RxNorm

Why Should Pharmacists Care?

Olivier Bodenreider

National Library of Medicine, NIH, DHHS
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Learning objectives

1- Explain the key elements, benefits, and limitations of RxNorm
2- Practice accessing RxNorm (RxNorm dataset, RxNav, APIs)
3- Identify companion resources linked to RxNorm
4- Identify issues with analyzing drugs in observational datasets
Self-Assessment Questions

Question 1: Which type of information is in scope for RxNorm?
Question 2: Which use cases are covered by RxNorm?
Self-Assessment Question 1

Which type of information is in scope for RxNorm?

- A. Drug names
- B. Drug codes
- C. Pricing information
- D. Drug-drug interactions
- E. Indications
Self-Assessment Question 2

Which use cases are covered by RxNorm?

• A. E-prescribing
• B. Information exchange
• C. Formulary development
• D. Reference value sets
• E. Analytics
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

Overview

- RxNorm basics
- Applications for using RxNorm
  - RxNav, RxClass, RxMix
- Follow-along examples
- Analyzing observational data with RxNorm
RxNorm – Why Should Pharmacists Care?
Part 1

RxNorm basics
Interoperability among drug vocabularies

- Exchange of information requires standardized names
  - Ordering drugs
  - Checking interactions
  - Inventory management
- No standard naming conventions for drugs
- Integrating drug vocabularies
- Unique identifiers for drugs
- Specify relations among drug entities
Source vocabularies in RxNorm

- Anatomical Therapeutic Chemical Classif.
- Vaccines Administered (HL7)
- DrugBank
- Gold Standard Drug Database
- Medi-Span Master Drug Data Base
- Multum MediSource Lexicon
- Micromedex RED BOOK
- Medical Subject Headings (MeSH)
- FDA Structured Product Labels
- First DataBank MedKnowledge
- VHA National Drug File - NDF-RT
- US Edition of SNOMED CT (drugs)
- VHA National Drug File

(terms in thousands, as of March 2017)
## Normalization Lexical level

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<tr>
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<tr>
<td>WARFARIN SODIUM@1 mg@ORAL@TABLET</td>
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<td>NDDF</td>
</tr>
<tr>
<td>[...]</td>
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</table>
Relations among drug entities

Ingredient: Azithromycin

C. Drug Comp.: Azithromycin 250 MG
C. Drug Form: Azithromycin Oral Tablet

C. Drug: Azithromycin 250 MG Oral Tablet

G. Pack: {6 (Azithromycin 250 MG Oral Tablet) } Pack

B. Drug Comp.: A. 250 MG [Zithromax]
B. Drug Form: A. Oral Tablet [Zithromax]

B. Drug: Zithromax 250 MG Oral Tablet

B. Pack: Z-PAK

Brand Name: Zithromax

A. 250 MG [Zithromax]
A. Oral Tablet [Zithromax]

Zithromax 250 MG Oral Tablet
What RxNorm does NOT contain

- Non-prescription drugs (limited coverage of OTC drugs)
- Non-drug entities (e.g., supplies)
- Drug classes / drug-class membership
- Indications, adverse events
- Drug-drug interactions
- Pricing information
- Dosing information

Available through services (APIs)
RxNorm – Why Should Pharmacists Care?
Part 2

RxNorm in action
Example  Mapping NDCs to ATC drug classes

- NDCs are attached to a clinical drug (SCD) or a branded (drug)
- Branded drugs are mapped to clinical drugs
- Clinical drugs are linked to their ingredient
- Many drug classification systems link classes to ingredient-level drugs (e.g., ATC, NDF-RT, EPC, MeSH pharmacologic action)
RxNav

- **Drug-centric browser**
  - RxNorm
    - Prescribable subset
  - RxTerms
  - NDF-RT
  - Pill images
  - Drug-drug interactions
- Supports navigation to the rich RxNorm and NDF-RT graphs
- Links to other drug resources
  - DailyMed, MedlinePlus, NLM Drug Information Portal
- Drug-centric “class view”
- Leverages the drug APIs
RxClass

- **Class-centric** browser for RxNorm drugs
  - ATC
  - DailyMed (Mechanism of action, Physiologic effect, Chemical structure, FDA classes)
  - MeSH (Pharmacologic actions)
  - NDF-RT (VA classes, Diseases for indications/contra-indications)

- Supports search by drug or by class

- Features
  - Display and navigation
    - All the drugs for a class
    - All the classes for a drug
  - Compute similarity among drug classes (based on shared drug members)
Application programming interfaces (APIs)

- Expose the content of RxNorm, RxTerms and NDF-RT (and other resources)
  - Logical structure, not storage format
  - Up-to-date information (monthly updates of RxNorm)
  - Additional features
    - Normalized and approximate matching; spelling correction
    - Drug-drug interactions checking (from DrugBank)
    - Link to drug classes (from ATC, DailyMed, MeSH, NDF-RT)
    - Archive of NDCs since 2007
    - Optimized graph traversal (pre-computed)

- For use in applications
  - Web services
  - SOAP, REST (XML, JSON)
  - Independent of any programming language
RxMix

- Graphical interface to the drug APIs
  - RxNorm, NDF-RT, RxTerms, RxImageAccess, Interactions, RxClass, MedEx, DailyMed
- Handles interoperability between functions
- Helps users compose complex queries
  - Find all the NDC codes for a given allergy class (e.g., barbiturates)
- Supports batch execution
RxNorm use cases

- **E-prescribing**
  - *NCPDP SCRIPT standard for e-prescribing requires RxNorm*

- **Information exchange**
  - *DoD and VA rely on RxNorm to mediate drug information across their electronic medical record systems*

- **Formulary development**
  - *CMS uses RxNorm in their Formulary Reference File, as part of the guideline for Medicare drug benefits*

- **Reference value sets**
  - *The drug value sets used in clinical quality measures for Meaningful Use are defined in reference to RxNorm*

- **Analytics**
  - *OHDSI, the Observational Health Data Sciences and Informatics research group, uses RxNorm to analyze prescription data*
RxNorm – Why Should Pharmacists Care?
Part 3

Follow-along examples
Follow-along examples

- Using **RxNav**
  - Find the ATC class for NDC 0186-5040-31 (Nexium 40 mg delayed-released capsule)
    - NDC → RxNorm branded drug → RxNorm ingredient → ATC ingredient → ATC class

- Using **RxClass**
  - Find all RxNorm ingredients from the same class as esomeprazole
    - Search classes by ingredient (or just click on a class in RxNav)
  - Find other classes with similar ingredients
    - Similar classes feature

- Using **RxMix** (Complete workflow)
Web applications

- Documentation
- RxNav
- RxClass
  - https://mor.nlm.nih.gov/RxClass/
- RxMix
<table>
<thead>
<tr>
<th>ATC code</th>
<th>Name</th>
<th>DDD</th>
<th>U</th>
<th>Adm. R</th>
<th>Note</th>
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<td>esomeprazole</td>
<td>30 mg</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg</td>
<td>P</td>
<td></td>
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</table>

**Esomeprazole (283742)**

**Esomeprazole 40 MG Delayed Release Oral Capsule (606730)**

**Esomeprazole 40 MG Delayed Release Oral Capsule [Nexium] (606731)**

00186504031

0186-5040-31

---

**Nexium (esomeprazole magnesium)**

**30 Delayed-Release Capsules**

Rx only

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<thead>
<tr>
<th>ATC code</th>
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<td>mg</td>
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- Esomeprazole (A02BC05)
- Esomeprazole 40 MG Delayed Release Oral Capsule (606730)
- Esomeprazole 40 MG Delayed Release Oral Capsule [Nexium] (606731)

- 00186504031
- 0186-5040-31
A
ALIMENTARY TRACT AND METABOLISM
A02
DRUGS FOR ACID RELATED DISORDERS
A02B
DRUGS FOR PEPTIC ULCER AND GASTRO-oesophageal reflux disease (GORD)
A02BC
Proton pump inhibitors

<table>
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<tr>
<th>ATC code</th>
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- Esomeprazole (283742)
- Esomeprazole 40 MG Delayed Release Oral Capsule (606730)
- Esomeprazole 40 MG Delayed Release Oral Capsule [Nexium] (606731)

00186504031
0186-5040-31
Esomeprazole [RxCUI = 283742]

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**Esomeprazole (283742)**

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**00186504031**

**0186-5040-31**
### dexrabeprazole

*not on the U.S. market*

Finding all PPI drugs in ATC

https://www.whocc.no/atc_ddd_index/
### Classes in other drug classification systems

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<td>A02BC54</td>
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</table>

List of abbreviations

Last updated: 2016-12-19
## RxClass

Exploring drug classes and their RxNorm drug members

### Class Browser

- **Anatomical Therapeutic Chemical (ATC1-4)**
  - ANANABOLIC AGENTS FOR SYSTEMIC USE
  - ANTIARRHYTHMICS, INTESTINAL
  - ANTIINFLAMMATORY ANTINFECTIVE AGENTS
  - ANTIEMETICS AND ANTIUSEANTS
  - ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
  - APPETITE STIMULANTS
  - BILE AND LIVER THERAPY
  - DIGESTIVES, INCL. ENZYMES
  - DRUGS FOR ACID RELATED DISORDERS
  - ANTACIDS
  - DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
    - Combinations for eradication of Helicobacter pylori
    - H2-receptor antagonists
    - Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)
    - Proton pump inhibitors
    - OTHER DRUGS FOR ACID RELATED DISORDERS
    - DRUGS FOR CONSTIPATION
    - DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
    - DRUGS USED IN DIABETES
    - MINERAL SUPPLEMENTS
    - OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS

### Search

- by class name/id
- by RxNorm drug name/id
- ingredient drug only
- Edit Drug Sources

#### Class: Proton pump inhibitors

- id: A02BC
- class type: ATC1-4

### Similar Classes

<table>
<thead>
<tr>
<th>Type</th>
<th>RXCUI</th>
<th>RxNorm Name</th>
<th>Relation</th>
<th>All classes</th>
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<td>IN</td>
<td>816346</td>
<td>dexlansoprazole</td>
<td>DIRECT</td>
<td>Show</td>
</tr>
<tr>
<td>IN</td>
<td>283742</td>
<td>Esomeprazole</td>
<td>DIRECT</td>
<td>Show</td>
</tr>
<tr>
<td>IN</td>
<td>17128</td>
<td>Lansoprazole</td>
<td>DIRECT</td>
<td>Show</td>
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<tr>
<td>IN</td>
<td>7646</td>
<td>Omeprazole</td>
<td>DIRECT</td>
<td>Show</td>
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<tr>
<td>IN</td>
<td>40790</td>
<td>Pantoprazole</td>
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<tr>
<td>IN</td>
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<td>Similarity</td>
<td>Platform</td>
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<tr>
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<td>Venn</td>
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<td>Venn</td>
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## Class 1: Proton pump inhibitors (A02BC) in ATC

Class 2: Proton Pump Inhibitors (N0000000147) in DailyMed (has_MoA)

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<td>Omeprazole</td>
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<tr>
<td>pantoprazole</td>
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</tr>
<tr>
<td>rabeprazole</td>
<td>114979</td>
<td>Both</td>
</tr>
<tr>
<td><strong>Amantadine</strong></td>
<td>620</td>
<td>Class2 only</td>
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<tr>
<td><strong>Rimantadine</strong></td>
<td>9386</td>
<td>Class2 only</td>
</tr>
</tbody>
</table>

- # Class1 Only: 0
- # Class2 Only: 2
- # Both: 0
- Equivalence Score: 0.70
- Inclusion Score: -1.0
### Proton pump inhibitors

#### Class Browser

- **Anatomical Therapeutic Chemical (ATC-4)
- **Established Pharmacologic Classes (EPC)
- **MeSH Pharmacologic Actions (MESHPA)
- **Disease
- **Chemical Structure (Chem)
- **Mechanism of Action (MoA)
- **Enzyme Interactions
- **Immunologically and Biologically Factor Interactions
- **Membrane Transporter Interactions
- **Fatty Acid Transporter Interactions
- **Ion Channel Interactions
- **Ion Transporter Interactions
- **Anion Transporter Interactions
- **Cation Transporter Interactions
- **Proton Pump Interactions
- **Proton Pump Inhibitors
- **M2 Protein Inhibitors
- **Symporter Interactions
- **Monosaccharide Transporter Interactions
- **Neurotransmitter Transporter Interactions
- **Physicochemical Activity
- **Receptor Interactions
- **Unknown Cellular or Molecular Interaction
- **Physiologic Effect (PE)
- **Pharmacokinetics (PK)
- **VA Classes (VA)

#### Search Results

- **Proton Pump Inhibitors**

#### Related Classes

- **RxCUI**: 620
- **RxNorm Name**: Amantadine

<table>
<thead>
<tr>
<th>Type</th>
<th>RxCUI</th>
<th>RxNorm Name</th>
<th>Relation</th>
<th>All classes</th>
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<td>620</td>
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<td>Omeprazole</td>
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<td>283742</td>
<td>Esomeprazole</td>
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<tr>
<td>IN</td>
<td>9386</td>
<td>Rimantadine</td>
<td>INDIRECT</td>
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</table>
Automating the mapping from NDC to ATC using RxMix
RxMix is an interface for building applications that allows users to combine functions of the RxNorm, RxTerms, NDF-RT, RxClass, Interactions and RxImageAccess APIs. It allows users to run either interactively or in batch mode.

Sample RxMix configurations

- Find drug interaction brands for Morphine (RXCUI = 7052)
- Find allergy drugs for Proton Pump Inhibitors (NUI =N0000000147)

APIs
- RxNorm
- NDF-RT
- RxTerms
- RxImageAccess
- Interaction
- RxClass
- DailyMed
- MedEx

References
**RXMix**

Create applications from RxNorm, RxTerms, NDF-RT, and RxImageAccess APIs

**WORKFLOW**

RxNorm.findRxNormByld

**BUILD**

Select Function

No function selected

**LOAD**

From workflow library

Remove Last  Save  From my workflows

**INPUT**

NDC: 0186-5040-31

**EXECUTE**

Clear  Run Interactive

**OUTPUT**

RXCUI

606731

...
<table>
<thead>
<tr>
<th>ATC code</th>
<th>Name</th>
<th>DDD</th>
<th>U</th>
<th>Adm.R</th>
<th>Note</th>
</tr>
</thead>
<tbody>
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<td>esomeprazole</td>
<td>30 mg</td>
<td>O</td>
<td></td>
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<td>esomeprazole 40 MG Delayed Release Oral Capsule (606730)</td>
<td>30 mg</td>
<td>P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**rxnorm:getRelatedByType ("606731", "IN") → 283742**
<table>
<thead>
<tr>
<th>UMLSCUI</th>
<th>term_type</th>
<th>name</th>
<th>RXCUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0957846</td>
<td>IN</td>
<td>Enamprazole</td>
<td>283742</td>
</tr>
</tbody>
</table>
Esomeprazole (A02BC05)

ATC code | Name | DDD | U. Adm. | Note
---------|------|-----|---------|-------
A02BC05  | esomeprazole | 30 mg | P | 
          |              | 30 mg | P |

Esomeprazole 40 MG Delayed Release Oral Capsule (606731)

rxclass:getClassByRxNormDrugId ("283742", "ATC", "ALL") → A02BC, Proton pump inhibitors
RxMix
Create applications from RxNorm, RxTerms, NDF-RT, and RxImageAccess APIs

Select Function
- No function selected

RxImageAccess
- get Pill Image info

Interaction
- find Drug Interactions

RxClass
- find Class By Name
- find Similar Classes By Drug List
- getClassByRxNormDrugId
- getClassByRxNormDrugName
- getClassBySpellingSuggestions

LOAD
- From workflow library

Remove Last
Save

INPUT
- NDC: 0186-5040-31

Basic Instructions
1. BUILD workflow using Select Function, then Add to Workflow
   (or select a button in LOAD section to load a workflow)
2. Enter INPUT value for interactive mode
   (or input file name for batch mode)

https://mos.nlm.nih.gov/RxMix/#login
### Output

<table>
<thead>
<tr>
<th>relaSource</th>
<th>term_type</th>
<th>drugName</th>
<th>RXCUI</th>
<th>rela</th>
<th>classID</th>
<th>name</th>
<th>classType</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC</td>
<td>IN</td>
<td>Esomeprazole</td>
<td>2833742</td>
<td></td>
<td>A02BC</td>
<td>Proton pump inhibitors</td>
<td>ATC1-4</td>
</tr>
<tr>
<td>ATC</td>
<td>MIN</td>
<td>Esomeprazole / Naproxen</td>
<td>994302</td>
<td></td>
<td>M11AE</td>
<td>Prostaglandin acid derivatives</td>
<td>ATC1-4</td>
</tr>
</tbody>
</table>
Esomeprazole (A02BC05)

- Esomeprazole 40 MG Delayed Release Oral Capsule [Nexium] (606731)
- Esomeprazole 40 MG Delayed Release Oral Capsule (606730)
- Esomeprazole 40 MG Delayed Release Oral Capsule (606731)
- Esomeprazole (28374)

 rxclass:getClassGraph("A02BC")

→ A02B, DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD);
A02, DRUGS FOR ACID RELATED DISORDERS;
A, ALIMENTARY TRACT AND METABOLISM
Analyzing observational data with RxNorm

RxNorm – Why Should Pharmacists Care?
Part 4
Source of observational data (drugs)

- Surescripts transactions
- Data from payers
  - Medicaid
  - Medicare Part D
- Commercial health analytics companies
  - Truven (120M patients)
  - PharMetrics Plus (100M patients)
  - Ambulatory EMR (35M patients)
  - Open Claims (250M patients)
- Networks of clinical data warehouses
  - PCORnet, OHDSI, Health Facts, ...
- Reagan-Udall Foundation for the FDA
  - IMEDS Research Lab (temporarily suspended)
Common use cases

- Pharmaco-epidemiology
  - Assess exposure to drugs (by ingredient or class)
  - Assess prescribed daily dose
  - Identify potentially inappropriate medications
    - Elderly (Beers)
    - Pregnant women (Briggs)
- Outcomes research
  - Comparative effectiveness
  - Pharmacovigilance and drug safety
- “Learning Health System”
Prescribed vs. defined daily dose

- **Dataset**
  - Surescripts feed
  - All prescriptions to ER patients
  - For 3 months in 2011 in a Bethesda hospital

- **Reference for defined daily dose: ATC**

- **Methods**
  - RxNorm clinical drug → RxNorm ingredient ↔ ATC ingredient → ATC defined daily dose ↔ prescribed daily dose
  - Restricted to systemic drugs (based on dose form)

- **Findings**
  - Confirmed feasibility
  - 25% of the prescriptions exactly match the ATC DDD
  - 50% of the prescriptions within 66-150% of the ATC DDD
  - 75% of the prescriptions within 50-200% of the ATC DDD

[Bodenreider, AMIA, 2014]
Methods  Example

RxNorm

Amoxicillin 500 MG Oral Capsule (308191)  →  Amoxicillin (723)  →  Oral Capsule

ATC/DDD Index

amoxicillin (J01CA04)  →  O  →  1 g

Surescripts

Amoxicillin 500 MG Oral Capsule (308191)  →  40 capsules  →  10 days  →  40 x 500 mg / 10 = 2 g
Results

Prescription classification

Frequency of drugs by level-1 ATC group in the Surescripts prescription dataset \(N=86,578\)

- ALIMENTARY TRACT AND METABOLISM (A)
- BLOOD AND BLOOD FORMING ORGANS (B)
- CARDIOVASCULAR SYSTEM (C)
- DERMATOLOGICALS (D)
- GENITO URINARY SYSTEM AND SEX HORMONES (G)
- SYSTEMIC HORMONAL PREP., EXCL. SEX HORMONES AND INSULINS (H)
- ANTIINFECTIVES FOR SYSTEMIC USE (J)
- ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (L)
- MUSCULO-SKELETAL SYSTEM (M)
- NERVOUS SYSTEM (N)
- ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS (P)
- RESPIRATORY SYSTEM (R)
- SENSORY ORGANS (S)
- VARIOUS (V)

Drugs:
- Atorvastatin
- Simvastatin
- Lisinopril
- Metoprolol
- Amlodipine
- Furosemide
- Atenolol
- Hydrochlorothiazide
- Zolpidem
- Sertraline
- Escitalopram
- Alprazolam
- Clonazepam
- Gabapentin
- Quetiapine
- Oxycodone
- Fluoxetine
- Duloxetine
Deviation of the prescribed daily dose (PDD) in Surescripts from the defined daily dose (DDD) in ATC for 68,462 oral solid dose form prescriptions.

- 86.1% of the prescriptions are within 33%-300% of the ATC DDD
- 3.5% > 300% of the ATC DDD
- 10.4% < 33% of the ATC DDD

- 76.1% of the prescriptions are within 50%-200% of the ATC DDD
- 49.5% of the prescriptions are within 66%-150% of the ATC DDD
- 28.6% of the prescriptions exactly match the ATC DDD
Issues

- No normalization of drugs in claims data
- NDCs contain clinically irrelevant details and need to be aggregated
- Many NDCs are obsolete and need to be mapped to current drugs for analysis
- Many drug classification systems link ingredients to classes, leading to ambiguous associations
Wrap-up
Key Takeaways

- **Use standards!**
  - Because it is a standard drug terminology (in the U.S.), RxNorm can help integrate, exchange and analyze prescription data

- **Try it at home!**
  - RxNav and RxClass are useful tools for exploring RxNorm drugs and classes from several drug classification systems
  - RxMix helps automate mapping across drug entities for non-programmers

- **Participate in research activities!**
  - Pharmacists are increasingly involved in research, especially with observational data from claims and electronic health records
Self-Assessment Question 1

Which type of information is in scope for RxNorm?

- ✔ A. Drug names
- ✔ B. Drug codes
- ✗ C. Pricing information
- ✗ D. Drug-drug interactions
- ✗ E. Indications
Self-Assessment Question 2

Which use cases are covered by RxNorm?

- A. E-prescribing
- B. Information exchange
- C. Formulary development
- D. Reference value sets
- E. Analytics
Medical Ontology Research

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