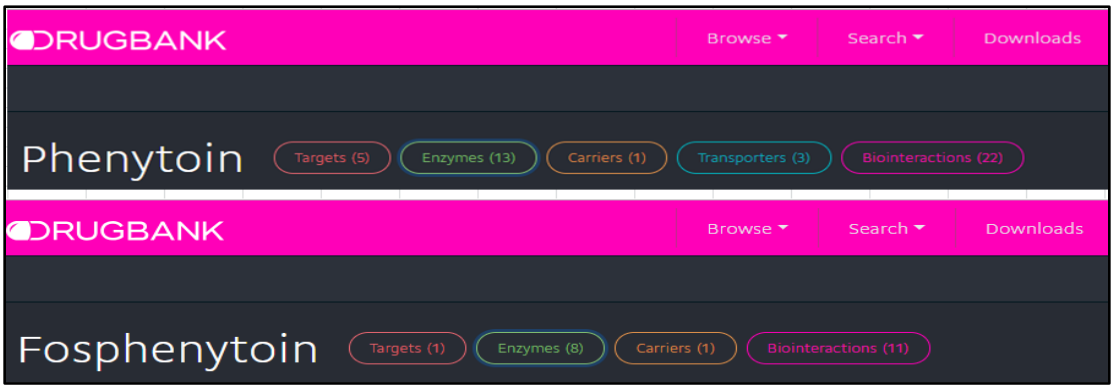
Increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with amphotericin; hydrochlorothiazide increases plasma concentration of fluconazole; plasma concentration of eplerenone increased by fluconazole (reduce dose of eplerenone); plasma concentration of eplerenone increased by itraconazole —avoid concomitant use

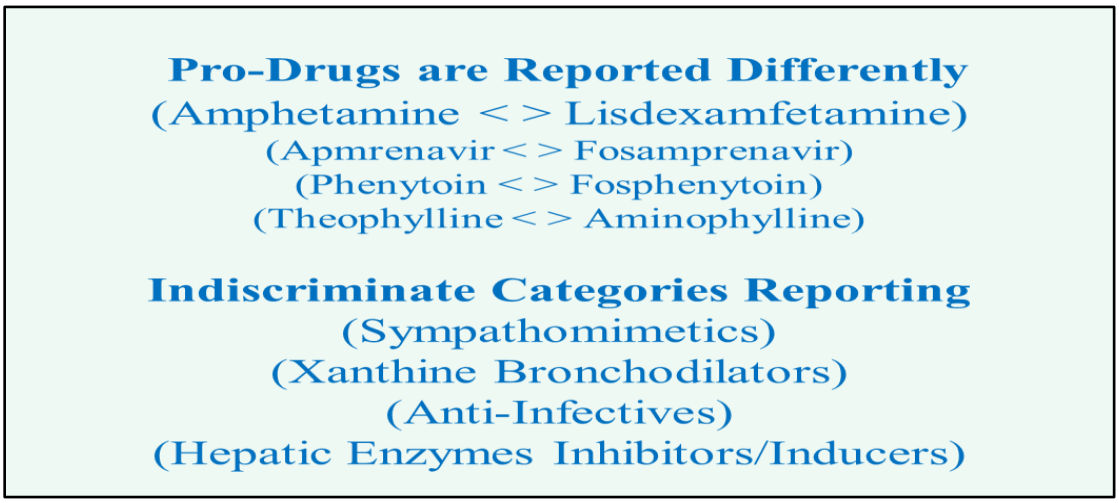
Amiodarone+Diuretics

Increased cardiac toxicity with amiodarone if hypokalaemia occurs with acetazolamide, loop diuretics or thiazides and related diuretics; amiodarone increases plasma concentration of eplerenone (reduce dose of eplerenone)

Canadian DrugBank & USP-DI

Fosphenytoin is a water-soluble phenytoin prodrug that is administered intravenously to ensure efficient delivery of the drug to the systemic circulation. Hence, both drugs should have the same profile. Interestingly, in the 2017 version of DrugBank database, interactions pertaining to Phenytoin and Fosphenytoin have been reported 454 and 303 times respectively.





As demonstrated below, flaws are often encountered when drugs dosage forms are not taken into consideration, or when *DDIs* are reported in an oversimplified manner.

The table provided hereunder demonstrates that about one third of Lexicomp reporting of DDIs is presented with only five computer generated interaction text.

Lexicomp			
Count	**Nam1**	**Nam2**	**Details**
748	Abiraterone	Afatinib	P-glycoprotein/ABCB1 Inhibitors may increase the serum conc. of Afatinib
6635	Abiraterone	Dabrafenib	May decrease the serum concentration of CYP3A4 Substrates
540	Abiraterone	TiZANidine	CYP1A2 Inhibitors (Weak) may increase the serum concentration of TiZANidine
300	Abiraterone	Amodiaquine	CYP2C8 Inhibitors may increase the serum concentration of Amodiaquine
5280	Alfentanil	Mag. Sulfate	May enhance the CNS depressant effect of CNS Depressants (188 reports)

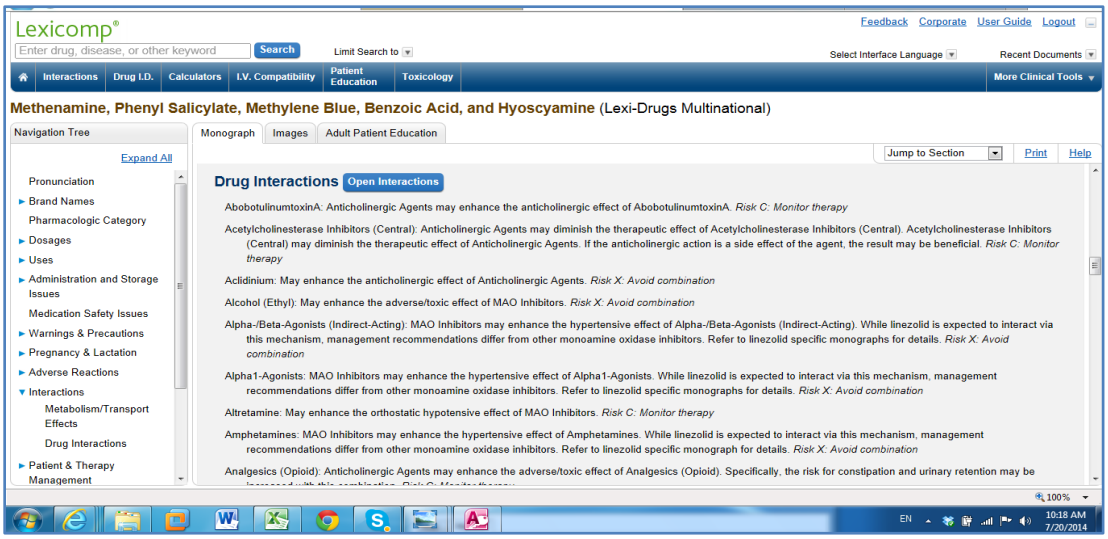
A similar situation regarding the computer-generated interaction text has been encountered in the reputed textbook entitled “Drugs Facts & Comparisons”. The first table provided hereunder is a snapshot representing 1,588 interactions text. These constitute close to 14.0% of the interactions reports provided by this database. It may be readily that text is overtly generalized and lacking specificity.

Drugs Facts & Comparisons		
Nam1	Nam2	Text
Buprenorphine	Bosentan	May decrease the serum concentration of CYP3A4 Substrates
Buprenorphine	Mifepristone	May increase the serum concentration of CYP3A4 Substrates
Dabrafenib	Phenytoin	May decrease the serum concentration of CYP2C19 Substrates
Efavirenz	Quazepam	May increase the serum concentration of CYP2B6 Substrates
Paclitaxel	Dabrafenib	May decrease the serum concentration of CYP2C8 Substrates
Peginterferon alfa-2b	Duloxetine	May decrease the serum concentration of CYP2D6 substrates
Peginterferon alfa-2b	Zafirlukast	May decrease the serum concentration of CYP2C9 substrates

As demonstrated below, further investigation of such reports reveals that the involvement of liver enzymes, in the interacting pairs of drugs, is far more complex and could not be sufficiently described by such redacted statements.

Nam1	Enzyme1	Nam2	Enzyme2	Description
Paclitaxel	Sub	Mifepristone	Sub, Inh	May increase the serum concentration of CYP2C8 Substrates
Peginterferon alfa-2b	Inh	Venlafaxine	Sub, Inh	May decrease the serum concentration of CYP2D6 substrates
Peginterferon alfa-2b	Ind	Zafirlukast	Sub, Inh	May decrease the serum concentration of CYP2C9 substrates
Riociguat	Sub	Dabrafenib	Sub, Inh	May decrease the serum concentration of CYP2C8 Substrates
Tacrolimus	Sub	Stiripentol	Sub, Inh	May increase the serum concentration of CYP3A4 Substrates
Tizanidine	Sub	Vemurafenib	Sub, Inh	May increase the serum concentration of CYP1A2 Substrates
Tocilizumab	Sub, Ind	Venlafaxine	Sub, Inh	May decrease the serum concentration of CYP3A4 substrates
Vemurafenib	Sub, Inh	Duloxetine	Sub	May increase the serum concentration of CYP1A2 substrates
Voriconazole	Sub, Inh	Luliconazole	Sub, Inh	May increase the serum concentration of CYP2C19 Substrates
Zolpidem	Sub, Inh	Peginterferon Alfa-2b	Sub, Inh	May decrease the serum concentration of CYP2D6 Substrates
Zolpidem	Sub	Simeprevir	Sub, Inh	May increase the serum concentration of CYP3A4 Substrates

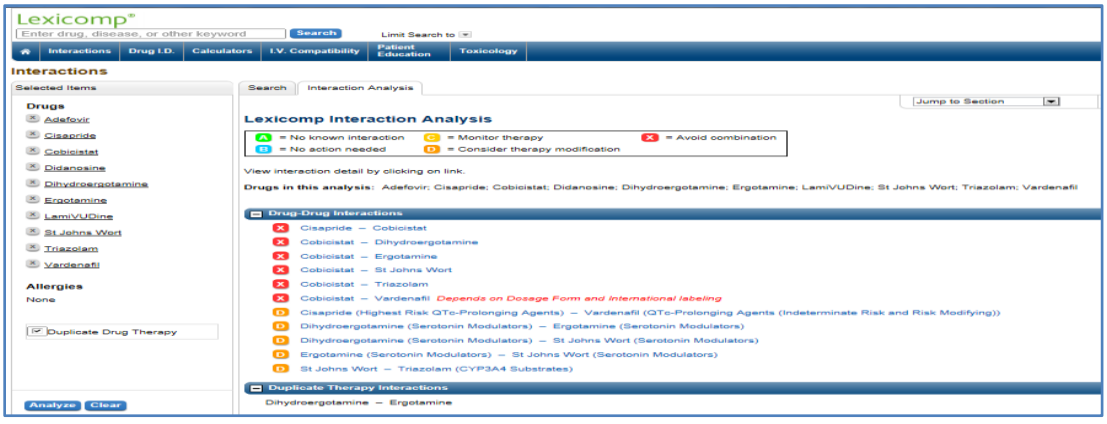
Another example of Lexicomp's reporting of the *DDIs* is provided below for a multiple-Ingredient OTC product, comprising of five ingredients. The interaction texts in the monograph do not specify which of these ingredients is interacting with other drugs!



Linezolid is EXCLUDED from IAs of the Same Drugs with MAO-Inhibitors.

Drug1	Drug2	N	E	O	Clinical Significance
Linezolid	Amphetamine	I	E	2	Risk D: Consider therapy modification
Linezolid	Amphetamine				
Linezolid	Benzphetamine	I	E	2	Risk D: Consider therapy modification
Linezolid	Benzphetamine				
Linezolid	CloZAPine	I	T	2	Risk X: Avoid combination
Linezolid	Clozapine				
Linezolid	Dextroamphetamine	I	E	2	Risk D: Consider therapy modification
Linezolid	Dextroamphetamine				
Linezolid	Ephedrine	I	E	2	Risk D: Consider therapy modification
Linezolid	Ephedrine				
Linezolid	Isocarboxazid	I	E	2	Risk X: Avoid combination
Linezolid	Isocarboxazid				

Interestingly, ten clinically significant (life-threatening) interactions are reported in Lexicomp's interaction monograph for *Cobicistat*. Notwithstanding, Lexicomp multiple interactions checker failed to identify four of these interactions?!



Doubtful Classification?!	
Anti-coagulants (DrugBank)	Anti-platelets (LexiComp)
Alprostadil	Cilostazol
Anagrelide	Citalopram
Becaplermin	Clomipramine
Ibudilast	Desvenlafaxine
Icosapent ethyl	Dihydrocodeine
Ifenprodil	Dosulepin
Ketanserin	Doxepin
Milrinone	Duloxetine
Nimesulide	Fluoxetine
Pentoxifylline	Fluvoxamine
Resveratrol	Imipramine

USP-DI Reporting of Transporters

The importance, as well as the clinical significance, of transporters in the bio-interactions of drugs has been gaining grounds over the past decade. Specifically noted is their role in the dynamics, distribution and extrusion of anticancer drugs. Close to 3,520 transporters have been defined by different drug information sources such as DrugBank, Lexicomp, USP-DI AND the FDA. Most frequently quoted transporter is the permeability glycoprotein (P-gp), which is also known as multidrug resistance protein (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1). The above mention sources identify about 550 involvements of this transporter in an array of bio-interaction. About 55 and 255 drugs act as inducers or inhibitors to this transporter respectively. On the other hand, it acts upon 255 substrates of drugs. Such vast number of drugs affecting, or being affected by this transporter, it may be verified that it is involved in about 257,000 (76.0%) theoretical bio-interactions.

Considering the above mention, it is surprising to recognize few dozens of interactions reported by the USP-DI in a remarkably confused manner. The two tables provided hereunder define a dozen of inhibitors (entries in **RED**) and a similar number of drug substrates (entries in **GREEN**). The table also contains the exact description for about 103 interactions in an extremely curt, and barely informative, text.

Drug1	Description
Darunavir	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Telaprevir	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Abiraterone	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Ulipristal	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Vandetanib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Vemurafenib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Crizotinib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Dronedarone	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Ranolazine	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Lomitapide	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Ivacaftor	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib

Drug2	Description
Topotecan	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Topotecan
Vincristine	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of VinCRIStine
Bosutinib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Bosutinib
Afatinib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib
Pazopanib	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of PAZOPanib
Rivaroxaban	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Rivaroxaban
Prucalopride	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Prucalopride
Everolimus	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Everolimus
Pomalidomide	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Pomalidomide
Silodosin	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Silodosin

In addition, examination of the below table reveals part of the confusion in USP-DI reporting of ACBC1's bio-interactions. It is worth noting that this table has been constructed consequent to exhaustive search in DrugBank bio-interactions database. Three out of the twelve drugs defined by the USP-DI as substrates are defined by the DrugBank as inhibitors. Interestingly, five drugs (entries marked by N/A) have not been identified for being involved in ACBC1's bio-interactions!

Type	Drug Name		Type	Drug Name
Sub	Telaprevir		*Inh*	Abiraterone
Sub	Topotecan		*Inh*	Vandetanib
Sub	Vincristine		*Inh*	Dronedarone
Sub	Bosutinib		*Inh*	Lomitapide
Sub	Vemurafenib		*Inh*	Ivacaftor
Sub	Afatinib			
Sub	Pazopanib		*N/A*	Darunavir
Sub	Crizotinib		*N/A*	Ulipristal
Sub	Rivaroxaban		*N/A*	Ranolazine
Sub	Dabigatran		*N/A*	Prucalopride
Sub	Pomalidomide		*N/A*	Everolimus
Sub	Silodosin			

Nam1	Type1	Nam2	Type2
Erythromycin	Inh	Rifaximin	Inh, Sub
Azithromycin	Inh	DOXOrubicin	Ind, Inh, Sub
Azithromycin	Inh	VinCRIStine	Inh, Sub
Azithromycin	Inh	Afatinib	Inh, Sub
Sofosbuvir	Inh, Sub	Rivaroxaban	Ind, Sub
Ranolazine	Inh, Sub	Lovastatin	Inh, Sub
rifampicin	Ind	Linagliptin	Inh, Sub
St. John's Wort	Ind	Pomalidomide	Inh, Sub
Cetirizine	Inh	Lumacaftor	Ind, Inh

Similar discrepancies have been encounter in Lexicomp and Drugs Facts and Comparisons in the reporting of bio-interactions implicating transporters. 745 and 183 interactions reports were respectively provided in these references in the same uninformative manner as shown above for the USP-DI. A sample of such drugs reported by Lexicomp is depicted the list provided hereunder.

Type	Name1		Type	Name2
Ind, Inh	Abiraterone		Inh	Rifaximin
Inh, Sub	Afatinib		Sub	Sofosbuvir
Sub	Aliskiren		Sub	Topotecan
Inh, Sub	Amiodarone		Sub	Bosutinib
Inh, Sub	Atorvastatin		Sub	PAZOPanib
Inh, Sub	Carbamazepine		Sub	Edoxaban
Inh, Sub	Carfilzomib		Sub	Dabigatran
Inh	Carvedilol		Sub	Ranolazine
Inh, Sub	Cimetidine		Sub	Everolimus
Inh, Sub	Cobicistat		Sub	Colchicine
Sub	Crizotinib		Sub	Silodosin
Inh, Sub	Cyclosporine		Inh, Sub	Afatinib
Sub	Dabigatran		Inh, Sub	Rivaroxaban
Inh, Sub	Daunorubicin		Inh, Sub	Linagliptin
Inh, Sub	Dexamethasone		Inh, Sub	Pomalidomide
Inh, Sub	Digoxin		Ind	Lumacaftor
Sub	Dipyridamole		Ind, Inh, Sub	DOXOrubicin
Sub	Docetaxel		Ind, Inh, Sub	VinCRIStine

It is worth mentioning that, to date, all drug information sources refer to the impact of transporters as causing an increase or a decrease in drugs plasma levels. This is rather misleading and overtly generalized since the role of transporter is basically related to the disposition or translocation of drugs, endogenous and/or xenobiotic toxicants. Only part of this role may produce such effect on drugs plasma levels. For example, *ABCB1* and *ABCC10* proteins are efflux transporters that couple the energy derived from ATP hydrolysis to the translocation of toxic substances and chemotherapeutic drugs out of cells.

Also, alteration in the activity of solute carrier organic anion transporters, such as *SLCO1B3* causes abnormalities such as hyperbilirubinemia. The same applies to *SLC22A1* which is an example of specific organic cation transporters prevailing mainly in the liver and to a much lesser extent in the kidney, intestine, and other organs. These transporters play a critical role in the elimination of many endogenous small organic cations as well as a wide array of drugs and environmental toxins. In addition, it must be stated that the role of UGTs are important phase II metabolic enzymes responsible for approximately 40-70% of endo and xenobiotic reactions. (https://www.ncbi.nlm.nih.gov/gene/6580).