A KNOWLEDGE INTENSIVE APPROACH FOR IDENTIFYING ADVERSE DRUG EVENTS IN CLINICAL TEXT

Sivaram Arabandi, MD
National Library of Medicine

May 2011
motivation

- In any given week
  - 4 out of 5 people will use medications
  - 1 in 3 will take 4 or more different medications
- At least 1.5 million preventable ADEs per year
  [IOM 2006 report estimate]
- Each ADE added about $8,750 (in 2006 dollars) to the cost of the hospital stay
- Estimated at $3.5 billion per year
- Only 10 to 20 percent of errors are reported
  [IHI 2008 report]

ADE = Adverse Drug Event
IOM = Institute of Medicine
IHI = Institute for Healthcare Improvement
how can ADEs be prevented?

- Acknowledge
- Recognize
- Understand
- Address
"Because health care data are often narrative, natural language processing (NLP) is another important technique for mining data for quality improvement and patient safety purposes."

NLP in medicine

- **1980 – 90s:**
  - Linguistic String Project-Medical Language Processor (LSP-MLP)
  - MedLEE
    - initially developed for Radiology reports
    - still in production (Columbia)
  - Metamap
  - and many more ....
NLP for ADE detection

- Melton & Hripcsak (2005):
  - MedLEE to identify 45 NYPORTS event types using discharge summaries
  - Sensitivity = 0.28
  - Specificity = 0.985

  - Pharmacovigilance using MedLEE
  - Recall = 0.75
  - Precision = 0.31

NYPORTS = New York Patient Occurrence Reporting & Tracking System
background

- “current applications, however, are rarely applied outside of the laboratories they have been developed in, mostly because of scalability and generalizability issues”

- “with few exceptions, we do not know which of the reviewed NLP-CDS systems are actually implemented or deployed, and what makes these systems worthwhile.”
  - Demner-Fushman D, Chapman WW, McDonald CJ. *What can natural language processing do for clinical decision support?*, J Biomed Inform. 2009
goal

“What will it take to extract information from narrative clinical text – reliably and generally”
What is missing?
What is holding us back?
investigate

- Can we
  - Exploit capabilities of existing systems?
  - Augment them with additional knowledge?
use case

- Adverse Drug Events [ADEs]

"A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

-- World Health Organization
identify

- Concepts & relations
  - Drugs, findings
- Normal vs. Abnormal
- Timeline (Events)
- ADEs “events of harm”
approach

- **Exploit** existing resources (UMLS, MedLEE, MetaMap)
  - Concepts & relations (drugs and finding)
- **Enhance** with rules and knowledge
  - Normal vs. Abnormal
  - Timeline (Events)
  - Identify “events of harm (ADEs)“
materials

- **Data**
  - Admission notes: ER note, H&P report, ....
  - Progress notes
  - Procedure reports: Lab, Radiology, ....
  - Discharge reports

- **Sources**
  - TREC reports
  - Clinical Center reports

TREC = Text REtrieval Conference
Concepts
Manifestations
Concept modification
A 76-year-old male with a 12-year history of idiopathic Parkinson's disease (PD) had been taking levodopa (L-dopa; 500 mg/day) and pramipexole (4 mg/day) for the past several years with relatively good control of his motor symptoms, primarily tremor and rigidity.
concepts: challenges

- Expressiveness of language
  - Ambiguity
  - Synonymy
  - Negation
  - Abbreviations
concepts: ambiguity

- **One term** that can **mean several things**
  - *Cold* = feeling cold, cold infection, chronic obstructive lung disease
  - *MS* = Multiple sclerosis, Mitral stenosis

“No recent catheterizations”

**Search Results (15)**
- C0007430  Catheterization
- C0004704  Balloon Dilatation
- C0006259  Catheterization, Bronchial
- C0007435  Catheterization, Central Venous
- C0007436  Catheterization, Peripheral
- C0018795  Cardiac Catheterization Procedures
- C0041953  Catheterization, Ureteral
- C0042019  Urinary Catheterization

“Patient's last functional evaluation approximately one year ago, with no reversibility / ischemia seen”

**Search Results (5)**
- C0278372  Functional assessment
- C2732531  Functional capacity evaluation scale
- C0200299  Special audiologic evaluation for functional hearing loss
- C0203889  Physical medicine evaluation of functional activities, initial 30 minutes
- C1971412  Comprehensive preoperative assessment performed for cataract surgery with intraocular lens
concepts: synonymy

- **Two or more terms** that mean the same thing
  - Myocardial infarction = MI, Heart Attack
  - Parkinson disease = Parkinson’s disease, PD, Paralysis agitans, ...
    BUT not Parkinsonism
negation

- Negation expressed in many ways
  - No
    - no history of cough
    - no evidence of tenderness
  - Patient denies ...
    - denies any headache.
    - denies any upper abdominal pain. He states he is very hungry right now. He has only lower abdominal cramps.
concepts: abbreviations

- **Acronyms**
  - Denies fevers/chills, **URI sx**
  - 76 yoF with hx **MI '96, s/p CVA, hx GERD**

- **Shortcuts**
  - 76 yoF with hx **MI '96, s/p CVA, hx GERD**
  - 56 yo F w/restless leg **synd adm for eval. No eating probl/GI sx ID 'ed. Wt 72.6kg, BMI=31.4. labs as yet u/a**

- **??**
  - Lymphs 11 %
findings

- Understanding at the data level
- No interpretation of normal or abnormal

- Continuous data → Numeric values and Units
  
  e.g.: Temp. = 98.6°F
  
  - Fahrenheit <→ Centigrade
  - Meter <→ Centimeter
  - Meter <→ Feet

- Fiszman et al. A Knowledge Intensive Approach to Mapping Clinical Narrative to LOINC

- Categorical data
  
  e.g.: swollen knee

\[\text{knee} \xrightarrow{\text{hasQuality}} \text{swollen}\]
use case

A 76-year-old male with a 12-year history of idiopathic Parkinson's disease (PD) had been taking levodopa (L-dopa; 500 mg/day) and pramipexole (4 mg/day) for the past several years with relatively good control of his motor symptoms, primarily tremor and rigidity.
A 76-year-old male with a 12-year history of idiopathic Parkinson's disease

finding:demo
  age>> [76,[idref,6],year,[idref,8]]
  parsemode>> mode2
  sectname>> report past history item
  sex>> male
    idref>> 12
  sid>> 1

idiopathic Parkinson's disease

problem:Parkinson's disease
  certainty>> high certainty
    idref>> 42
  descriptor>> idiopathic
    idref>> 26
  idref>> 28
  parsemode>> mode4
A 76-year-old male with a 12-year history of idiopathic Parkinson's disease
next: enhanced processing

- Identify
  - Abnormal findings
  - Sequence of events
  - Identify ADE

- Processing approach
  - Knowledge intensive
  - Rule based
Abnormal manifestation
abnormal manifestation

- Bodily feature
  - Physiological vs. Pathological

- Vitals: temperature
  - temp = 98.6° F → NORMAL
  - temp = 102.6° F → ABNORMAL

- Sign:
  - red, swollen knee → ABNORMAL
abnormal manifestation

- Weight gain
  - Hypothyroidism $\rightarrow$ ABNORMAL
  - Pregnancy $\rightarrow$ NORMAL

- Pulse rate = 110/min.
  - In Adult resting $\rightarrow$ ABNORMA
  - In Adult exercising $\rightarrow$ NORMAL
  - In Child resting $\rightarrow$ NORMAL
knowledge sources

- **UMLS**
  - **Metathesaurus**
    - Concepts classified into Semantic Types

- **Additional models**

- **Reference ranges**
  - **LOINC ?**

<table>
<thead>
<tr>
<th></th>
<th>newborn</th>
<th>1 – 12 months</th>
<th>1 – 2 years</th>
<th>2 – 6 years</th>
<th>6 – 12 years</th>
<th>12 years - adults</th>
<th>adult athletes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>120 - 160</td>
<td>80 - 140</td>
<td>80 - 130</td>
<td>75 - 120</td>
<td>75 - 110</td>
<td>60 - 100</td>
<td>40 - 70</td>
</tr>
</tbody>
</table>
challenges

- Prospects for success? Feasibility?
  - Knowledge is available
  - Needs processing

- Approach
  - Develop rules
  - Limit in some principled way
    - Adults only or a few drugs, findings, disease
Temporality
temporal relations

- Basic ordering of events

“did the symptom precede the medication or follow it?”

<table>
<thead>
<tr>
<th>Med</th>
<th>Dose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>75/25 forty-five units in the morning and 30 units in the evening</td>
<td>Current</td>
</tr>
<tr>
<td>Cozaar</td>
<td>50 mg daily</td>
<td>Current</td>
</tr>
<tr>
<td>Lipitor</td>
<td>10 mg nightly</td>
<td>Current</td>
</tr>
</tbody>
</table>

Date: 10 Aug 2008
50-year-old Caucasian male who presenting with severe nausea which started about 2 days ago. Since then he has been having about 20 episodes of vomiting. The patient also complains of some chills and fever and complains of postnasal drip. The patient has not moved his bowels in the last 2 days but he moved bowels today.

PAST MEDICAL HISTORY: Significant for
1. Diabetes mellitus diagnosed at the age of 40.
3. Dyslipidemia.
4. Hypertension.
Date: 10 Aug 2008

50-year-old Caucasian male who presenting with severe nausea which started about 2 days ago. Since then he has been having about 20 episodes of vomiting. The patient also complains of some chills and fever and complains of postnasal drip. The patient has not moved his bowels in the last 2 days but he moved bowels today.

PAST MEDICAL HISTORY: Significant for
1. Diabetes mellitus diagnosed at the age of 40.
3. Dyslipidemia.
4. Hypertension.
knowledge sources

- UMLS
- Additional models of the world
- Reference ranges
- Time models
  - Time Ontology in OWL
    http://www.w3.org/TR/owl-time/
  - Clinical Narrative Temporal Relation Ontology [CNTRO]
processing events

- **Events**
  - Patient was admitted on **July 24, 2007 10:27 am**
  - Lymphoma was diagnosed in **August 2003**
  - Patient almost drowned in the **summer of 2001**
  - Patient broke his right arm in the **mid-seventies**

- **Relationships between events**
  - Patient started coughing **2 days after fever started**
  - Patient has a headache for the **last 4 days**
processing events

- **CNTRO**
  - **Terms:** Event, Time, Duration, Granularity, Precision and TemporalRelationStatement.
  - **Relations:** equal, before, after, meet, overlap, contain, during, start, and finish

Lymphoma was diagnosed in **August 2003**

```xml
<event1> rdf:type Event;
    rdfs:label "Lymphoma was diagnosed";
    hasTimeStamp <tInst1>;
<tInst1> rdf:type TimeInstant;
    hasOrigTime "August 2003";
    hasGranularity "month";
```

*Modified from: Tao et. Al.. CNTRO: A Semantic Web Ontology for Temporal Relation Inferencing in Clinical Narratives*
Adverse drug events
adverse drug event

- Abnormal finding is NOT same as 'Harm'

- The patient must have suffered actual harm
  e.g.: in a patient on Coumadin, simply a high INR is not a ADE unless excessive bleeding occurs (a hematoma).
Use case

Joint pain
Joint movement restricted
Arthritis
has indication
treated with
Ibuprofen
Day 1
Day 5
Day 5
Day 15
ADE?
50 yr. old male patient presenting with knee pain.
10 days earlier, patient was diagnosed with Arthritis and put on Ibuprofen 400 mg bid.
Joint pain

Joint movement restricted

diagnosis

Arthritis

has indication
treated with

Ibuprofen

Joint swelling

Stomach ache

Day 1

Day 5

Day 5

Day 15

ADE?
**Knowledge about Diseases**
- Signs & Symptoms
- Lab findings
- Radiology etc.

**Knowledge about Drugs**
- Indications
- Contra-indications
- Adverse events
- Drug interactions

**Arthritis**
- has indication
- treated with

**Ibuprofen**

**DON’T KNOW about**
- Disease <-> Manifestations
- Drug information

**KNOW so far**
- Diagnosis
- Medication name
- Event time line
Rheumatoid Arthritis:

- **Symptoms & Signs:** Joint pain, swelling, warmth, stiffness, extremity weakness, deformities, ....
- **X-ray:** joint effusion, narrowing of inter-articular space, decalcification, ....
medications

- **Ibuprofen:**
  - **Indications:** pain, fever, arthritis, bursitis, gout, ...
  - **Contra-indications:** asthma, pregnancy, drug allergy, ...
  - **Drug interactions:** aspirin, dicumarol, ketoralac, ...
  - **Adverse events:** stomach ulcers/bleeding, higher risk of MI/stroke, ...
50 yr. old male patient presenting with **knee pain**. 10 days earlier, patient was diagnosed with **Arthritis** and put on **Ibuprofen** 400 mg bid.
Joint pain

Joint movement restricted

Ibuprofen

Day 1

Day 5

Day 5

Day 15

Arthritis

Joint swelling

Stomach ache

Joint pain

swelling

warmth

stiffness

manifestation of

ADE?
Joint pain

Joint movement restricted

Arthritis

Ibuprofen

Indications:
- pain, fever, arthritis

Adverse events:
- stomach ulcers & bleeding,
  higher risk of MI/stroke, ...

Joint swelling

Stomach ache

ADE?
Warfarin

Ibuprofen

Arthritis

Drug interaction: MAJOR
Potential for serious gastrointestinal bleeding

Melena

ADE?
RULE
IF finding follows drug
AND finding does not precede drug
AND finding is not a manifestation of the disease
AND finding is a known adverse effect of the drug

-> THEN, this is a potential ADE
Where is the **knowledge** to solve this?
Knowledge resources
knowledge resources

**NEED:**
- Disease → manifestations
- Drugs → indications/contra-indications, adverse effects
- Drug – Drug interactions

**Traditional: books, articles, etc.**

**Computable sources – some with additional processing**
- Drugs:
  - RxNorm/NDF-RT
  - MedlinePlus, DailyMed, FDA
  - Research databases - ADESSA
- Clinical Decision Support Systems (*think MYCIN*):
  - $D_X \, plain^\circledast$
  - Quick Medical Reference (QMR)
  - Isabel
  - DiagnosisPro
- Web pages
RxNorm/NDF-RT

- Normalized names for medications
- Maps to many drug vocabularies
- Contains brand names, dose forms
- Mechanism of action, Pharmacokinetics
- Indications & Contra-indications
- Drug interactions
- Adverse events???

<table>
<thead>
<tr>
<th>Kind</th>
<th>Subject</th>
<th>Predicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>IBUPROFEN</td>
<td>isa</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Asthma</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Bronchial Hyperreactivity</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Drug Hypersensitivity</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Pregnancy</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Pregnancy Third Trimester</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Pregnancy, Abdominal</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>Cl_with Rhinitis</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>may_prevent Pain</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>may_treat Arthritis, Juvenile Rheumatoid</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>may_treat Arthritis, Rheumatoid</td>
</tr>
<tr>
<td>Disease</td>
<td>IBUPROFEN</td>
<td>may_treat Bursitis</td>
</tr>
</tbody>
</table>
MedlinePlus / DailyMed

- NLM websites
- Wealth of drug related information

Ibuprofen
(eye byoo' proe fen)

Why is this medication prescribed?
How should this medicine be used?
Other uses for this medicine
What special precautions should I follow?
What special dietary instructions should I follow?
What should I do if I forget a dose?

What side effects can this medication cause?
What storage conditions are needed for this medicine?
In case of emergency/overdose
What other information should I know?
Brand names
Brand names of combination products
D<sub>x</sub> plain®

- Disease → list of symptoms
- Set of symptoms → differential diagnosis

Evidence of “ARTHRITIS, RHEUMATOID” (COMMON)

The following clinical manifestations (if present) would support this disease:
- subcutaneous nodule
- uveitis, bilateral
- rheumatoid vasculitis
- Baker cyst
- carpal tunnel syndrome
- joint dislocation
- uveitis
- fever unknown origin
- migratory polyarthritis
- extremity deformity
- extremity deformity, upper
- finger deviation, ulnar
- finger swelling
- joint effusion
- joint warmth
- joint induration
- knuckle swelling
- muscle atrophy
Adverse Drug Event [ADE]

- Actual harm
  - Have suffered an ADE
  - Have potentially suffered an ADE

- Potential for harm
  - Can suffer a known ADE from the medications
  - Can suffer an ADE based on LBD information

LBD = Literature Based Discovery (e.g. Semantic Medline)
ADE detection: SemRep

- Rofecoxib (Vioxx) – NSAID and a selective COX-2 inhibitor
- Introduced: 1999
- Withdrawn: 2004
  - increased risk of MI & stroke

Could we have detected this using SemRep?
Citations

PMID: 11595413

Date of Publication: 2001 Jan-Dec

Title: The ever-emerging anti-inflammatories. Have there been any real advances?

Abstract:
Gastrointestinal (GI) Adverse Drug Reactions (ADRs) from the NSAIDs are a major cause of morbidity and mortality in arthritic patients taking these drugs. The recent much heralded development of COX-2 selective drugs (celecoxib, rofecoxib), the objective of which has been to spare inhibition of the production of COX-1 derived mucosal protective prostaglandins, may have represented an advance in reducing the risk of serious ADRs--ulcers and bleeding--but does not appear to have reduced the incidence of symptomatic side-effects (nausea, vomiting, epigastric pain/heartburn, abdominal discomfort) which are a major reason for withdrawal from NSAID therapy, especially in the long term. The rationale of COX-2 selectivity from these newer drugs is controversial since there may be pharmacokinetic differences from established carboxylic-NSAIDs that accounts for their apparent lower ulcerogenicity. Moreover, concerns have been recently expressed that as COX-2 is important in ulcer healing, control of prostacyclin production and renal function that they may have adverse reactions from these effects. Indeed, recent reports of enhanced risk of congestive heart failure with rofecoxib are of importance and may relate to impaired prostacyclin production.

Moreover, there are other therapeutic strategies that have yielded equally low ulcerogenic NSAIDs (e.g. the prodrug, nabumetone; the established COX-2 inhibitory drug, nimesulide) and even the well-established NSAIDs ibuprofen and diclofenac have relatively low upper GI ulcerogenicity and have been used as benchmark standards in comparative trials of the
conclusions

- Existing work – identify concepts & relations
- Enhancements
  - Abnormal manifestations
  - Timelines
- Additional Knowledge and Rules needed
acknowledgment

- Olivier Bodenreider
- Tom Rindflesch
- Marcelo Fiszman
- Jim Cimino
- Lan Aronson
- Clem McDonald
- May Cheh