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>
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<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>
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<tr>
<td>MTHSPL</td>
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<td>AZITHROMYCIN 250 mg ORAL TABLET, FILM COATED</td>
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<td>0093-7146</td>
<td>AZITHROMYCIN MONOHYDRATE 250 mg ORAL TABLET, FILM COATED_#1</td>
</tr>
</tbody>
</table>

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**308460  Azithromycin 250 MG Oral Tablet**
Normalized form

- **Strength**: 250 MG
- **Ingredient**: Azithromycin
- **Dose form**: Oral Tablet

Semantic clinical drug component

Semantic clinical drug form

Semantic clinical drug
Normalized relations

- **Ingredient**: Azithromycin
- **C. Drug Comp.**: Azithromycin 250 MG
- **C. Drug Form**: Azithromycin Oral Tablet
- **B. Drug Comp.**: Azithromycin 250 MG
- **B. Drug Form**: Azithromycin Oral Tablet [Zithromax]
- **C. Drug**: Azithromycin 250 MG Oral Tablet
- **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
    - 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/

<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>
<tr>
<td>J01CA05</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/DDD Index**
- Level 5 drug
- Adm. Code
- Defined Daily Dose

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

**ATC classes**
- L1
- L2
- L3
- L4
Amoxicillin
500 MG Oral Capsule
(308191)

Methods

Example

RxNorm

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) - Atorvastatin, Simvastatin, Lisinopril, Metoprolol
- DERMATOLOGICALS (D)
- GENITO URINARY SYSTEM AND SEX HORMONES (G)
- SYSTEMIC HORMONAL PREP., EXCL. SEX HORMONES AND INSULINS (H)
- ANTI-INFECTIVES FOR SYSTEMIC USE (J)
- ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (L)
- MUSCULO-SKELETAL SYSTEM (M)
- NERVOUS SYSTEM (N) - Zolpidem, Sertraline, Escitalopram, Alprazolam, Clonazepam, Gabapentin, Quetiapine, Oxycodone, Fluoxetine, Duloxetine
- VARIOUS (V)
Deviations 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**
**Methods Example**

**RxNorm**
- 55111047901
- Zolpidem tartrate 10 MG
  - Oral Tablet (854873)
- zolpidem
- Oral Tablet

**Medicare**
- 55111047901
- Demographic data
  - 470,523 prescriptions

**Beers**
- Zolpidem
- Oral Pill
  - DFG filter
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
  ● https://rxnav.nlm.nih.gov/

◆ RxNorm
  ● https://www.nlm.nih.gov/research/umls/rxnorm/

◆ RxTerms (interface terminology for RxNorm)

◆ DailyMed (Structured Product Labels)

◆ Druginfo
  ● http://druginfo.nlm.nih.gov/
References


https://rxnav.nlm.nih.gov/

Contact: RXNAVINFO@LIST.NIH.GOV

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