Translation of Open-Source Analytics into Patient-Centered Care

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Funding Disclosures

- Funding from Bayer, Janssen, Lilly, Merck
  - Research
  - Consulting
  - Coming up with great drug names (Zaxyrbeard)
We’ve Arrived!
OMOP-IMEDS SYMPOSIUM 2013
HYATT REGENCY BETHESDA, ONE BETHESDA METRO CENTER, BETHESDA, MD 20814, USA
MEETING ROOM - HAVERFORD/BACCARAT
NOVEMBER 5 – 6, 2013
The ‘Bedside’ of Drug Safety Informatics

Communication of new and established drug safety evidence to improve patient care
5.4 Hepatic Effects
Borderline elevations of liver enzymes may occur, including 13% to 24% of patients with NSAIDs. These elevations are usually minor, and more serious elevations of ALT or AST (approximately 5%) or the upper limit of normal (greater than 10 times upper limit) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities have been resolved with discontinuation of NSAIDs.

5.5 Renal Effects
A serum creatinine rise may occur, which may require discontinuation of NSAIDs.

5.6 Skin Reactions
Clinical trials of Celebrex have shown that Celebrex has caused serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), typically occurring within the first 12 to 48 days of therapy. However, some patients may experience skin reactions after more than 12 to 48 days of therapy. It is recommended that patients be closely monitored for any signs of skin reactions, and treatment should be discontinued if such reactions occur.

5.7 Neurological Reactions
As with all NSAIDs, Celebrex can lead to the onset of neuropraxia or worsening of pre-existing neuropraxia. It may also cause peripheral neuropathy in patients with peripheral vascular disease.

5.8 Concomitant NSAID Use
The concurrent use of a non-steroidal anti-inflammatory drug with Celebrex may increase the risk of serious complications due to the potential for increased risk of adverse reactions.

5.9 Concomitant Disease States
Patients with concomitant disease states may have an increased risk of adverse reactions.

5.10 Laboratory Tests
Abnormal renal or liver function tests may occur during Celebrex therapy. Laboratory tests should be performed at baseline and periodically during therapy.

6.2 Pre-marketing Controlled Clinical Trials
Table 1 lists all adverse events, regardless of causality, occurring in patients receiving Celebrex from 12 controlled studies conducted in patients with OA or RA that included a placebo and a positive control group. Several adverse events occurred in greater than 1% of patients in these clinical trials.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Celebrex</th>
<th>Placebo</th>
<th>NAP</th>
<th>DCP</th>
<th>BUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>4.1%</td>
<td>2.8%</td>
<td>7.7%</td>
<td>9.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9%</td>
<td>3.6%</td>
<td>5.3%</td>
<td>9.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12.0%</td>
<td>3.9%</td>
<td>9.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.2%</td>
<td>1.0%</td>
<td>4.3%</td>
<td>6.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.3%</td>
<td>2.0%</td>
<td>4.2%</td>
<td>6.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2.8%</td>
<td>3.6%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.9%</td>
<td>2.2%</td>
<td>3.0%</td>
<td>2.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.3%</td>
<td>1.7%</td>
<td>1.7%</td>
<td>1.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>5.9%</td>
<td>4.3%</td>
<td>4.0%</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>5.9%</td>
<td>2.2%</td>
<td>2.1%</td>
<td>2.2%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

References:

Disclaimer:
This information is for educational purposes only and is not intended to replace medical advice from a healthcare professional. Always consult your healthcare provider for guidance on the appropriate use of Celebrex.
BOXED WARNING

Cardiovascular Risk - CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal...

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal anti-inflammatory drugs (NSAIDs) may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.
A quantitative analysis of adverse events and "overwarning" in drug labeling.

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# Common Things Being Common

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Post-Marketing Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (76%)</td>
<td>Angioedema (29%)</td>
</tr>
<tr>
<td>Vomiting (69%)</td>
<td>Stevens-Johnson (24%)</td>
</tr>
<tr>
<td>Headache (66%)</td>
<td>Hypersensitivity (47%)</td>
</tr>
<tr>
<td>Dizziness (63%)</td>
<td>Thrombocytopenia (42%)</td>
</tr>
<tr>
<td>Rash (60%)</td>
<td>Anaphylactic reaction (28%)</td>
</tr>
<tr>
<td>Pruritis (59%)</td>
<td>TEN (21%)</td>
</tr>
<tr>
<td>Diarrhea (57%)</td>
<td>Erythema multiforme (22%)</td>
</tr>
<tr>
<td>Urticaria (51%)</td>
<td>Hepatitis (26%)</td>
</tr>
<tr>
<td>Fever (46%)</td>
<td>Urticaria (51%)</td>
</tr>
</tbody>
</table>
ADEs per Label for 10 Common Drug Classes

- SSRI's: 384
- Atypical Antipsychotics: 241
- 5-HT1 Agonists (Triptans): 227
- Proton Pump Inhibitors: 185
- ACE-Inhibitors: 165
- Statins: 127
- NSAIDs: 121
- Benzodiazepines: 118
- Beta Blockers: 111
- Bisphosphonates: 103
- All Drugs: 70

Mean Number of ADE's per label
Average drug label lists whopping 70 side effects

Lengthy lists meant to protect against lawsuits, but can overwhelm doctors and patients.
Guidance for Industry

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided (see § 201.57(c)(7) and the Glossary at the end of this guidance for a definition of Adverse Reaction). Such lists are not informative and tend to obscure the more clinically meaningful information.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2006
Labeling
Labeled Adverse Reactions by Year of Approval

Labeled ADE's
Enter PENELOPE

Personalized
Exploratory
Navigation &
Evaluation
Of
Labels for
Product
Effects

**Geriatric use**
Clinical studies of baclofen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Selecting drugs may cause confusion and over-sedation in the elderly: elderly patients generally should be started on low doses of KEMSTROBE and observed closely.

**Adverse Reactions**
The most common adverse reaction during treatment with baclofen is transient drowsiness (10-65%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen tablets, compared to 30% of those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (3-15%) and fatigue (2-4%).

Others reported:
- Neurological: Confusion (1-11%), headache (4-8%), somnolence (2-7%) and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, blurred speech, coordination disorder, tremor, rigidity, dyskinesia, ataxia, blurred vision, myasthenia, strabismus, myoclonus, mydriasis, diplopia, dysarthria, epistaxis, seizure.
- Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.
- Gastrointestinal: Nausea (4-12%), constipation (2-6%), and, rarely, dry mouth, nausea, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.
- Genitourinary: Urinary frequency (2-6%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.
- Other: Instances of rash, purpura, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen:
- Increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.
PENELOPE

• PENELOPE leverages OHDSI’s evidence generation and curation tools to provide context to safety information on drug labels
• The nature of this context may differ for different stakeholders (e.g., providers, researchers, patients)
A Big Supporting Cast

ACHILLES: Database profiling

HERMES: Vocabulary exploration

CIRCE: Cohort definition

HERACLES: Cohort characterization

LAERTES: Drug-AE evidence base

PLATO: Patient-level predictive modeling

HOMER: Population-level causality assessment
LAERTES

**Source to Drug Mapping**
- Freetext, ATC -> RxNorm
- MeSH, UMLS -> RxNorm
- SPL Set ID -> RxNorm
- NDC/GenSeq Num -> RxNorm
- NDC/GPI/ATC -> RxNorm

**Evidence Sources**
- Spontaneous adverse event data (FAERS, VigiBase™, ClinicalTrials.gov)
- Literature (PubMed, SemMed)
- Product labeling (SPL, SPC)
- Indications / Contraindications (FDB™)
- Observational healthcare data (claims + EHR)

**Source to HOI Mapping**
- MedDRA -> SNOMED
- MeSH, UMLS -> SNOMED
- Freetext -> MedDRA® -> SNOMED
- ICD-9-CM -> SNOMED
- ICD-9-CM, ICD-10 -> SNOMED

**Conditions (SNOMED)**

**Drug classifications (ATC, NDF-RT)**
Shall We Take a Look?
PENELOPE - it takes a community!

Anthony Sena Janssen

Frank DeFalco Janssen

Rich Boyce UPitt

Matt Levine Columbia

Hamed Abedtash Indiana U

Wen Zhang UPitt

Erica Voss Janssen

Lee Evans LTC Consulting

Patrick Ryan Janssen
Join the journey

Interested in OHDSI?
Questions or comments?