Drug analytics from claims data
*Resources, methods and applications*

Olivier Bodenreider, MD, PhD

Senior Scientist

Department of Clinical Pharmacy and Translational Sciences
March 22, 2021
Disclaimer

The views and opinions expressed do not necessarily state or reflect those of the U.S. Government, and they may not be used for advertising or product endorsement purposes.
Outline

◆ Resources
  ● Drug terminologies
  ● RxNorm

◆ Methods
  ● Mapping NDCs to RxNorm
  ● Linking RxNorm entities to ATC

◆ Applications
  ● OHDSI – Characterizing treatment pathways
Resources
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
RxNorm

- Standard drug terminology
- Developed by the National Library of Medicine
- Integrates 13 drug vocabularies (interoperability)
- Scope
  - Prescription drugs (U.S. market)
  - Only terminology (not a drug knowledge base)
- Updated monthly
- Use cases
  - E-prescribing
  - Information exchange
  - Formulary development
  - Reference value sets
  - Analytics

https://www.nlm.nih.gov/research/umls/rxnorm/
Anatomical Therapeutic Chemical Classif. 7
Vaccines Administered (HL7) 0
DrugBank 28
Gold Standard Drug Database 47
Multum MedSource Lexicon 87
Micromedex RED BOOK 71
Medical Subject Headings (MeSH) 25
FDA Structured Product Labels 205
First DataBank MedKnowledge 117
US Edition of SNOMED CT (drugs) 103
United States Pharmacopeia (USP) 5
VHA National Drug File 67

Source vocabularies in RxNorm (terms in thousands, as of March 2021)
## Normalization: Lexical level

<table>
<thead>
<tr>
<th>Name</th>
<th>Code</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>WARFARIN (COUMADIN) NA 1MG TAB</td>
<td>4005203</td>
<td>VANDF</td>
</tr>
<tr>
<td>warfarin 1 mg oral tablet</td>
<td>3617</td>
<td>MMSL</td>
</tr>
<tr>
<td>WARFARIN NA 1MG TAB,UD</td>
<td>4014039</td>
<td>VANDF</td>
</tr>
<tr>
<td>WARFARIN NA 1MG TAB,UD [VA Product]</td>
<td>N0000161787</td>
<td>NDFRT</td>
</tr>
<tr>
<td>WARFARIN SODIUM 1 mg ORAL TABLET</td>
<td>14198</td>
<td>NDFF</td>
</tr>
<tr>
<td>WARFARIN SODIUM 1 mg ORAL TABLET [Warfarin Sodium]</td>
<td>60429-784</td>
<td>MTHSPL</td>
</tr>
<tr>
<td>Warfarin Sodium 1 MG Oral Tablet</td>
<td>104045</td>
<td>MMX</td>
</tr>
<tr>
<td>WARFARIN SODIUM 1 mg ORAL TABLET [Warfarin Sodium]</td>
<td>63629-4017</td>
<td>MTHSPL</td>
</tr>
<tr>
<td>WARFARIN SODIUM 1 mg ORAL TABLET [Warfarin Sodium]</td>
<td>53808-0985</td>
<td>MTHSPL</td>
</tr>
<tr>
<td>Warfarin Sodium 1 MILLIGRAM In 1 TABLET ORAL TABLET</td>
<td>15330-100</td>
<td>MTHSPL</td>
</tr>
<tr>
<td>WARFARIN SODIUM 1.09 MG ORAL TABLET</td>
<td>281572</td>
<td>MTHFDA</td>
</tr>
<tr>
<td>Warfarin Sodium 1mg Oral tablet</td>
<td>933</td>
<td>GS</td>
</tr>
<tr>
<td>Warfarin sodium 1mg tablet (product)</td>
<td>319733000</td>
<td>SNOMEDCT_US</td>
</tr>
<tr>
<td>Warfarin Sodium Tab 1 MG</td>
<td>6749</td>
<td>MDDB</td>
</tr>
<tr>
<td>Warfarin Sodium, 1 mg oral tablet</td>
<td>3617</td>
<td>MMSL</td>
</tr>
<tr>
<td>WARFARIN SODIUM@1 mg@ORAL@TABLET</td>
<td>14198</td>
<td>NDFF</td>
</tr>
</tbody>
</table>

---

**Warfarin Sodium 1 MG Oral Tablet (855288)**
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**: Z-PAK
- **B. Drug Comp.**: Azithromycin 250 MG [Zithromax]
- **B. Drug Form**: Azithromycin Oral Tablet [Zithromax]
- **B. Drug**: Zithromax 250 MG Oral Tablet
- **Brand Name**: Zithromax

**Pack**: 6 (Azithromycin 250 MG Oral Tablet)
RxNorm Example

azithromycin [RxCUI = 18631]

IN/MIN
- azithromycin

PIN
- azithromycin anhydrous
- azithromycin dihydrate
- azithromycin monohydrate

BN
- AzaSite
- Zithromax
- Zmax

SCDC
- azithromycin 10 MG/ML
- azithromycin 1000 MG
- azithromycin 20 MG/ML
- azithromycin 250 MG

SBDC
- azithromycin 10 MG/ML [AzaSite]
- azithromycin 1000 MG [Zithromax]
- azithromycin 20 MG/ML [Zithromax]
- azithromycin 250 MG [Zithromax]

SCD/GPCK
- azithromycin 10 MG/ML Ophthalmic Solution
- azithromycin 1000 MG Powder for Oral Suspension
- azithromycin 20 MG/ML Oral Suspension
- azithromycin 250 MG Oral Capsule

SBD/BPCK
- AzaSite 1 % Ophthalmic Solution
- TRI-PAK
- Z-PAK
- Zithromax 1 GM Powder for Oral Suspension

SCDG
- azithromycin Injectable Product
- azithromycin Ophthalmic Product
- azithromycin Oral Liquid Product
- azithromycin Oral Powder Product

DFG
- Injectable Product
- Ophthalmic Product
- Oral Liquid Product
- Oral Powder Product

SBDG
- AzaSite Ophthalmic Product
- Zithromax Injectable Product
- Zithromax Oral Liquid Product
- Zithromax Oral Powder Product
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)
Methods
Example: Analyzing opioid prescriptions in the Medicare dataset

- NDCs are used to identify medications in claims data
- Drug classification systems are used to define drug classes, such as opioids
- RxNorm can be used to bridge between NDCs and popular drug classification systems (e.g., ATC)
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, MED-RT, EPC, MeSH pharmacologic actions, SNOMED CT)
Linkages among drug entities

oxycodone [N02AA05]

oxyCODONE [7804]

Abuse-Deterrent 12 HR oxyCODONE Hydrochloride 10 MG Extended Release Oral Tablet [1860157]

12 HR OxyCONTIN 10 MG Extended Release Oral Tablet [1049504]

59011041010

59011-410-10
Identifying opioid drugs from a drug class

- ATC – Anatomical Therapeutic Chemical drug classification system

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>N02AA01</td>
<td>morphine</td>
</tr>
<tr>
<td>N02AA02</td>
<td>opium</td>
</tr>
<tr>
<td>N02AA03</td>
<td>hydromorphone</td>
</tr>
<tr>
<td>N02AA04</td>
<td>nicomorphine</td>
</tr>
<tr>
<td>N02AA05</td>
<td>oxycodone</td>
</tr>
<tr>
<td>N02AA08</td>
<td>dihydrocodeine</td>
</tr>
<tr>
<td>N02AA10</td>
<td>papaveretum</td>
</tr>
<tr>
<td>N02AA51</td>
<td>morphine, combinations</td>
</tr>
<tr>
<td>N02AA53</td>
<td>hydromorphone and naloxone</td>
</tr>
<tr>
<td>N02AA55</td>
<td>oxycodone and naloxone</td>
</tr>
<tr>
<td>N02AA56</td>
<td>oxycodone and naltrexone</td>
</tr>
<tr>
<td>N02AA58</td>
<td>dihydrocodeine, combinations</td>
</tr>
<tr>
<td>N02AA59</td>
<td>codeine, combinations excl. psycholeptics</td>
</tr>
<tr>
<td>N02AA79</td>
<td>codeine, combinations with psycholeptics</td>
</tr>
</tbody>
</table>
Issues: Obsolete NDCs

**oxycodone [N02AA05]**

**oxyCODONE [7804]**

- Abuse-Deterrent 12 HR oxyCODONE Hydrochloride 10 MG Extended Release Oral Tablet [1860157]
- 12 HR OxyCONTIN 10 MG Extended Release Oral Tablet [1049504]

**Obsolete NDCs can be queried under Historical NDCs in RxNav**

- 2 Current NDCs: 59011041010, 59011041020
- 129 Obsolete NDCs:
  - 10544059120
  - 10544059130
  - 16590067710
  - 16590067715
  - 16590067720
  - [...]

**ATC code** | **Name** | **DDD** | **U** | **Adm.R.** | **Note**
--- | --- | --- | --- | --- | ---
N02AA05 | oxycodone | 75 | mg | O | 
30 | mg | P |
<table>
<thead>
<tr>
<th>RXCUI</th>
<th>Direct Structure</th>
<th>drugClass</th>
<th>drugID</th>
<th>drugObsID</th>
<th>observedDate</th>
<th>expiredDate</th>
<th>isExpired</th>
</tr>
</thead>
<tbody>
<tr>
<td>1049504</td>
<td>405920000000</td>
<td>201101</td>
<td>201206</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>486920880100</td>
<td>201101</td>
<td>201206</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>486920880250</td>
<td>201101</td>
<td>201206</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381300</td>
<td>201101</td>
<td>201607</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381301</td>
<td>201101</td>
<td>201607</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381302</td>
<td>201101</td>
<td>201402</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381303</td>
<td>201101</td>
<td>201607</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381304</td>
<td>201101</td>
<td>201607</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>54868381305</td>
<td>201101</td>
<td>201607</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>59011010010</td>
<td>201101</td>
<td>201306</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>59011010020</td>
<td>201101</td>
<td>201306</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>59011010025</td>
<td>201101</td>
<td>201309</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>59011041010</td>
<td>201101</td>
<td>202103</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>59011041020</td>
<td>201101</td>
<td>202103</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629377501</td>
<td>201101</td>
<td>201709</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629377502</td>
<td>201101</td>
<td>201709</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629377503</td>
<td>201102</td>
<td>201709</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629377504</td>
<td>201102</td>
<td>201709</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629377505</td>
<td>201102</td>
<td>201709</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629386101</td>
<td>201409</td>
<td>201708</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1049504</td>
<td>63629386102</td>
<td>201409</td>
<td>201708</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Applications
Characterizing treatment pathways at scale using the OHDSI network

George Hripcsak, Patrick B. Ryan, Jon D. Duke, Nigam H. Shah, Rae Woong Park, Vojtech Huser, Marc A. Suchard, Martijn J. Schuemie, Frank J. DeFalco, Adler Perotte, Juan M. Banda, Christian G. Reich, Lisa M. Schilling, Michael E. Matheny, Daniella Meeker, Nicole Pratt, and David Madigan

Observational Health Data Sciences and Informatics (OHDSI)
https://ohdsi.org/
Characterizing treatment pathways at scale using the OHDSI network

◆ Objectives: analyze the variability of pharmacological treatment interventions over three years across three diseases (type-2 diabetes mellitus, hypertension, or depression)

◆ Inclusion criteria: exposure to an antidiabetic, antihypertensive, or antidepressant medication for 3 years, as well as presence of at least one diagnostic code for the corresponding disease

◆ Exclusion criteria: based on diagnostic data (e.g., exclusion of schizophrenia patients from the depression cohort)
Characterizing treatment pathways at scale using the OHDSI network

- Materials: 11 datasets representing a total of 255 million patients
  - EHR data (South Korea, U.K., U.S.) 67M
  - Claims data (U.S., Japan) 188M
- Methods: Analyze the sequences of medications that patients were placed on during those 3 years, to reveal patterns and variation in treatment among data sources and diseases
Characterizing treatment pathways at scale using the OHDSI network

◆ Results

● Patients with 3 years of uninterrupted therapy
  - 327,110 diabetes patients
  - 1,182,792 hypertension patients
  - 264,841 depression patients

● Treatment pathways
A Diabetes

- Metformin
- pioglitazone
- sitagliptin
- Glipizide
- glimepiride
- Gliclazide
- Glyburide
- rosiglitazone
- Insulin, Glargine, Human
- exenatide
- Insulin, Aspart, Human
- liraglutide
- saxagliptin
- Insulin, Lispro, Human
- Glucose
- Insulin, Isophane, Human
Differences across diseases

- **Diabetes**
  - Metformin is the first line of treatment and often the only treatment

- **Hypertension**
  - Slight predominance of HCTZ, frequently paired with other medications

- **Depression**
  - Even spread of medications

- **Unique treatment pathways (within a cohort)**
  - 10% TDM
  - 25% HTN

---

National Library of Medicine
Lister Hill National Center for Biomedical Communications
Differences across countries

- Metformin less often used in Japan
- Wide variety of starting medications
- The most common medication varies by source
Medical Ontology Research

Contact: olivier@nlm.nih.gov
Web: mor.nlm.nih.gov

Olivier Bodenreider

National Library of Medicine
Lister Hill National Center for Biomedical Communications