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

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

RxNorm Example

Ingredient
Azithromycin

C. Drug Comp.
Azithromycin 250 MG

C. Drug Form
Azithromycin Oral Tablet

C. Drug
Azithromycin 250 MG Oral Tablet

Brand Name
Zithromax

B. Drug Comp.
Azithromycin 250 MG

B. Drug Form
Azithromycin Oral Tablet [Zithromax]

B. Drug
Zithromax 250 MG Oral Tablet

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

B. Pack
Z-PAK
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
    - NDF-RT, MeSH and ATC
  - All classes for a given drug
  - All drug members for a given class
  - Class-class similarity

http://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
  ● Link between drug classes and their drug members
  ● Similarity between drug classes
◆ 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

http://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 → 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
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

J \textbf{ANTIINFECTIVES FOR SYSTEMIC USE}
J01 \textbf{ANTIBACTERIALS FOR SYSTEMIC USE}
J01C \textbf{BETA-LACTAM ANTIBACTERIALS, PENICILLINS}
J01CA \underline{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></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g</td>
<td>P</td>
<td></td>
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</tr>
</tbody>
</table>
Methods Overview

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

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

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

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

**Example**

**RxNorm**
- Amoxicillin 500 MG Oral Capsule (308191)
- 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

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

**Prescription classification**

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Bar Chart</th>
<th>Common Drugs</th>
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</thead>
<tbody>
<tr>
<td>ALIMENTARY TRACT AND METABOLISM (A)</td>
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<tr>
<td>BLOOD AND BLOOD FORMING ORGANS (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDIOVASCULAR SYSTEM (C)</td>
<td></td>
<td>Atorvastatin, Simvastatin, Lisinopril, Metoprolol, Amlodipine, Furosemide, Hydrochlorothiazide</td>
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<tr>
<td>DERMATOLOGICALS (D)</td>
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<tr>
<td>GENITO URINARY SYSTEM AND SEX HORMONES (G)</td>
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<tr>
<td>SYSTEMIC HORMONAL PREP., EXCL. SEX HORMONES AND INSULINS (H)</td>
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<td>ANTIINFECTIVES FOR SYSTEMIC USE (J)</td>
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<tr>
<td>ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (L)</td>
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</tr>
<tr>
<td>MUSCULO-SKELETAL SYSTEM (M)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NERVOUS SYSTEM (N)</td>
<td></td>
<td>Zolpidem, Sertraline, Escitalopram, Oxycodone, Gabapentin, Quetiapine, Fluoxetine, Duloxetine</td>
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<tr>
<td>ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS (P)</td>
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<tr>
<td>RESPIRATORY SYSTEM (R)</td>
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<tr>
<td>SENSORY ORGANS (S)</td>
<td></td>
<td></td>
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<tr>
<td>VARIOUS (V)</td>
<td></td>
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</tbody>
</table>
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%)
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 clinical data model

- **Reference list for risk during pregnancy:** Briggs textbook

- **Methods**
  - RxNorm clinical drug $\rightarrow$ ingredient $\leftrightarrow$ Briggs drug $\rightarrow$ 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
Challenges

◆ Obsolete identifiers
  ● Needed for analytics

◆ Reuse of identifiers
  ● NDCs (time-indexed)

◆ Insufficient coverage in ontologies
  ● International drugs
  ● Over-the-counter drugs

◆ Granularity of knowledge
  ● Ingredient-class vs. clinical drug-class

◆ Heterogeneity of drug classification
  ● Different use cases