**LabeledIn: Cataloging Labeled Indications for Human Drugs**

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Motivation: existing public resources are
- Not computable
- In complete
- Dose-form non-specific

Method: double-annotation by experts with computer aids for improved efficiency

Results:
- 250 popular human drugs in PubMed Health website, e.g.
  - Antidepressant drugs
  - Pain medicine
- ~8,000 drug and indication pairs are
  - Structured & Normalized
  - Dose-form specific
- Highly reliable (human inter-annotator agreement is ~95%)
- Open access

Future Directions
- Increase the drug coverage
- Improve productivity by advanced computer techniques
Most searched topics in PubMed: authors; diseases; genes; chemical/Drugs

Dogan et al., Understanding PubMed® user search behavior through log analysis, Database, 2009
Drug-Disease Treatment Relationships

- Question-Answering System
  - Google Knowledge Graph

- Enriching hyperlinks in online health resources
  - Cross-linking Drug and Disease Monographs

- Clinical decision support
  - Medication and Nomenclature Errors (Khare et al. 2013)
  - Recommend Medications

- Computational Methods
  - Drug Repurposing (Li and Lu 2012)
  - Identification of Side Effects
Existing Resources on Drug-Disease Relationships Not Computable

Uses of This Medicine

Diltiazem is used alone or together with other medicines to treat severe chest pain (angina) or high blood pressure (hypertension). High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, and kidneys, resulting in a stroke, heart failure, or kidney failure. High blood pressure may also increase the risk of heart attacks. These problems may be less likely to occur if blood pressure is controlled.

NOT STRUCTURED

Incomplete (Barriere et al. 2011)

No Differentiation of Dose Forms

- Ketorolac Drug
  - Injection for pain
  - Ophthalmic Solution for conjunctivitis

NOT NORMALIZED

NOT PRECISE
PERPHENAZINE tablet, film coated
[Sandoz Inc]

INDICATIONS AND USAGE

Perphenazine is indicated for use in the treatment of schizophrenia and for the control of severe nausea and vomiting in adults. Perphenazine has not been shown effective for the management of behavioral complications in patients with mental retardation.

CLINICAL PHARMACOLOGY
...

Source: FDA Drug Labels (from DailyMed)
Related Work

- **Automatic approaches:**
  - Filter using side effects (SIDER 2, Kuhn et al. 2010)
  - Frequency of occurrence in other drug resources (MEDI, Wei et al. 2013)
  - NLP approach (SPL-X, Kung et al., 2013)
  - Limited in precision and recall

- **Manual Annotations**
  - *LabeledIn* (Khare, et al., 2014): an expert validated computable resource on drug indications
  - Reliable but expensive to scale
PERPHENAZINE tablet, film coated
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CLINICAL PHARMACOLOGY...

Khare, Li, & Lu: LabeledIn: Cataloging Labeled Indications for Human Drugs, JBl, 2014
Human Review Process

- 3 human reviewers (knowledgeable in biomedicine and indexing)
- Two rounds of review
  - Round #1: Annotating independently
  - Round #2: Resolving disagreements
- Annotation guidelines (e.g. NOT to include contraindications or side effects)
- Pilot study of 100 drug labels for practicing as well as developing guidelines
- Inter-annotator agreements (IAAs)

<table>
<thead>
<tr>
<th></th>
<th>Round1</th>
<th>Round1+Round2</th>
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<tbody>
<tr>
<td>Absolute Agreement</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Kappa Agreement</td>
<td>77%</td>
<td>88%</td>
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Text-mined pre-annotations vs. Human-reviewed results

Pre-annotations (#2950)

Rejected

Accepted

Human-adjusted/added

LabeledIn (#1,715)

Automatic indication detection Accuracies:

<table>
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<tr>
<th>Precision</th>
<th>Recall</th>
<th>F₁ Measure</th>
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<tr>
<td>0.55</td>
<td>0.94</td>
<td>0.69</td>
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STROMECTOL is indicated for the treatment of Strongyloidiasis of the intestinal tract.

STROMECTOL is indicated for the treatment of Onchocerciasis due to nematode parasite. This indication is based on randomized double blind, placebo controlled and comparative studies...
Results: LabeledIn

- Current size
  - 250 ingredients
  - 8,151 drug labels
  - 1,513 drugs <ingredient, dose form, strength> & 7,805 drug-disease pairs

- Features
  - Open access
  - Computable
  - Human-validated
  - Source-linked (original label + human annotations)

- Applications:
  - Computational drug discovery (e.g. re-purposing)
  - Improving existing resources (e.g. SIDER)
  - Decision Support in EMRs (Mayo Clinic)
  - Enabling automatic machine-learning methods
  - Enabling crowdsourcing experiments

Khare, Li, & Lu: LabeledIn: Cataloging Labeled Indications for Human Drugs, JBI 2014
**Imprecise Mentions**

myocardial infarction

**Unrelated Diseases**

...are indicated in the treatment of symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication

**Non-Disease Mentions**

Aspirin may be continued, ...use of NSAIDs including salicylates has not been fully explored (see PRECAUTIONS , Drug Interactions )

**More Specific**

partial onset seizures

**Disjoint Mentions**

biliary and renal colic

**Comprehensive Disease Definition**

Zollinger-Ellison syndrome
Limitations & Future Directions

- To include more drugs into LabeledIn
- To further improve manual curation efficiency by using advanced computer techniques
  - Machine learning
  - Crowdsourcing
  - etc
- To link some general indications to specific procedure/conditions (e.g. “nausea” and “vomiting” due to “cancer chemotherapy”)
- To improve automatic disease tagging quality in step 2
Acknowledgements

- Three Human indexers
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Questions?

Thank you!

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LabeledIn freely available at: ftp.ncbi.nlm.nih.gov/pub/lu/LabeledIn/