Leveraging RxNorm and drug classifications for analyzing prescription datasets

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Disclaimer

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Outline

◆ Drug ontologies
  ● RxNorm
  ● Drug classification systems

◆ RxNorm in action – 3 use cases
  ● Comparing prescribed vs. defined daily dose
  ● Identifying potentially inappropriate medications for elderly patients
  ● Identifying potential risk in drug prescriptions during pregnancy

◆ Discussion
Relevance to AMIA’s informatics areas

- **Translational Bioinformatics**
  - Interoperability between drugs in research and healthcare

- **Clinical Research Informatics**
  - Analysis of observational datasets (e.g., OHDSI, PCORnet)

- **Clinical Informatics**
  - E-prescribing
  - Information exchange
  - Reference for drugs for clinical decision systems (drug allergies, drug-drug interactions)

- **Consumer Health Informatics**
  - Facilitating access to Medline Plus

- **Public Health Informatics**
  - Drug value sets (e.g., for opioid addiction)
Drug ontologies
RxNorm

- Terminology integration system
  - Structured Product Labels, First DataBank, Micromedex, Multum, MeSH, SNOMED CT, NDF-RT, ATC, ...

- Scope
  - Drug names and codes
  - Drugs available on the U.S. market

- Developer: National Library of Medicine
- Publicly available*
- Monthly updates
- Size: > 10k ingredients; 19k clinical drugs
- Uses: e-prescription, information exchange, analytics

https://www.nlm.nih.gov/research/umls/rxnorm/
## Normalization  Lexical level

<table>
<thead>
<tr>
<th>Source</th>
<th>Code</th>
<th>String</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSL</td>
<td>5977</td>
<td>azithromycin 250 mg oral tablet</td>
</tr>
<tr>
<td>RXNORM</td>
<td>308460</td>
<td>Azithromycin 250 MG Oral Tablet</td>
</tr>
<tr>
<td>MTHSPL</td>
<td>54868-5478</td>
<td>AZITHROMYCIN 250 mg ORAL TABLET, FILM COATED</td>
</tr>
<tr>
<td>MMX</td>
<td>124911</td>
<td>Azithromycin 250 MG Oral Tablet_#1</td>
</tr>
<tr>
<td>NDDF</td>
<td>26721</td>
<td>AZITHROMYCIN 250 mg ORAL TABLET_#1</td>
</tr>
<tr>
<td>GS</td>
<td>22681</td>
<td>Azithromycin 250mg Oral tablet_#2</td>
</tr>
<tr>
<td>NDFRT</td>
<td>N0000158080</td>
<td>AZITHROMYCIN 250MG TAB</td>
</tr>
<tr>
<td>MTHSPL</td>
<td>21695-012</td>
<td>AZITHROMYCIN ANHYDROUS 250 mg ORAL TABLET, FILM COATED</td>
</tr>
<tr>
<td>MTHSPL</td>
<td>60505-2581</td>
<td>AZITHROMYCIN DIHYDRATE 250 mg ORAL TABLET, FILM COATED [Azithromycin Dihydrate]</td>
</tr>
<tr>
<td>SNOMEDCT_US</td>
<td>375555002</td>
<td>Azithromycin dihydrate 250mg tablet</td>
</tr>
<tr>
<td>MTHSPL</td>
<td>66116-418</td>
<td>AZITHROMYCIN MONOHYDRATE 250 mg ORAL TABLET, FILM COATED</td>
</tr>
<tr>
<td>MTHSPL</td>
<td>0093-7146</td>
<td>AZITHROMYCIN MONOHYDRATE 250 mg ORAL TABLET, FILM COATED_#1</td>
</tr>
</tbody>
</table>

To find the correct code and description for Azithromycin 250 MG Oral Tablet, the code **308460** is highlighted. This code clearly matches the desired description.
Normalized relations

Ingredient

Azithromycin

C. Drug Comp.

Azithromycin 250 MG

C. Drug

Azithromycin 250 MG Oral Tablet

C. Drug Form

Azithromycin Oral Tablet

B. Drug Comp.

Azithromycin 250 MG

B. Drug

Azithromycin Oral Tablet

B. Drug Form

Azithromycin Oral Tablet [Zithromax]

B. Pack

Zithromax 250 MG Oral Tablet

G. Pack

{6 (Azithromycin 250 MG Oral Tablet) } Pack

Brand Name

Zithromax

B. Pack

Z-PAK

C. Drug Comp.

Azithromycin

C. Drug Form

Azithromycin Oral Tablet

B. Drug Comp.

Azithromycin 250 MG

B. Drug Form

Azithromycin Oral Tablet [Zithromax]
Applications

◆ RxNav
  • Drug-centric browser
  • Links among drug entities (graph)
  • Links to other sources of information
    ▪ Drug classes
    ▪ Drug-drug interactions from DrugBank

◆ RxClass
  • Drug class-centric browser
    ▪ ATC, NDF-RT, DailyMed (SPL), MeSH
  • All classes for a given drug
  • All drug members for a given class
  • Class-class similarity

https://rxnav.nlm.nih.gov/
Application Programming Interfaces (APIs)

◆ RxNorm
  ● Map drug names and codes to RxNorm
    ▪ Including approximate matches and spelling suggestions
  ● Navigate among drug entities (e.g., brand to generic)

◆ RxClass
  ● Map drug class names and codes to classification systems
    ▪ ATC, NDF-RT, DailyMed (SPL), MeSH
  ● Link between drug classes and their drug members
  ● Similarity between drug classes

◆ Related APIs
  ● RxTerms, NDF-RT, Interactions

◆ Usage
  ● 30,000 unique users per month
  ● 1B calls in 2015
RxNav

RxNav is a browser for several drug information sources, including RxNorm, RxTerms and NDF-RT. RxNav finds drugs in RxNorm from the names and codes in its constituent vocabularies.

Launch RxNav

https://rxnav.nlm.nih.gov/
Use case #1

Comparing prescribed vs. defined daily dose

[Bodenreider, AMIA, 2014]
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 $\rightarrow$ RxNorm ingredient $\leftrightarrow$ ATC ingredient $\rightarrow$ ATC defined daily dose $\leftrightarrow$ 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
ATC/DDD Index

◆ Origin
  ● World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (Norway)
  ● For drug utilization research / pharmaco-epidemiology
    ■ Not for clinical purposes

◆ Organization
  ● Drug classification on 4 levels
    ■ Anatomical
    ■ Therapeutic
    ■ Chemical
  ● Drugs (5th level)
  ● Daily dose
    ■ For a given route

http://www.whocc.no/atc_ddd_index/

J ANTIINFECTIVES FOR SYSTEMIC USE
  J01 ANTIBACTERIALS FOR SYSTEMIC USE
  J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS
  J01CA Penicillins with extended spectrum

<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>
<tr>
<td>J01CA04</td>
<td>amoxicillin</td>
<td>1 g</td>
<td>O</td>
<td></td>
<td>P</td>
</tr>
</tbody>
</table>
Methods Overview

**RxNorm**
- Clinical drug
- Ingredient
- Dose Form

**ATC classes**
- L1
- L2
- L3
- L4

**ATC/DDD Index**
- Level 5 drug
- Adm. Code
- Defined Daily Dose

**Surescripts**
- Clinical drug
- Total amount
- Duration
- Prescribed Daily Dose

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Amoxicillin 500 MG Oral Capsule (308191)

RxNorm

Amoxicillin (723)
Oral Capsule

ATC/DDD Index

amoxicillin (J01CA04)
1 g

Surescripts

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)

- 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
- 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
- 10.4% < 33% of the ATC DDD
- 3.5% > 300% of the ATC DDD
Use case #2

Identifying potentially inappropriate medications for elderly patients
PIMs for elderly patients

◆ Dataset
  ● Medicare Part D
  ● 1M beneficiaries ≥ 65
  ● All prescriptions for one year (2009)

◆ Reference list of PIMs: Beers list

◆ Methods
  ● NDC → RxNorm clinical drug → ingredient ↔ Beers
  ● Restricted to systemic drugs (based on dose form)

◆ Findings
  ● 47% of all beneficiaries were prescribed at least 1 PIM
  ● Top PIMs: zolpidem (6.3%), nitrofurantoin (4.5%)
Methods Overview

**RxNorm**
- NDC
- Clinical drug
- Ingredient
- Dose Form

**Medicare**
- NDC
- Demographic data
- Number of prescriptions

**Beers**
- Ingredient
- Systemic DFG
- DFG filter

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Methods  Example

RxNorm

55111047901

Zolpidem tartrate 10 MG Oral Tablet (854873)

Oral Tablet

zolpidem

Beers

zolpidem

Oral Pill

DFG filter

Medicare

55111047901

Demographic data 470,523 prescriptions
Specific challenge

♦ Obsolete identifiers
  ● NDC = drug + manufacturer + packaging information
    ➤ 200,000 active NDCs
    ➤ 400,000 obsolete NDCs in the past 10 years
  ● Obsolete NDCs
    ➤ Removed from RxNorm (e-prescribing use case)
    ➤ Needed for analytics (longitudinal datasets)
  ● RxNorm API provides access to obsolete NDCs
    ➤ Mapping obsolete NDCs to active drugs
    ➤ List of all NDCs – active or obsolete – for a given drug
Use case #3

Identifying potential risk in drug prescriptions during pregnancy
Potential risk during pregnancy

◆ Dataset
  ● Large prescription dataset from private insurer (150M patients)
  ● 3.7M pregnant women; 19M prescriptions (2003-2014)
  ● OMOP common data model

◆ Reference list for risk during pregnancy: Briggs textbook

◆ Methods
  ● RxNorm clinical drug → ingredient ↔ Briggs drug → fetal risk
  ● Restricted to systemic drugs (based on dose form)

◆ Findings
  ● 41.2% compatible with pregnancy or probably compatible
  ● 55.6% potential risk
  ● 3.29% high risk or contraindicated
Discussion
RxNorm supports interoperability

◆ Need to map across
  ● Identifiers (e.g., NDC to RxNorm; RxNorm to ATC)
    ▪ Facilitated by RxNorm concepts
      – Coming soon: DrugBank codes in RxNorm
  ● Levels of granularity (e.g., NDC to clinical drug; clinical drug to ingredient; ingredient to class)
    ▪ Facilitated by RxNorm relations
  ● Reference datasets (e.g., Beers, Briggs) and standard terminologies (RxNorm)
    ▪ Facilitated by the RxNorm API mapping functions
  ● Obsolete and active identifiers (e.g., NDCs)
    ▪ Facilitated by the RxNorm API status functions
Remaining challenges

- Obsolete identifiers
  - Needed for analytics
- Reuse of identifiers
  - NDCs (time-indexed)
- Insufficient coverage in RxNorm
  - International drugs
  - Over-the-counter drugs
- Granularity of knowledge
  - Ingredient-class vs. clinical drug-class
- Heterogeneity of drug classification
  - Different use cases
NLM drug resources

- RxNav, RxClass, Drug APIs

- RxNorm

- RxTerms (interface terminology for RxNorm)

- DailyMed (Structured Product Labels)

- Druginfo
References

