A useful tool for drug interaction evaluation: The University of Washington Metabolism and Transport Drug Interaction Database

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Abstract

The Metabolism and Transport Drug Interaction Database (http://www.druginteractioninfo.org) is a web-based research and analysis tool developed in the Department of Pharmaceutics at the University of Washington. The database has the largest manually curated collection of data related to drug interactions in humans. The tool integrates information from the literature, public repositories, reference textbooks, guideline documents, product prescribing labels and clinical review sections of new drug approval (NDA) packages. The database's easy-to-use web portal offers tools for visualisation, reporting and filtering of information. The database helps scientists to mine kinetics information for drug-metabolising enzymes and transporters, to assess the extent of *in vivo* drug interaction studies, as well as case reports for drugs, therapeutic proteins, food products and herbal derivatives. This review provides a brief description of the database organisation, its search functionalities and examples of use.

Keywords: *drug–drug interactions, database, metabolism, transporters, cytochrome P450 enzymes*

Introduction

Adverse drug reactions (ADRs) remain one of the leading causes of morbidity and mortality in healthcare. In January 2000 the Institute of Medicine reported that between 44,000 and 98,000 deaths occur annually from medical errors in American hospitals.[1] Of this total, an estimated 7,000 deaths occur due to ADRs. It is estimated that drug–drug interactions (DDIs) represent 3–5 per cent of all in-hospital medication errors and that they are also an important cause of patient visits to emergency departments.[2] Among the factors that contribute to the occurrence of a DDI are patient age, number and type of concomitant medications and disease stage. In recent years, while healthcare providers have been offered access to and have benefitted from numerous drug information tools that have provided them with guidance on how drugs can be co-administered, researchers within the drug development community have had access to a more limited portfolio of data repositories. These scientists need to browse the vast literature for primary scientific data (ie datasets on metabolic isozymes, transporters, substrates, inducers, and inhibitors) that will provide them with context for their research findings and help with their drug interaction programme.

The University of Washington's Metabolism and Transport Drug Interaction Database (DIDB;

http://www.druginteractioninfo.org) was initially designed with extensive input from scientists from pharmaceutical companies and was tailored to their various needs. Later, the tool capabilities were expanded and its use was extended to other groups (Table 1).

The database contains *in vitro* and *in vivo* kinetics information for drug-metabolising enzymes and transporters, pharmacokinetics parameters/pharmacodynamic measures and side effects reported in clinical drug interaction studies. Each dataset integrates both the experimental design and the primary results. The database can be searched not only by main concepts in the field of drug interaction (ie drug name, enzyme, transporter, etc.), but also by related topics such as QTc prolongation or impact of genetic variability on drug exposure in the context of a drug interaction. Even though the DIDB was initially designed for evaluation of drug interaction profiles of small molecule compounds, a new dataset related to therapeutic proteins has been added recently.

A menu of pre-defined queries allows users to analyse and integrate both preclinical and clinical data. In addition, drug and disease monographs (composed by the DIDB editorial team) add to the information mining and data retrieval power of the queries by highlighting the most relevant datasets. As shown previously,[3] the DIDB has been used extensively by researchers and clinicians interested in correlating *in vitro* and *in vivo* findings associated with metabolic enzymes and transporters. The database is also widely used in clinical programmes, including the management of drug interactions of new drugs in multicentre trials.[4]

Table 1. Metabolism and Transport Drug Interaction Database (DIDB) users

Institution	Group	Examples of database use
Pharmaceutical industry & CROs	DMPK Clinical pharmacology Clinical	Tool for **IVIVE Modelling**: to define acceptable input parameters and validate models Helps **optimise design** of *in vitro* and *in vivo* drug interaction studies Provides **context for results** obtained for candidate compounds Provides **access to labelling** of recently marketed drugs DIDB as a research tool: publications – presentations
Regulatory agencies	Reviewers	Provides **context for results** submitted for candidate compounds Helps **update guidance documents (DDI, pharmacogenetics)** DIDB as a research tool: publications – presentations
Academia	Metabolism Pharmacokinetics Clinical pharmacology	Didactic tool Resource for courses on DDI DIDB as a research tool: publications – presentations

CRO, contract research organisation; DDI, drug–drug interaction; DMPK, drug metabolism and pharmacokinetics.

Database design and content

Structure

The DIDB application has a typical multi-tier architecture in a Microsoft® .NET environment. (The web part of the database, which is accessed by the user over the internet, is hosted on a Microsoft Windows 2003 server running IIS and version 2.0 of the ASP.NET framework. All data are stored on a Microsoft SQL Server 2005 database.) The use of the web facilitates worldwide access, as well as upgrades and updates; the DIDB is updated daily.

Content

The current DIDB datasets are extracted from more than 8,300 published articles referenced in

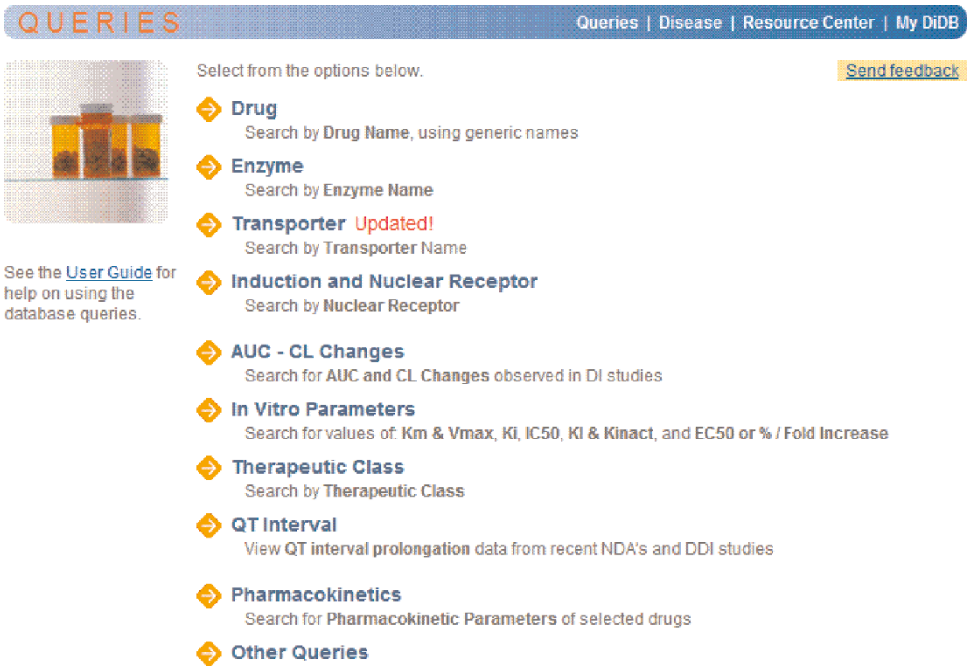


Figure 1. Ten sets of queries allow users to perform focused searches. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

PubMed (from 1966 to the present), 70 new drug applications (NDAs) and 368 product labels (from 1998 to the present). The unit of information (citation) is either a published research article or the 'NDA Clinical Reviews' section available from the *FDA Approved Drug Products* website.[5]

Detailed records are generated from each research article or NDA, highlighting study results as well as experimental conditions. The records are structured in the database according to a defined hierarchy; for example, relevant information collected from *in vitro* studies pertains to the role of particular metabolic enzymes in the various metabolic pathways of substrates and the inhibition and induction spectra of drugs toward metabolic enzymes. Particular attention is paid to experimental conditions used in determination of enzyme kinetics parameters, including K_m, K_i, IC_{50}, K_I–K_{inact} and EC_{50}. *In vivo* studies include pharmacokinetic studies with blood level measurements, pharmacokinetic–pharmacodynamic studies, as well as case reports.

Recently, a new section analysing DDIs in the context of specific diseases and their co-morbidities (*Disease-Oriented Database*) was added to the DIDB. This section allows users to retrieve overall summaries on DDIs related not only to drugs used to treat the disease, but also to drugs used to treat the main co-morbidities of that disease.

Search platform

The DIDB search interface utilises a list of pre-structured searches called 'queries'. These are set along intuitive themes such as drug, enzyme, therapeutic class, transporter, etc. and thus allow the user quickly to select the appropriate search without the need for extensive training (Figure 1).

Examples of queries and output

The following section will provide two examples of use of the DIDB, highlighting the three-step logic used to perform a search:

– Defining the issue (background and question)

– Selecting the search strategy
– Analysing and interpreting the result.

Example 1. *Notion of interchangeability of CYP3A substrates*

Background and question

In its last guidance document,[6] the US Food and Drug Administration (FDA) proposed that CYP3A inhibitors be classified based on the magnitude of change in plasma area under the curve (AUC) of oral midazolam or other sensitive CYP3A substrate. For instance, if the ratio $AUC_{inhibited}/AUC_{control}$ (AUC_R) of oral midazolam (or other sensitive CYP3A substrate) is ≥ 5, the inhibitor is considered a strong CYP3A inhibitor. If the ratio is $\geq 2 \leq 5$, the inhibitor is classified as moderate and, finally, if the ratio is $\geq 1.25 \leq 2$, it is considered a weak inhibitor. A similar classification has been proposed for the other CYP enzymes. By using a clear and consistent categorisation of drugs as substrates and inhibitors, the FDA hopes to facilitate analyses across DDI studies and to help healthcare providers to administer these drugs safely through a consistent labelling language. In addition to the CYP3A probe substrate midazolam, the FDA provides a list of other sensitive CYP3A substrates (ie that exhibit an AUC_R of ≥ 5 when given concomitantly with a CYP3A inhibitor). These sensitive substrates are: budesonide, buspirone, eplerenone, eletriptan, felodipine, fluticasone, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam and vardenafil.

Broad applicability of the above proposal rests on the assumption that the classification of a CYP3A inhibitor would be independent of the sensitive substrate used. In order to test the assumption of *substrate independence*, the DIDB was interrogated for: 1) a comprehensive list of *sensitive substrates* and 2) any discrepancies when classifying inhibitors with different sensitive substrates.

Search strategy

The AUC_R (ie $AUC_{inhibited}/AUC_{control}$) of substrates was used as the metric to assess the degree of interaction and to classify inhibitors.

Step 1: Identify all inhibitors of midazolam and retrieve the maximal midazolam AUC_R observed

To obtain a comprehensive list of sensitive substrates, all inhibitors of midazolam were retrieved using the DIDB section '*AUC and CL Changes Queries*' and the query '*Percent AUC with Object*' (Figure 2).

Result output

For midazolam as a substrate (ie object), the display shown in Figure 3 has an alphabetical list of 44 inhibitors which increase midazolam AUC by at least 20 per cent (*in vivo* cut-off to classify a study as positive).

Each *precipitant* (inhibitor) in the list has its own folder containing more detailed information: the exact value of the AUC change observed in the study; dosing regimen of the *object* (substrate) and

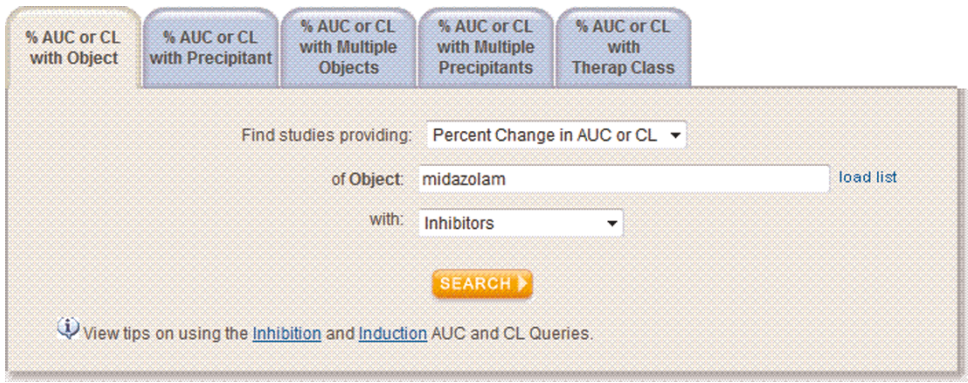


Figure 2. Query labelled 'Percent AUC or CL with object' used to find *in vivo* inhibitors of CYP3A4 using midazolam. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

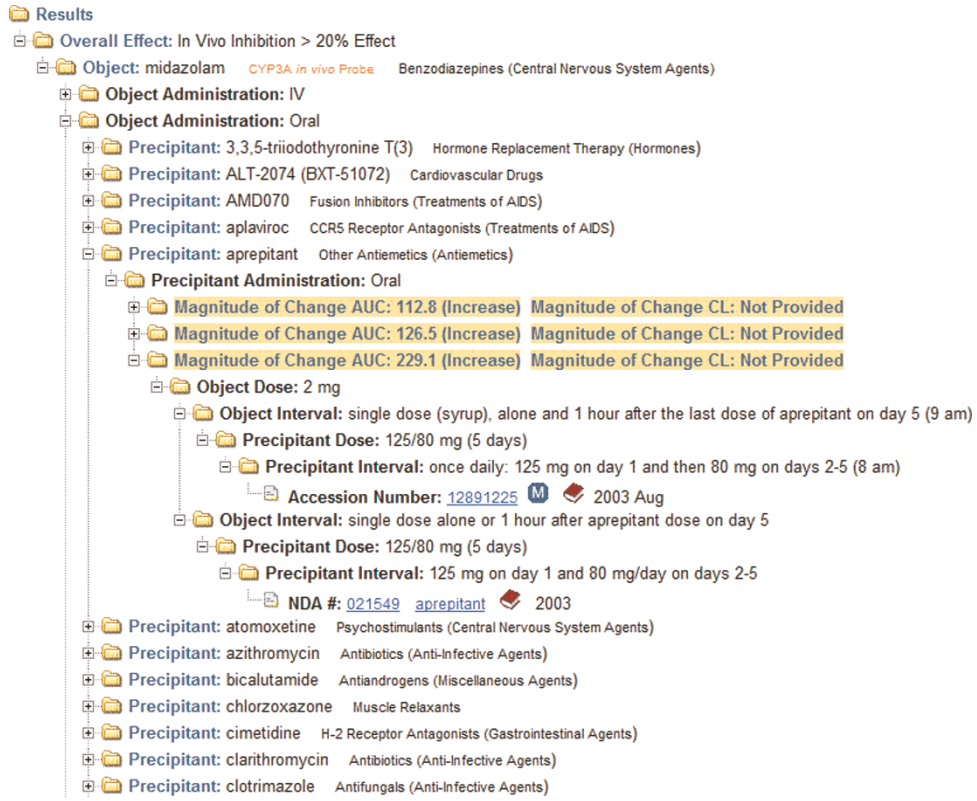


Figure 3. List of precipitants (inhibitors) evaluated with midazolam (partial view). These precipitants have increased the AUC of midazolam by 20 per cent or more. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

the *precipitant* (inhibitor); and a link to the source article identified by either an accession number (PMID number) or an NDA number. By clicking directly on this number, the full description of the article can be retrieved (study design, population, the drug's dosing regimen, results of pharmacokinetic measurements, side effects, etc.). Two additional features are available next to the accession/NDA number: abstract of the article (visualised with the M icon) and reference PK parameters for drugs (retrieved by clicking on the icon).

There are several options for displaying the results in a table and performing filter operations, as well as exporting capabilities into Microsoft Excel® or Microsoft Word®.

When the list of inhibitors obtained with oral midazolam is exported into an Excel file (Figure 4) and the maximal increase is kept for each inhibitor, the following graphical display is easily obtained using potent and moderate inhibitors (Figure 5).

Step 2: Using CYP3A inhibitors to identify all other sensitive substrates

The obtained list of inhibitors (potent and moderate) will be then used in a different query, '*Percent AUC with multiple precipitants*', to find substrates. Selecting a percentage change in substrates AUC of 400 per cent or more (ie $AUC_R \geq 5$) will narrow the results sets to sensitive substrates (Figure 6).

Result output

The 44 inhibitors for which there are available studies with midazolam yielded the 13 drugs identified in the FDA draft guidance as CYP3A-sensitive substrates (namely, budesonide, buspirone, eplerenone, eletriptan, felodipine, fluticasone, lovastatin,

Object	Precipitant	↑ Change AUC (%)	AUCratio	Accession # or NDA #	Published
midazolam	aplaviroc	21.2	1.212	Accession #: 16638741	2006 May
midazolam	aprepitant	112.8	2.128	NDA # 021549	2003
midazolam	aprepitant	126.5	2.265	NDA # 021549	2003
midazolam	aprepitant	229.1	3.291	Accession #: 12891225	2003 Aug
midazolam	aprepitant	229.1	3.291	NDA # 021549	2003
midazolam	atomoxetine	20.1	1.201	Accession #: 14610241	2004 Feb
midazolam	azithromycin	26.6	1.266	Accession #: 8720318	1996 Feb
midazolam	bicalutamide	27.3	1.273	Accession #: 15509184	2004
midazolam	chlorzoxazone	67.8	1.678	Accession #: 11736864	2001 Nov
midazolam	cimetidine	34.6	1.346	Accession #: 3802710	1987 Jan
midazolam	cimetidine	36.5	1.365	Accession #: 2939688	1986 Feb
midazolam	cimetidine	49.7	1.497	Accession #: 10223772	1999 Apr
midazolam	cimetidine	101.6	2.016	Accession #: 6152615	1984 Sep
midazolam	clarithromycin	257.2	3.572	Accession #: 8880291	1996 Sep
midazolam	clarithromycin	405.5	5.055	Accession #: 9728893	1998 Aug
midazolam	clarithromycin	448.3	5.483	Accession #: 17495878	2008 Jan
midazolam	clarithromycin	531.9	6.319	Accession #: 17635500	2008 Jan
midazolam	clarithromycin	600	7	Accession #: 9728893	1998 Aug
midazolam	clarithromycin	739.3	8.393	Accession #: 16432272	2006 Feb
midazolam	clarithromycin	861	9.61	Accession #: 9728893	1998 Aug
midazolam	clotrimazole	61.1	1.611	Accession #: 20233179	2010 Feb
midazolam	cobicistat (GS-9350)	876.6	9.766	Accession #: 20043009	2010 Mar
midazolam	cobicistat (GS-9350)	1235.4	13.354	Accession #: 20043009	2010 Mar
midazolam	cobicistat (GS-9350)	1803.3	19.033	Accession #: 20043009	2010 Mar
midazolam	conivaptan	249.3	3.493	NDA # 021697	2005
midazolam	conivaptan	476	5.76	NDA # 021697	2005
midazolam	cranberry juice	33	1.33	Accession #: 19114462	2009 Mar
midazolam	diltiazem	275	3.75	Accession #: 8198928	1994 Mar
midazolam	diltiazem	301	4.01	Accession #: 19420129	2009 Aug
midazolam	erythromycin	132.1	2.321	Accession #: 17585116	2007 Jul
midazolam	erythromycin	231.6	3.316	Accession #: 17585116	2007 Jul
midazolam	erythromycin	233	3.33	Accession #: 17585116	2007 Jul
midazolam	erythromycin	281.4	3.814	Accession #: 8720318	1996 Feb
midazolam	erythromycin	341.7	4.417	Accession #: 8453848	1993 Mar
midazolam	FK1706	100.9	2.009	Accession #: 19889885	2010 Feb
midazolam	fluconazole	244.2	3.442	Accession #: 9049584	1997

Figure 4. Excel download (partial view) of the results of the query that retrieved CYP3A4 inhibitors using midazolam (oral) as a substrate (same results as in Figure 3). Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

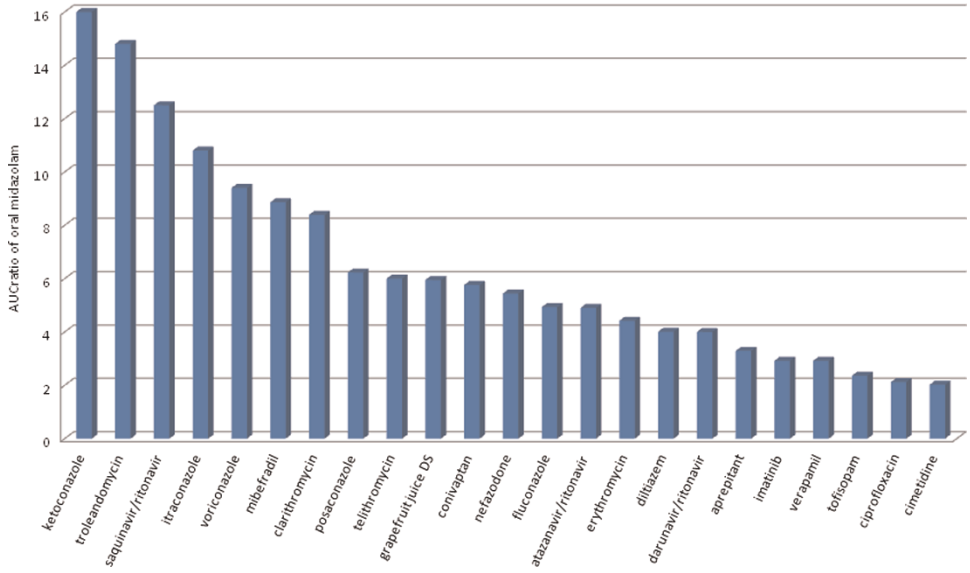


Figure 5. Potent and moderate CYP3A inhibitors and their effects (AUC_R) on the probe substrate midazolam.

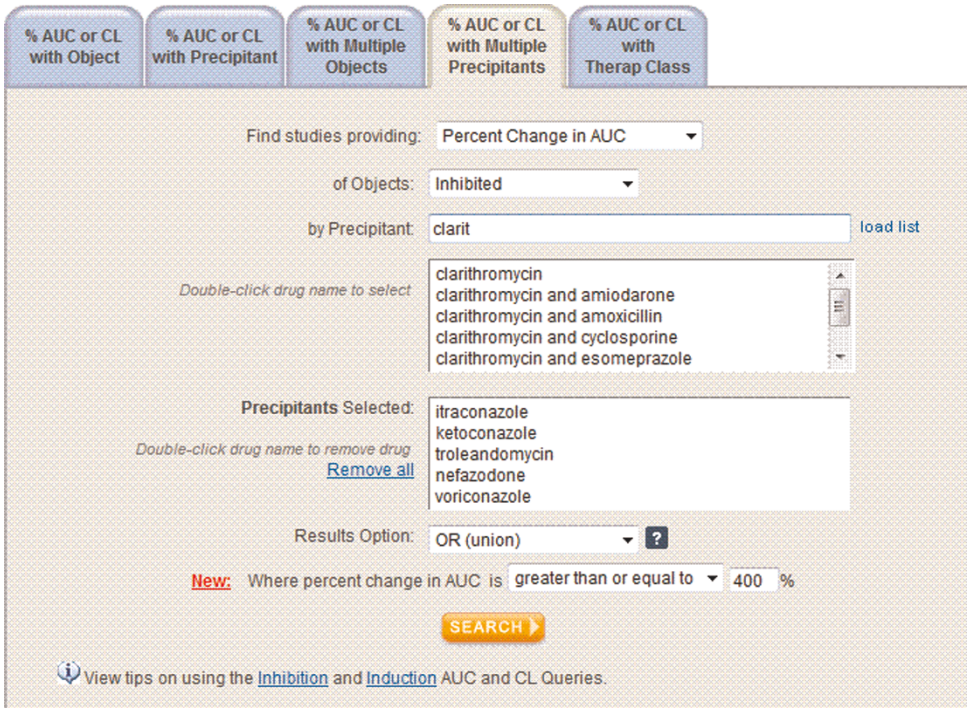


Figure 6. Query labelled 'Percent AUC or CL with multiple precipitants' used to find *in vivo* CYP3A4-sensitive substrates ($AUC_R \geq 5$ or percentage change in AUC ≥ 400 per cent). Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil) but also 20 new ones, as shown in Figure 7.

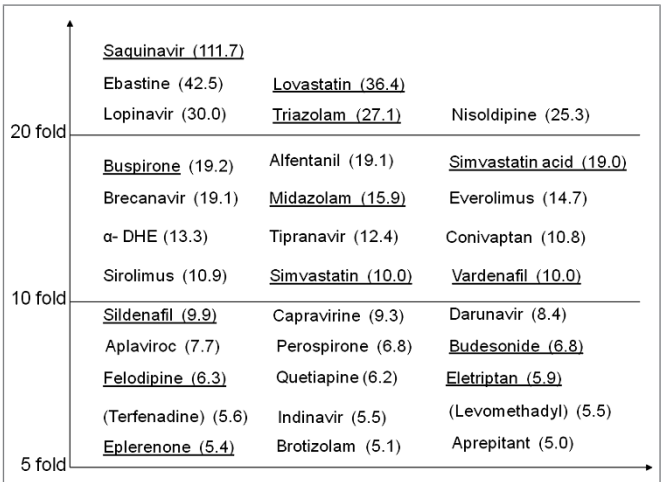


Figure 7. Thirty-three sensitive CYP3A substrates identified in the DIDB. Drugs that are underlined were listed in the latest FDA draft guidance.[6] The sensitive substrates are presented in three quadrants, based on their AUC_R (# in brackets) when co-administered with a known CYP3A inhibitor.

Step 3: Search for discrepancies when classifying inhibitors with different sensitive substrates

In order to test if the classification with midazolam is applicable to other sensitive substrates, the attributed potencies with midazolam and the newly identified sensitive substrates were compared. Only inhibitors tested with a comparable dose regimen were included in the analysis. Among the eight 'potent inhibitors' (exhibiting a substrate $AUC_R \geq 5$) (clarithromycin, itraconazole, ketoconazole, mibefradil, nefazodone, saquinavir, telithromycin and troleandomycin) and the five moderate inhibitors (exhibiting an $AUC_R \geq 2 \leq 5$) (diltiazem, erythromycin, fluconazole, grapefruit juice and verapamil), the classification was maintained in 34 cases (83 per cent) and 31 cases (74 per cent), respectively; however, exceptions were observed and are listed in Table 2.

Analysis and interpretation

These discrepancies do not invalidate the proposed classification. Some of these differences could

Table 2. Examples of exceptions to midazolam classification for seven CYP3A4 inhibitors.

Inhibitor	Classification with sensitive substrate	Sensitive substrate
Potent with midazolam		
Clarithromycin	moderate	saquinavir
Ketoconazole	moderate	saquinavir
Nefazodone	moderate	triazolam
Troleandomycin	moderate	triazolam
Moderate with midazolam		
Erythromycin	potent	simvastatin/ buspirone
Diltiazem	potent	buspirone
Fluconazole	weak	saquinavir

arise simply because of the absolute boundaries (2.0- and 5.0-fold) of the classification; some discrepancies could also be related to: (i) transporter effects in specific substrate-inhibitor pairs; (ii) intrinsic differences among substrates in sensitivity to inhibition (including fraction metabolised by CYP3A and intestinal metabolism); and/or (iii) inhibition of minor enzymes by CYP3A inhibitors.[7] Similar findings have recently been reported by other groups.[8,9] These differences in *in vivo* sensitivities of CYP3A substrates need to be considered when selecting a CYP3A probe substrate for clinical DDI studies.

Example 2. *Analysis of drug interactions in the context of a disease and its co-morbidities*

Background and question

Assessment of the DDI risk potential of a new molecular entity (NME) during drug development takes into consideration the clinical outcome of administration of the NME and focuses not only on the drugs used to treat the primary disease, but also on those used to treat co-morbidities. Moreover, questions arise regarding the roles of environmental factors (food, herbal medications) and patient characteristics (genotype, age, etc.) that may also alter drug disposition.

In the problem at hand, an NME is being developed for the treatment of hypertension. This NME is mainly metabolised by CYP2D6, with some contribution from CYP3A4. It was also found that this NME is a moderate CYP3A4 inhibitor, yielding an AUC ratio of midazolam of 3.2.

Because hypertension is a condition that often co-exists with hyperlipidaemia, the developer wanted to evaluate whether drugs that treat this condition would have any clinically relevant impact on the disposition of this new antihypertensive drug; in addition, given the inhibitory profile of this NME, the user wanted to determine whether any drugs used in hyperlipidaemia were likely to be affected by this new antihypertensive.

Search strategy

First query

Within the DIDB website, the disease monograph for dyslipidaemia will be used (Figure 8). This monograph has been compiled using in-depth analyses of the metabolic profiles and effects of all compounds used in the treatment of dyslipidaemia (cholesterol absorption inhibitors, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors — statins — and fibric acid derivatives). The atherosclerosis/dyslipidaemia monograph is organised into summaries, ten individual drug monographs and two specific queries.

Result output

For all the drugs considered within the three subclasses cited above, complete profiles are presented within a table that highlights the main characteristics of each drug considered as an inhibitor/ inducer (Figure 9).

For each compound shown in Figure 9, the table provides the enzymes and/or transporters affected and a corresponding DDI risk level. Four risk levels have been created based on a combination of the following characteristics: (i) sensitivity to inhibition and induction of the involved enzymes and/ or transporters; (ii) therapeutic range; (iii) documented clinical interactions.

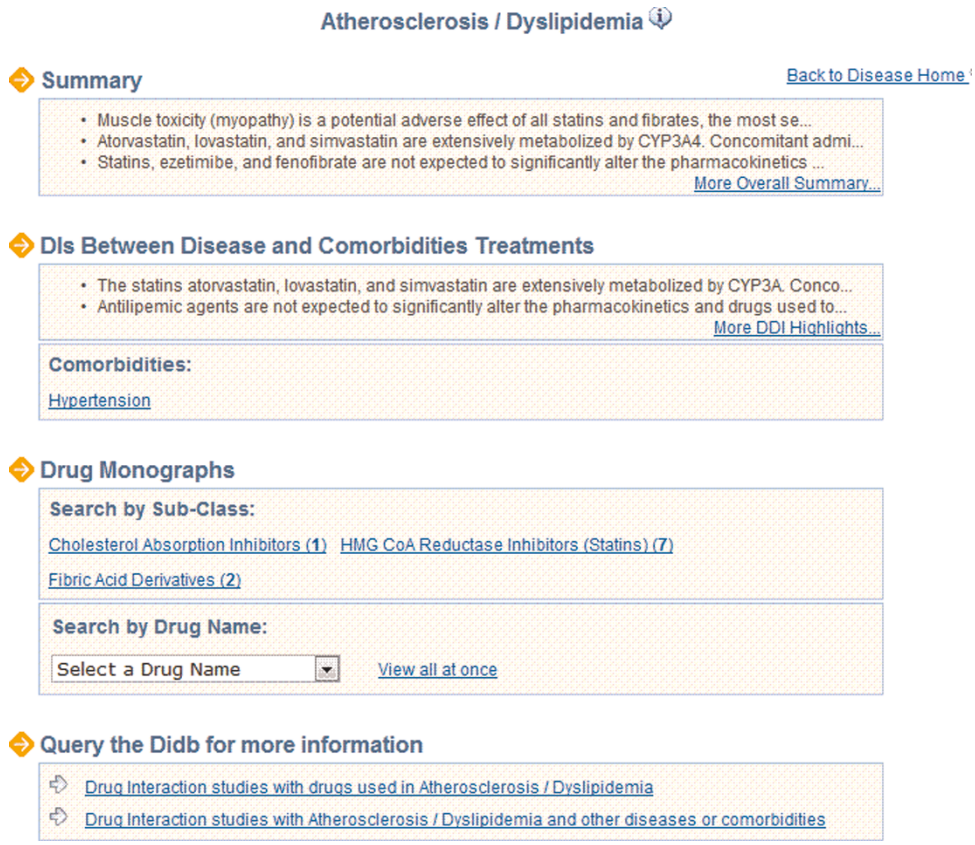
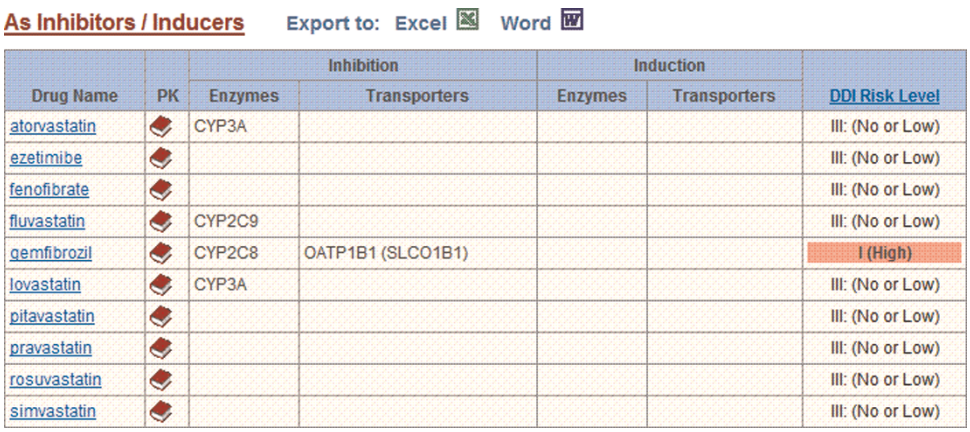


Figure 8. One-page presentation of the different sections (summaries, individual drug monographs and queries) within the monograph for atherosclerosis/dyslipidaemia. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).



Drug Name	PK	Inhibition		Induction		DDI Risk Level
		Enzymes	Transporters	Enzymes	Transporters	
atorvastatin		CYP3A				III: (No or Low)
ezetimibe						III: (No or Low)
fenofibrate						III: (No or Low)
fluvastatin		CYP2C9				III: (No or Low)
gemfibrozil		CYP2C8	OATP1B1 (SLCO1B1)			I (High)
lovastatin		CYP3A				III: (No or Low)
pitavastatin						III: (No or Low)
pravastatin						III: (No or Low)
rosuvastatin						III: (No or Low)
simvastatin						III: (No or Low)

Figure 9. Complete DDI profile of ten antilipaemics presented within a table that highlights the main characteristics of each drug considered as an inhibitor or an inducer. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

Analysing results of the first query

The inhibitory profiles of the ten antilipaemics listed in Figure 9 show that most of these drugs do not exhibit any risk of increasing the exposure of co-administered drugs. Only one compound, gemfibrozil, exhibits a relatively high inhibitory risk potential towards CYP2C8 and OATP1B1. None of the drugs are expected to alter the disposition of CYP2D6 substrates such as the NME.

Second query

To address the CYP3A inhibitory potential of the NME and assess whether its weak inhibitory potency might affect certain antilipaemics, the overall view that highlights the main characteristics of all antilipaemics as substrates is used (Figure 10).

Result output

The table in Figure 10 shows that three statins (atorvastatin, simvastatin and lovastatin) are extensively metabolised by CYP3A4.

Analyzing the results of the second query

An analysis of the DDI profiles of these three statins (Figure 11) shows that they are susceptible to CYP3A inhibition, as indicated by 3.3-, 15- and tenfold increases in AUC for atorvastain, lovastatin and simvastatin, respectively, in the presence of the potent CYP3A inhibitor itraconazole (the three drugs are also sensitive to potent inducers). Moreover, a search of the database shows that concomitant administration of the calcium channel blockers diltiazem and verapamil, known as moderate inhibitors of CYP3A, also increase significantly the exposure of atorvastatin, lovastatin and simvastatin (1.5- to fivefold) and lead to muscle toxicity. Based on these observations, a moderate CYP3A inhibitor, such as the NME under consideration, is expected to have a similar effect to diltiazem or verapamil on the exposure of the three statins, and dosage adjustment may be required for these drugs when co-prescribed with the NME.

Analysis and interpretation

The new disease section has multiple uses and it allows a rapid assessment of the DDI potential of an NME in comparison with other marketed drugs used to treat the same disease, and also the DDI potential of this NME with drugs used to treat

Drugs used in Atherosclerosis / Dyslipidemia

Back to Disease Monograph

As Substrates Export to: Excel Word

Drug Name	PK	Routes of Elimination	Main Enzymes	Main Transporters	DDI Risk Level
atorvastatin		Extensive Metabolism	CYP3A	OATP1B1 (SLCO1B1) P-gp (ABCB1) BCRP (ABCG2)	I (High)
ezetimibe			UGT	MRP2 (ABCC2) P-gp (ABCB1)	III: (No or Low)
fenofibrate			Esterase UGT		III: (No or Low)
fluvastatin		Extensive Metabolism	CYP2C9	OATP1B1 (SLCO1B1)	II (Intermediate)
gemfibrozil		Extensive Metabolism	UGT2B7 CYP2C8		III: (No or Low)
lovastatin CYP3A *in vivo* Probe		Extensive Metabolism	CYP3A	P-gp (ABCB1)	I (High)
pitavastatin		Biliary Excretion (unchanged)		OATP1B1 (SLCO1B1)	II (Intermediate)
pravastatin				OATP1B1 (SLCO1B1) P-gp (ABCB1) MRP2 (ABCC2)	I (High)
rosuvastatin		Biliary Excretion (unchanged)		OATP1B1 (SLCO1B1) BCRP (ABCG2)	I (High)
simvastatin CYP3A *in vivo* Probe		Extensive Metabolism	CYP3A	OATP1B1 (SLCO1B1) P-gp (ABCB1)	I (High)

Figure 10. Complete DDI profile of antilipaemics presented within a table that highlights the main characteristics of each drug considered as a substrate. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

Figure 11. Example of the drug monograph section called '*Main enzymes and associated interactions*' for three statins that are CYP3A substrates: atorvastatin, lovastatin and simvastatin. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

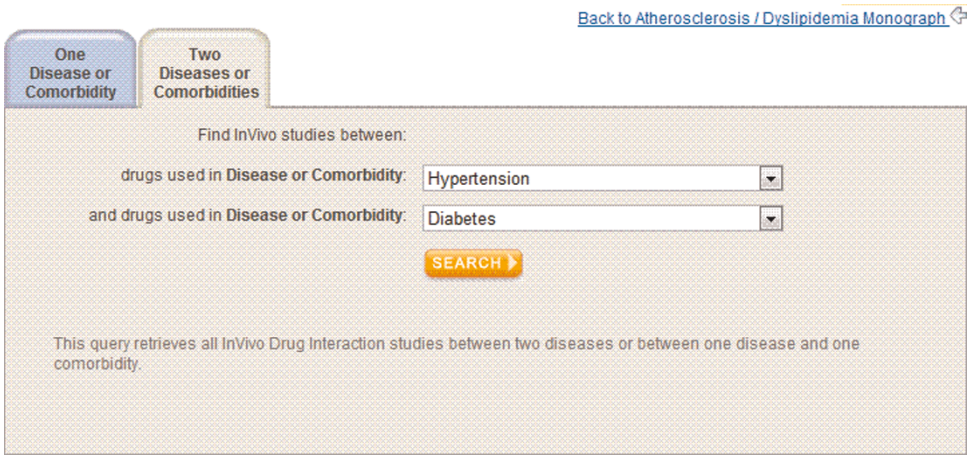


Figure 12. Query labelled '*Two diseases or comorbidities*' used to retrieve all DI studies between antihypertensives and antidiabetics. Display from the Metabolism and Transport Drug Interaction Database© (http://www.druginteractioninfo.org).

co-morbidities of that disease. Additionally, the complete DDI profile of a disease is provided in summarised tabulated views.

Clinical investigators may also be interested in using two specific queries that yield the DDI profile resulting from the coexistence of any two

diseases of interest (eg hypertension and diabetes) (Figure 12).

Ongoing developments

For almost a decade, the DIDB has been widely used by scientists and clinicians working in the field of DDI. The tool is constantly being optimised as a result of feedback from a large base of users, including requests for specific searches. These can be in the form of new queries or special reports tailored by the DIDB team. New features currently being developed include the addition of datasets pertaining to emerging areas (therapeutic proteins, pharmacogenomics). The DIDB is also enhanced with tools that allow users to focus rapidly on important DDI reports and sort through the large body of literature. Examples of such tools include: graphical displays of the extent of DDI (AUC_R, changes in the clearance of substrates) and 'flagging' important drug characteristics (narrow therapeutic range drugs, probe substrates, potent inhibitors or inducers).

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