Center for Drug Evaluation and Research (CDER) Drug Safety Oversight Board
March 16, 2017

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

https://www.nlm.nih.gov/pubs/plan/lrpdocs.html

DDI services at NLM

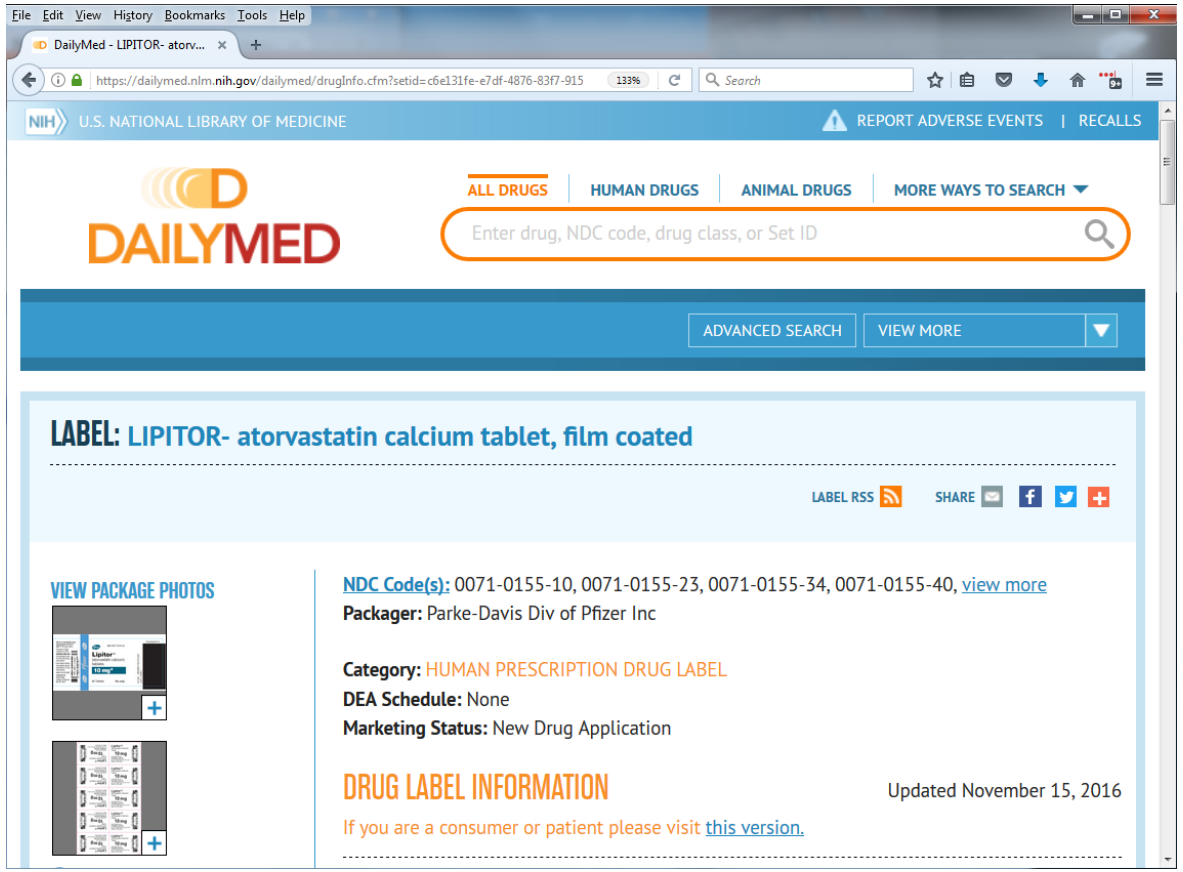
Drug information services at NLM

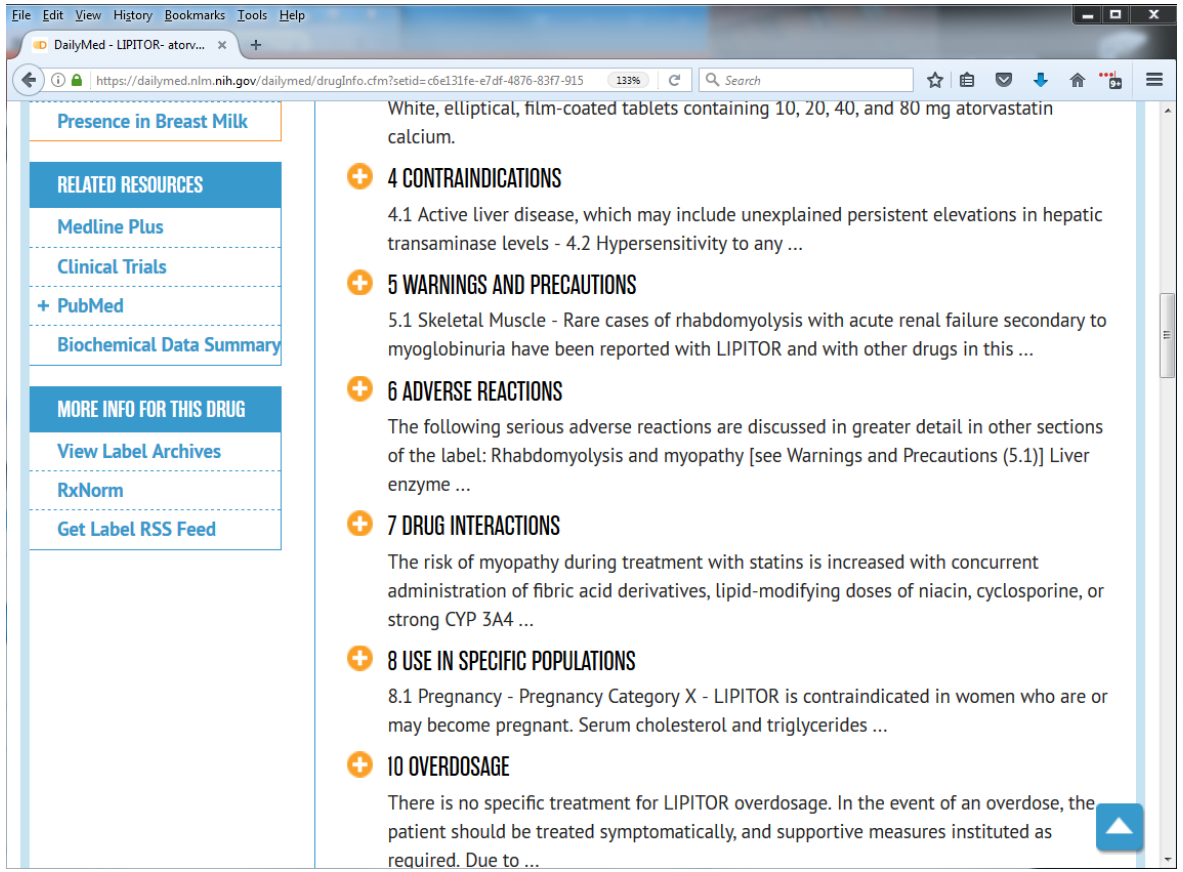
- FDA Structured Product Labels
  - DailyMed website
  - DailyMed API
- RxNorm
  - Standard vocabulary for drugs
  - Drug terminology integration
- RxNorm-based applications and services
  - RxNav
  - RxNorm APIs
- ChemIDPlus (part of ToxNet)
- MedlinePlus Drugs and supplements (consumer health information)
- 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 fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithro [see *WARNINGS AND PRECAUTIONS, SK PHARMACOLOGY (12.3)*].

7.1 Strong Inhibitors of CYP 3A4

LIPITOR is metabolized by cytochrome with strong inhibitors of CYP 3A4 can le atorvastatin. The extent of interaction a variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC wa administration of LIPITOR 80 mg wit to that of LIPITOR alone [see *CLINIC* taking clarithromycin, caution should [see *WARNINGS AND PRECAUTIONS, ADMINISTRATION (2.6)*].

Combination of Protease Inhibitors: concomitant administration of LIPITO inhibitors, as well as with the hepatit that of LIPITOR alone [see *CLINICAL* taking the HIV protease inhibitor tipr inhibitor telaprevir, concomitant use the HIV protease inhibitor lopinavir

inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus 20 mg and should be used with cauti *SKELETAL MUSCLE (5.1)* and *DOSAG* the HIV protease inhibitor nelfinavir the dose of LIPITOR should not exce recommended.

Itraconazole: Atorvastatin AUC was s administration of LIPITOR 40 mg and *PHARMACOLOGY (12.3)*]. Therefore, i used when the LIPITOR dose exceeds *SKELETAL MUSCLE (5.1)* and *DOSAG*

7.2 Grapefruit Juice

Contains one or more components that concentrations of atorvastatin, especiall (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolit Inhibitors of the OATP1B1 (e.g., cyclosp atorvastatin. Atorvastatin AUC was sign administration of LIPITOR 10 mg and cy LIPITOR alone [see *CLINICAL PHARMA*

administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see *CLINICAL PHARMACOLOGY (12.3)*]. The co-administration of LIPITOR with cyclosporine should be avoided [see *WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE (5.1)*].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rh inhibitors are co-administered with gen with gemfibrozil should be avoided [see

7.5 Other Fibrates

Because it is known that the risk of myo inhibitors is increased with concurrent be administered with caution when use *WARNINGS AND PRECAUTIONS (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may combination with niacin; a reduction in setting [see *WARNINGS AND PRECAUT*

7.7 Rifampin or other Inducers of Cytoch

Concomitant administration of LIPITOR efavirenz, rifampin) can lead to variable atorvastatin. Due to the dual interaction co-administration of LIPITOR with rifam of LIPITOR after administration of rifam reduction in atorvastatin plasma concen

reduction in atorvastatin plasma concentrations.

7.8 Digoxin

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

7.9 Oral Contraceptives

Co-administration of LIPITOR and 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.

CLOSE

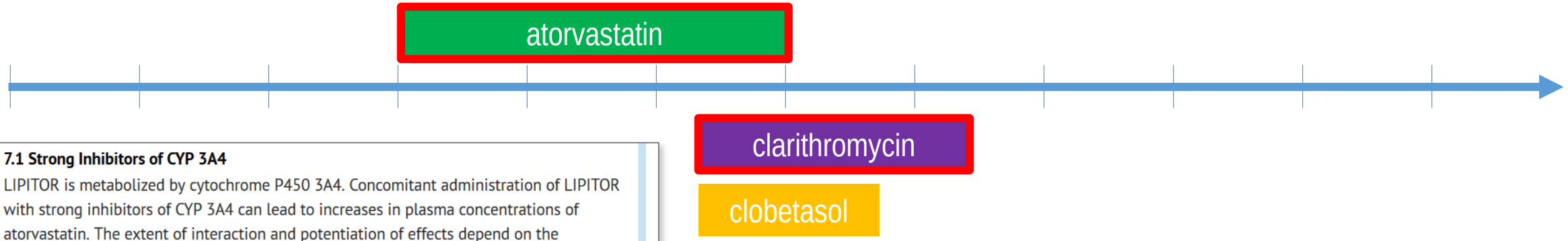
8 USE IN SPECIFIC POPULATIONS

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

10 OVERDOSAGE

Any potential interactions in this meds list?

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



7.1 Strong Inhibitors of CYP 3A4

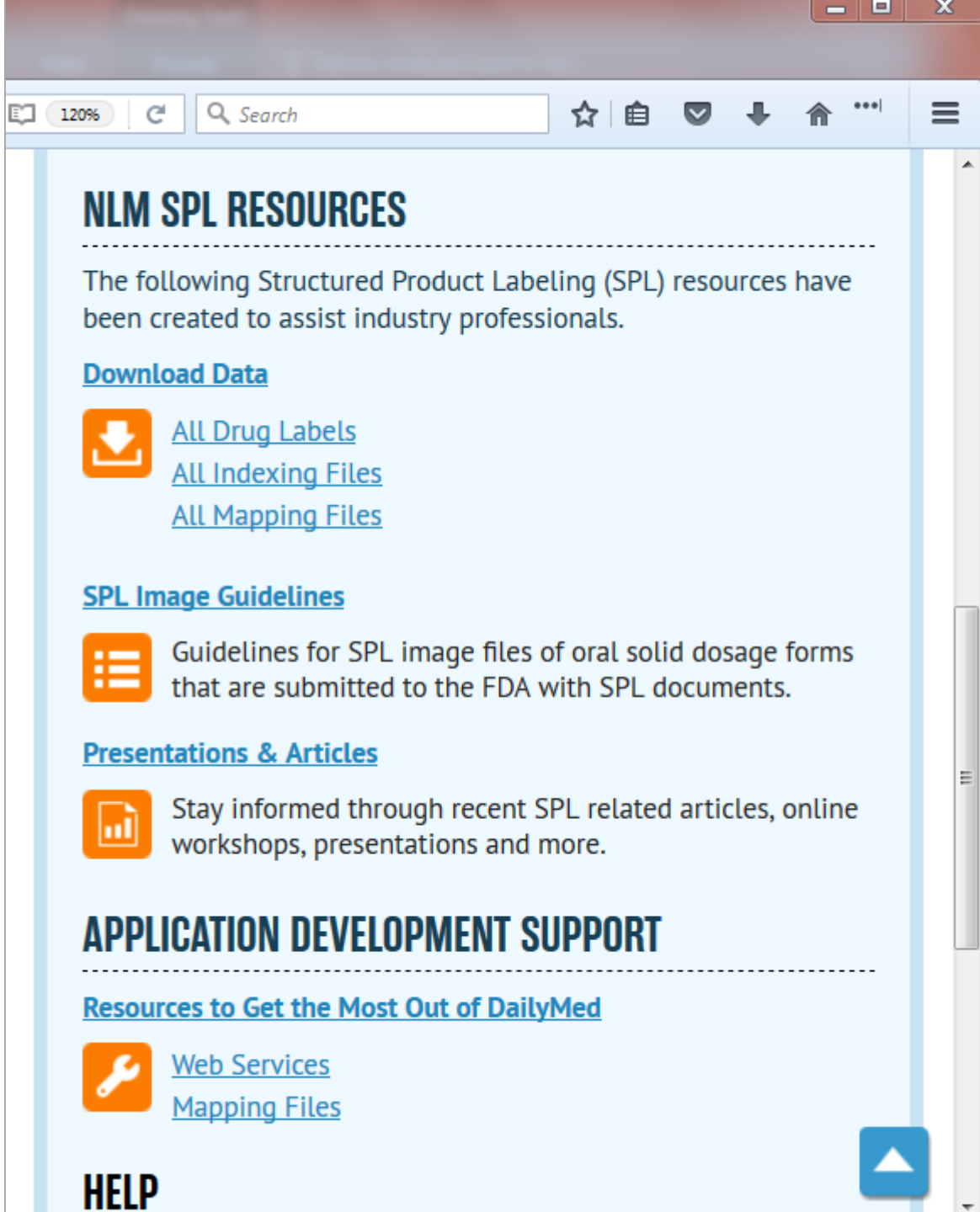
LIPITOR is metabolized by cytochrome P450 3A4. Concomitant administration of LIPITOR with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

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



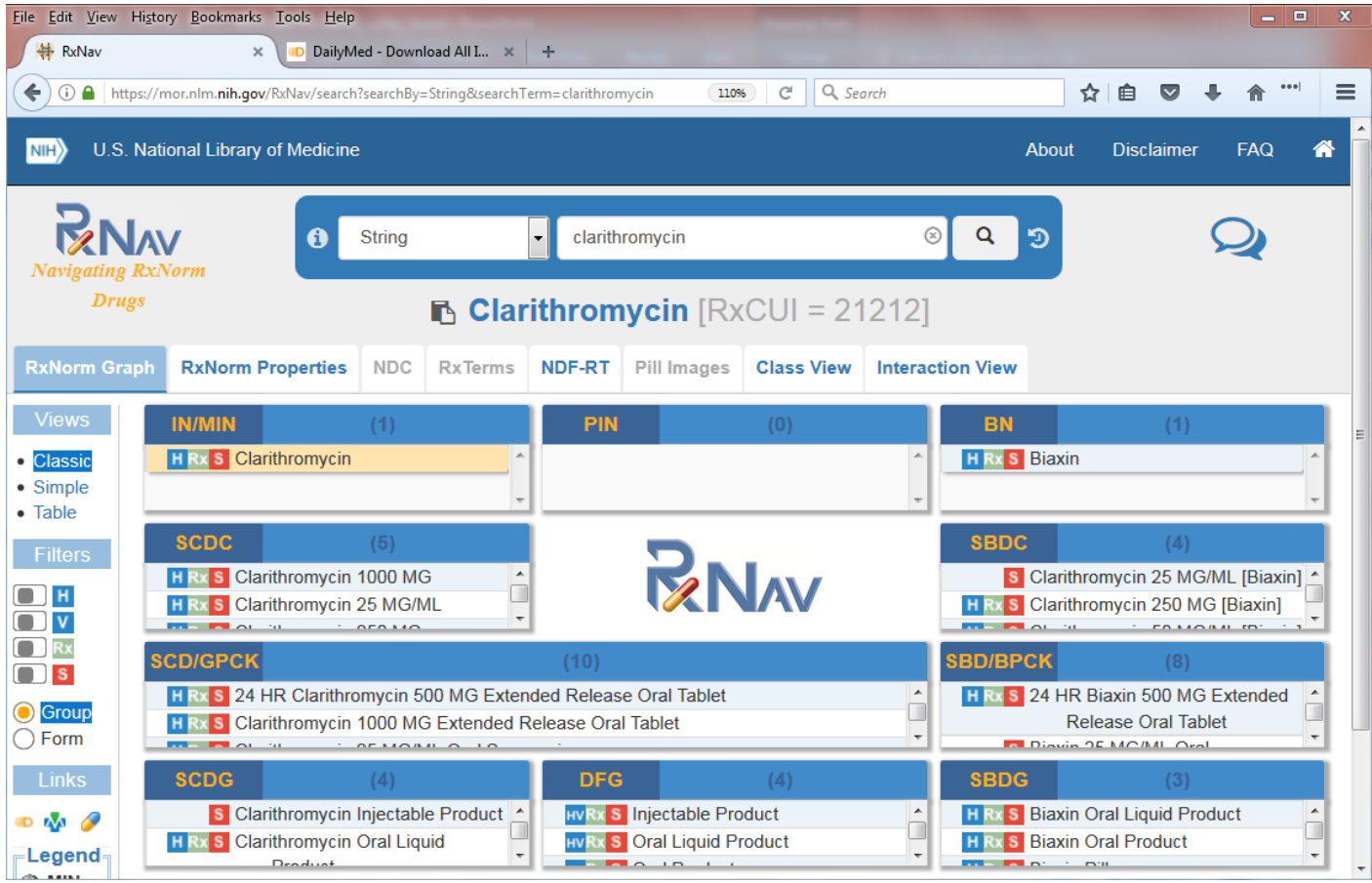
RxNorm

- 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/

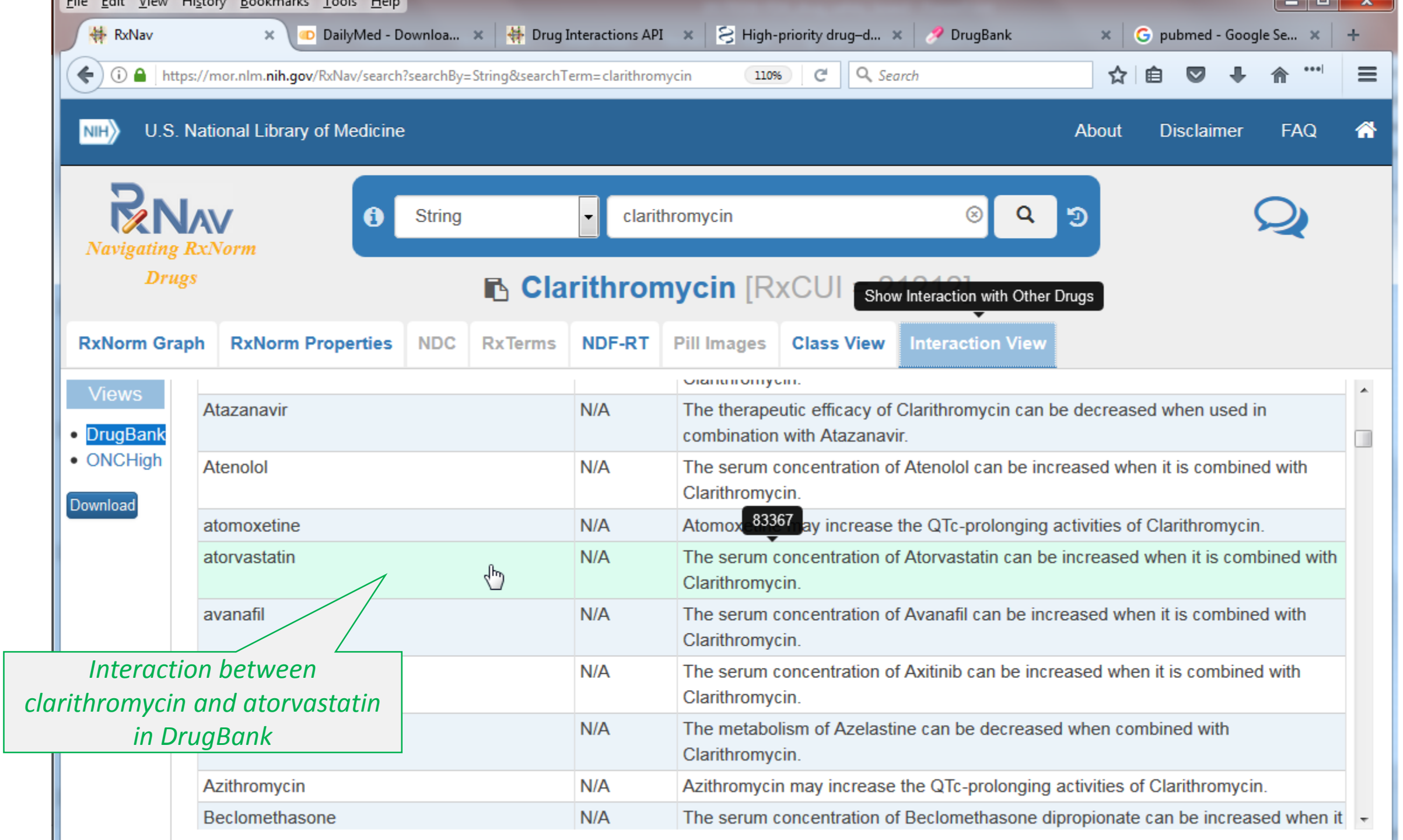
DDI information in the drug API

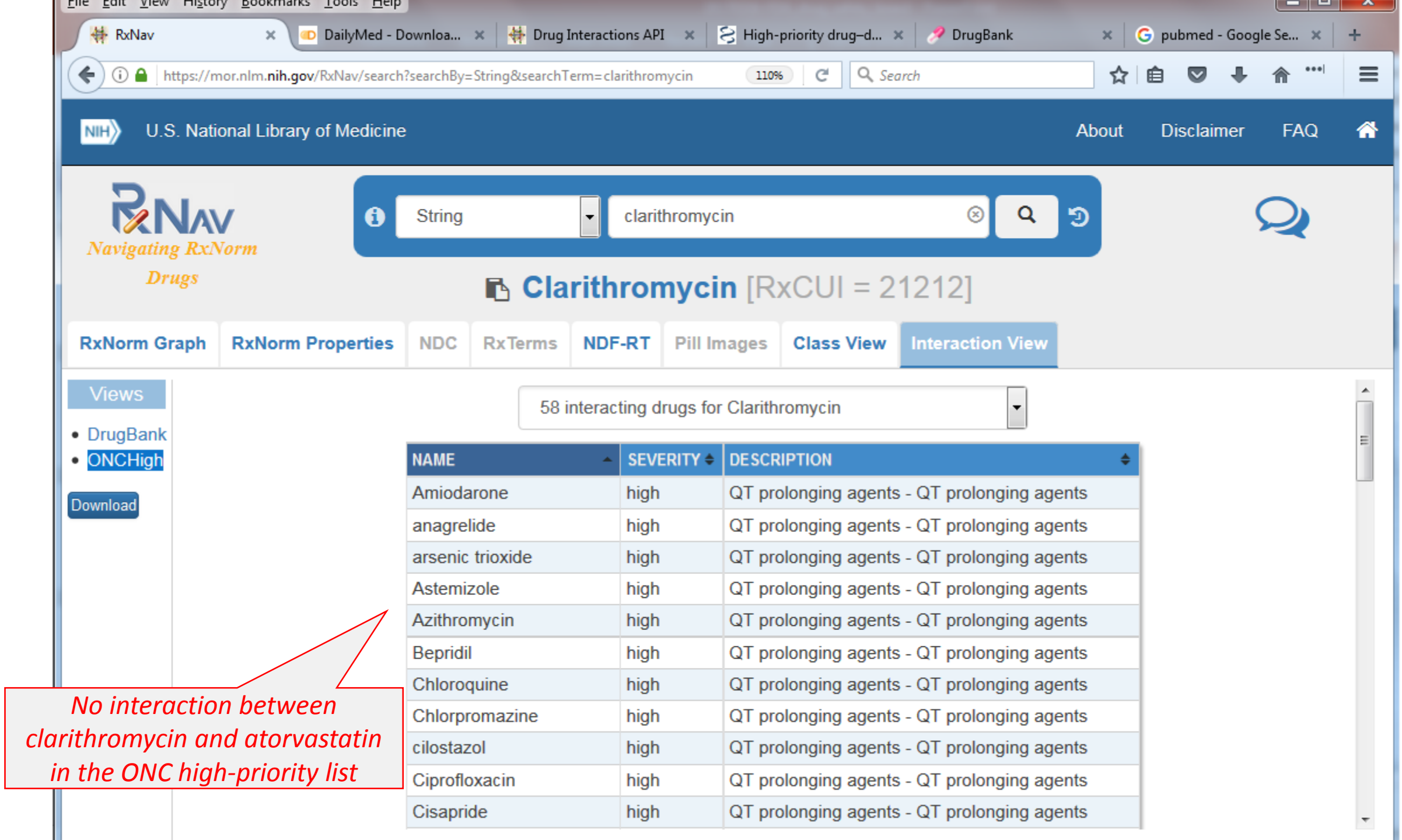
- No curation from NLM
  - DDI information simply exposed (machine-readable)
- Sources
  - DrugBank 
    - The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
    - DDI: no notion of severity; short textual description

https://www.drugbank.ca/

  - 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.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/


RxNav
DailyMed - Downloa...
Drug Interactions API
High-priority drug–d...
DrugBank
pubmed - Google Se...
https://mor.nlm.nih.gov/RxNav/search?searchBy=String&searchTerm=clarithromycin
U.S. National Library of Medicine
About
Disclaimer
FAQ
Navigating RxNorm Drugs
String
clarithromycin
Clarithromycin [RxCUI
Show Interaction with Other Drugs
RxNorm Graph
RxNorm Properties
NDC
RxTerms
NDF-RT
Pill Images
Class View
Interaction View
Views
DrugBank
ONCHigh
Download
Atazanavir
N/A
The therapeutic efficacy of Clarithromycin can be decreased when used in combination with Atazanavir.
Atenolol
N/A
The serum concentration of Atenolol can be increased when it is combined with Clarithromycin.
atomoxetine
N/A
83367
atorvastatin
N/A
The serum concentration of Atorvastatin can be increased when it is combined with Clarithromycin.
avanafil
N/A
The serum concentration of Avanafil can be increased when it is combined with Clarithromycin.
N/A
The serum concentration of Axitinib can be increased when it is combined with Clarithromycin.
N/A
The metabolism of Azelastine can be decreased when combined with Clarithromycin.
Azithromycin
N/A
Azithromycin may increase the QTc-prolonging activities of Clarithromycin.
Beclomethasone
N/A
The serum concentration of Beclomethasone dipropionate can be increased when it
Interaction between clarithromycin and atorvastatin in DrugBank


File Edit View History Bookmarks Tools Help
RxNav
DailyMed - Downloa...
Drug Interactions API
High-priority drug–d...
DrugBank
pubmed - Google Se...
https://mor.nlm.nih.gov/RxNav/search?searchBy=String&searchTerm=clarithromycin
110%
Search
U.S. National Library of Medicine
About
Disclaimer
FAQ
RxNav
Navigating RxNorm Drugs
String
clarithromycin
Clarithromycin [RxCUI = 21212]
RxNorm Graph
RxNorm Properties
NDC
RxTerms
NDF-RT
Pill Images
Class View
Interaction View
Views
DrugBank
ONCHigh
Download
58 interacting drugs for Clarithromycin
NAME
SEVERITY
DESCRIPTION
Amiodarone high QT prolonging agents - QT prolonging agents
anagrelide high QT prolonging agents - QT prolonging agents
arsenic trioxide high QT prolonging agents - QT prolonging agents
Astemizole high QT prolonging agents - QT prolonging agents
Azithromycin high QT prolonging agents - QT prolonging agents
Bepridil high QT prolonging agents - QT prolonging agents
Chloroquine high QT prolonging agents - QT prolonging agents
Chlorpromazine high QT prolonging agents - QT prolonging agents
cilostazol high QT prolonging agents - QT prolonging agents
Ciprofloxacin high QT prolonging agents - QT prolonging agents
Cisapride high QT prolonging agents - QT prolonging agents
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 DDI information

Materials and methods

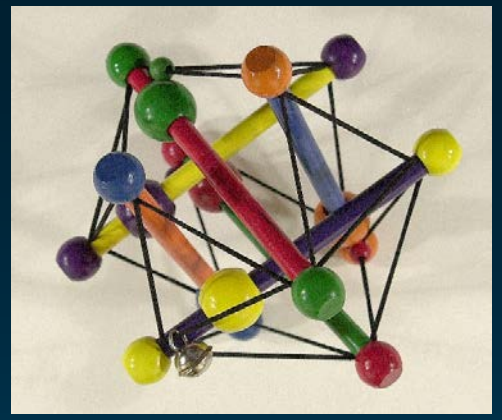
- Materials: DDI tables from
  - First DataBank (FDB)
  - Micromedex
  - Multum
- Methods
  - Mapped drugs to RxNorm
  - Compared at the clinical drug, ingredient, and DDI rule levels
  - Evaluated against the ONC high-priority list of DDIs
  - Applied to a prescription data set to simulate their use 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

U.S. National Library of Medicine