Services for drug-drug interactions (DDI) and DDI research at NLM

Olivier Bodenreider
Senior Scientist and Chief, Cognitive Science Branch
Lister Hill National Center for Biomedical Communications
National Library of Medicine (NLM)

• World’s largest biomedical library
• Maintains and makes available a vast print collection
• Produces electronic information resources on a wide range of topics that are searched billions of times each year by millions of people around the globe
• Supports and conducts research, development, and training in biomedical informatics and health information technology

https://www.nlm.nih.gov/about/
NLM strategic plan (2006-2016)*

• **Goal 1.** Seamless, Uninterrupted Access to Expanding Collections of Biomedical Data, Medical Knowledge, and Health Information

• **Goal 2.** Trusted Information Services that Promote Health Literacy and the Reduction of Health Disparities Worldwide

• **Goal 3.** Integrated Biomedical, Clinical, and Public Health Information Systems that Promote Scientific Discovery and Speed the Translation of Research into Practice

• **Goal 4.** A Strong and Diverse Workforce for Biomedical Informatics Research, Systems Development, and Innovative Service Delivery

DDI services at NLM
Drug information services at NLM

- FDA Structured Product Labels
  - DailyMed website
  - DailyMed API

- RxNorm
  - Standard vocabulary for drugs
  - Drug terminology integration

- RxNorm-based applications and services
  - RxNav
  - RxNorm APIs

- ChemIDPlus (part of ToxNet)
- MedlinePlus Drugs and supplements (consumer health information)
- PubMed Health (reviews of clinical effectiveness research)
DailyMed – Access to 94,000 SPLs

https://dailymed.nlm.nih.gov/
DDIs in DailyMed
7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibrinolytic acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, itraconazole) [see WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY (12.3)]

7.1 Strong Inhibitors of CYP 3A4
LIPITOR is metabolized by cytochrome enzymes CYP 3A4, and co-administration with strong inhibitors of CYP 3A4 can lead to an increased risk of myopathy with atorvastatin. The extent of interaction and the magnitude of the potential increased risk are variable by inhibitor.

Clarithromycin: Atorvastatin AUC was increased by 57% when co-administered with clarithromycin 500 mg bid for 5 days to that of LIPITOR alone [see CLINICAL PHARMACOLOGY (12.3)]. Taking clarithromycin, caution should be used when co-administering LIPITOR with clarithromycin. The co-administration of LIPITOR with clarithromycin is not recommended.

Itraconazole: Atorvastatin AUC was increased by 140% when co-administered with itraconazole 200 mg once daily for 7 days to that of LIPITOR alone [see CLINICAL PHARMACOLOGY (12.3)]. Taking itraconazole, caution should be used when co-administering LIPITOR with itraconazole. The co-administration of LIPITOR with itraconazole is not recommended.

Combination of Protease Inhibitors: LIPITOR is not recommended in combination with protease inhibitors, as well as with the protease inhibitor telaprevir, or concomitant administration of LIPITOR 80 mg with telaprevir 750 mg bid for 14 days to that of LIPITOR alone [see CLINICAL PHARMACOLOGY (12.3)]. Taking protease inhibitors, caution should be used when co-administering LIPITOR with protease inhibitors. The co-administration of LIPITOR with protease inhibitors is not recommended.

7.2 Grapefruit Juice
Contains one or more components that can significantly increase plasma concentrations of atorvastatin, especially in those who are metabolizers (12.1) [see CLINICAL PHARMACOLOGY (12.3)]. Taking grapefruit juice, caution should be used when co-administering LIPITOR with grapefruit juice. The co-administration of LIPITOR with grapefruit juice is not recommended.

7.3 Cyclosporine
Atorvastatin and atorvastatin-metabolites are inhibitors of the OATP1B1 (e.g., cyclosporine) transporter. Atorvastatin AUC was significantly increased when co-administered with LIPITOR 10 mg and cyclosporine 5 mg/kg once daily to that of LIPITOR alone [see CLINICAL PHARMACOLOGY (12.3)]. Taking cyclosporine, caution should be used when co-administering LIPITOR with cyclosporine. The co-administration of LIPITOR with cyclosporine is not recommended.

7.4 Gemfibrozil
Due to an increased risk of myopathy/renal toxicity when atorvastatin is co-administered with gemfibrozil, co-administration of LIPITOR with gemfibrozil should be avoided [see WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY (12.3)]. Taking gemfibrozil, caution should be used when co-administering LIPITOR with gemfibrozil. The co-administration of LIPITOR with gemfibrozil is not recommended.

7.5 Other Fibrates
Because it is known that the risk of myopathy/renal toxicity is increased when atorvastatin is co-administered with fibrates, co-administration of LIPITOR with fibrates should be avoided [see WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY (12.3)]. Taking fibrates, caution should be used when co-administering LIPITOR with fibrates. The co-administration of LIPITOR with fibrates is not recommended.

7.6 Niacin
The risk of skeletal muscle effects may be increased when LIPITOR is co-administered with niacin; a reduction in atorvastatin dose may be considered [see WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY (12.3)]. Taking niacin, caution should be used when co-administering LIPITOR with niacin. The co-administration of LIPITOR with niacin is not recommended.

7.7 Rifampin or other Inducers of Cytochrome P450 3A4 Enzymes
Concurrent administration of LIPITOR with rifampin or ritonavir may lead to variable reductions in atorvastatin plasma concentrations. Due to the dual interaction of LIPITOR with rifampin or ritonavir, co-administration of LIPITOR with rifampin or ritonavir is not recommended.

7.8 Dipyridamole
When single or multiple doses of LIPITOR and dipyridamole were co-administered, steady state plasma dipyridamole concentrations increased by approximately 20%. Patients taking dipyridamole should be monitored appropriately.

7.9 Oral Contraceptives
Co-administration of LIPITOR with an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see CLINICAL PHARMACOLOGY (12.3)]. These increases should be considered when selecting an oral contraceptive for a woman taking LIPITOR.

7.10 Warfarin
LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.11 Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy - Pregnancy Category X - LIPITOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides are elevated during pregnancy.

10 OVERDOSAGE

10.1 Symptoms
There is no experience with acute or chronic overdosage with LIPITOR. However, the clinical manifestations and management of overdosage are consistent with other HMG-CoA reductase inhibitors. In general, symptomatic and supportive therapy should be administered in cases of suspected overdosage. LIPITOR should not be used in patients with only asymptomatic hypercholesterolemia or hypertriglyceridemia.
Any potential interactions in this meds list?

<table>
<thead>
<tr>
<th>Bene. ID</th>
<th>NDC</th>
<th>Amount</th>
<th>Date</th>
<th>Dur.</th>
<th>RXCUI</th>
<th>RXN_NAME</th>
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</thead>
<tbody>
<tr>
<td>49441R0</td>
<td>00071015723</td>
<td>30</td>
<td>84</td>
<td>30</td>
<td>617311</td>
<td>atorvastatin 40 MG Oral Tablet</td>
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<tr>
<td>49441R0</td>
<td>51672125802</td>
<td>30</td>
<td>107</td>
<td>21</td>
<td>562032</td>
<td>Clobetasol 0.5 MG/ML Topical Cream</td>
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<tr>
<td>49441R0</td>
<td>68774012260</td>
<td>28</td>
<td>107</td>
<td>14</td>
<td>197517</td>
<td>Clarithromycin 500 MG Oral Tablet</td>
</tr>
</tbody>
</table>

7.1 Strong Inhibitors of CYP 3A4
LIPICTOR is metabolized by cytochrome P450 3A4. Concomitant administration of LIPICTOR with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of LIPICTOR 80 mg with clarithromycin (500 mg twice daily) compared to that of LIPICTOR alone [see CLINICAL PHARMACOLOGY (12.3)]. Therefore, in patients taking clarithromycin, caution should be used when the LIPICTOR dose exceeds 20 mg.

Impossible to analyze automatically (human-readable, not machine-readable)
DailyMed API

- Application Programming Interface (API)
  - Retrieve a label by ID
  - List all codes for drugs in any label
  - No specific support for DDI

- SPL mapping/indexing files
  - Various structured files relating drugs to classes (EPC, MoA, PE, etc)
  - No specific support for DDI*
RxNorm

- Developed by NLM
- Covers (mostly) prescription drugs
- Terminology scope
  - Standard names and codes for drug entities
  - Standard relations among drug entities (e.g., brand → generic)
  - Integrates names and codes from 15 sources (including all major compendia)
- No clinical information (indications, drug classes, DDI)

https://www.nlm.nih.gov/research/umls/rxnorm/
RxNav and RxNorm API

- Browser for RxNorm
  - Supported by APIs
- Links RxNorm drugs to other information sources
  - Drug classes (from DailyMed)
  - Pill images
  - DDI information
    - DrugBank
    - ONC “high-priority list”

https://mor.nlm.nih.gov/RxNav/
DDI information in the drug API

• **No curation from NLM**
  • DDI information simply exposed (machine-readable)

• **Sources**
  • DrugBank
    • The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
    • DDI: no notion of severity; short textual description
  • ONC high-priority list
    • Set of high-severity, clinically significant drug–drug interactions (DDIs) for use in electronic health records (EHRs) developed by D. Bates’ group for ONC

https://www.drugbank.ca/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/
**Interaction between clarithromycin and atorvastatin in DrugBank**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>The therapeutic efficacy of Clarithromycin can be decreased when used in combination with Atazanavir.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>The serum concentration of Atenolol can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Atomoxetine may increase the QTc-prolonging activities of Clarithromycin.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>The serum concentration of Atorvastatin can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Avanafil</td>
<td>The serum concentration of Avanafil can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Azithromycin may increase the QTc-prolonging activities of Clarithromycin.</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>The serum concentration of Beclomethasone dipropionate can be increased when it is combined with Clarithromycin.</td>
</tr>
</tbody>
</table>
No interaction between clarithromycin and atorvastatin in the ONC high-priority list
DDI research at NLM
2 recent projects

• Extracting drug-drug information from Structured Product Labels
  • Collaboration with FDA

• Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support
  • Collaboration with drug compendia
Multiple projects with FDA

- Extracting adverse events from MEDLINE indexing
- Using PubMed for pharmacovigilance
- Extracting drug-drug information from Structured Product Labels
- Creating a collection of Structured Product Labels annotated for adverse events coded to MedDRA
Extracting drug-drug information from Structured Product Labels

• Inter-agency agreement (ongoing)
  • FDA Office of the Chief Scientist Office of Health Informatics
• To support the FDA Structured Product Labeling indexing initiative
• Natural language processing (NLP) pipeline
  • Extract drug-drug interaction (DDI) information from drug labels
  • Codify them in standard terminologies
• Curation by FDA domain experts
• Expected to result in structured DDI information
  • SPL indexing file for DDI
  • Clinical decision support
Comparison of three commercial knowledge bases for detection of drug–drug interactions in clinical decision support

Kin Wah Fung; Joan Kapusnik-Uner; Jean Cunningham; Stefanie Higby-Baker; Olivier Bodenreider

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Materials and methods

• Materials: DDI tables from
  • First DataBank (FDB)
  • Micromedex
  • Multum

• Methods
  • Mapped drugs to RxNorm
  • Compared at the clinical drug, ingredient, and DDI rule levels
  • Evaluated against the ONC high-priority list of DDIs
  • Applied to a prescription data set to simulate their use in clinical decision support
Results (1/2)

• Wide differences in numbers of DDIs among compendia
  • All sources: 8.6 M unique clinical drug pairs
  • First DataBank: 1.6 M
  • Micromedex: 4.5 M
  • Multum: 4.8 M

• Limited overlap among sources
  • 79% found only in 1 source
  • 5% found in all 3 sources
Results (2/2)

- More agreement than disagreement in the severity rankings
  - Especially for contraindications
- 99.8% of the alerts of the ONC list covered by the 3 sources
- Impact on CDS: number of alerts potentially generated (alerts per 1000 prescriptions)
  - First DataBank: 25
  - Micromedex: 145
  - Multum: 84
Medical Ontology Research

Contact: olivier.bodenreider@nih.gov
Web: https://mor.nlm.nih.gov

Olivier Bodenreider
Lister Hill National Center for Biomedical Communications
Bethesda, Maryland - USA

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