OHDSI Network in Action: The Risk of Angioedema associated with Levetiracetam Use
OHDSI Network Studies
OHDSI Network Studies

Idea
Anyone interested in looking at ASA effects on osteoporosis?

jon_duke

Hi, I'm an endocrinologist at MUNC and have been looking at this question of whether aspirin causes bone loss and can lead to osteoporosis. The data out there are pretty conflicting. Here's the conclusion for a recent review paper.

Despite a positive effect on bone mineral density, the limited human epidemiological studies revealed that aspirin could not reduce fracture risk. A study even suggested that the use of aspirin increased fracture risk. As a conclusion, aspirin may increase bone mineral density but its effect on fracture prevention is inconclusive. More data are needed to determine the effects of aspirin and bone health in human.

Is anyone else interested in taking a look at this?
Anyone working on opioid crisis related projects?

shawndolley

Folks, I am engaging with some stakeholders with funding opportunities for work related to preventing, stopping, understanding the US opioid addiction public health crisis. If anyone here is doing or interested in working in this area, can you let me know at sdolley@cloudera.com or dial 202.460.4660?

May 16

Andrew  Andrew Williams

Hi Shawn
I’m interested in finding out more.
Andrew

May 16

farbodr  Fred R.

I’m interested too. We are in process of setting up OMOP (still a couple of months away). We’ve done some prelim work using claims data for about 800k members. Would love to get involved in something like this.

FR

May 16
Protocols under Development

- Risk of Osteoporosis with Exposure to Aspirin
- Learning Effective Clinical Treatment Pathways from Data
- Investigation of global incidence and outcome of sudden cardiac arrest
- Characterization of Oral Antibiotics for Acne Treatment
- Large-scale modeling of patients with thyroid conditions
- Treatments in cancer
- New Study Template

Protocol

ohdsi.org/web/wiki
< Title of the research study >

**Objective:** *<summarize study objective>*

**Rationale:** *<summarize study rationale>*

**Project Lead(s):** *<initial proposers, list may grow>*

**Coordinating Institution(s):** *<your institution>*

**Additional Participants:** *<usually blank initially, list will grow as individuals are added who are not project leads>*

**Full Protocol:** *<if available, a link to protocol. not necessary for initial planning>*

**Initial Proposal Date:**

**Launch Date:** *<fill out once finalized>*

**Study Closure Date:** *<fill out once finalized>*

**Results Submission:** *<method of submission, eg. Email or SFTP>*

**Requirements**

**CDM:** *<V4 or V5 or both>*

**Table Accessed:** *<e.g., person, drug_exposure, observations>*
OHDSI Network Studies

This repository is for developing study packages for OHDSI studies. Once completed, they can be moved to the StudyProtocols repository.

Preliminary Code

github.com/ohdsi
if (runAnalyses) {
    writeLines("Running analyses")
    cmAnalysisListFile <- system.file("settings",
        "cmAnalysisList.txt",
        package = "AlendronateVsRaloxifene")
    cmAnalysisList <- CohortMethod::loadCmAnalysisList(cmAnalysisListFile)
    drugComparatorOutcomesListFile <- system.file("settings",
        "drugComparatorOutcomesList.txt",
        package = "AlendronateVsRaloxifene")
    drugComparatorOutcomesList <- CohortMethod::loadDrugComparatorOutcomesList(drugComparatorOutcomesListFile)
    CohortMethod::runCmAnalyses(connectionDetails = connectionDetails,
        cdmDatabaseSchema = cdmDatabaseSchema,
        exposureDatabaseSchema = workDatabaseSchema,
        exposureTable = studyCohortTable,
        outcomeDatabaseSchema = workDatabaseSchema,
        outcomeTable = studyCohortTable,
        outputFolder = cmOutputFolder,
        oracleTempSchema = oracleTempSchema,
        cmAnalysisList = cmAnalysisList,
        cdmVersion = 5,
        drugComparatorOutcomesList = drugComparatorOutcomesList,
        getDbCohortMethodDataThreads = 1,
        createStudyPopThreads = min(3, maxCores),
        createPsThreads = 1,
        psCvThreads = min(16, maxCores),
        computeCovarBalThreads = min(3, maxCores),
        trimMatchStratifyThreads = min(10, maxCores),
        fitOutcomeModelThreads = max(1, round(maxCores/4)),
        outcomeCvThreads = min(4, maxCores),
        refitPsForEveryOutcome = FALSE)
OHDSI Network Studies

Repository of OHDSI Collaborative Research Protocols

Add topics

315 commits  5 branches  0 releases  8 contributors

Branch: master  New pull request  Create new file  Upload files  Find file  Clone or download

schuemie Merge pull request #16 from yuxitian/master  Latest commit 0ede1ed8 16 days ago

- AlendronateVsRaloxifene  table for trimming percentage  16 days ago
- AspirinOsteoporosis  Update README.md  2 years ago
- CelecoxibVsNsNSAIDs  Protocol amended and package changed accordingly: fixed some issues ...  a year ago
- CiCalibration  More plots  20 days ago
- DrugsInPeds  Updated drug classification in pediatrics study  4 months ago

Final Code
OHDSI Network Studies

Requirements

- A database in Common Data Model version 5 in one of these platforms: SQL Server, Oracle, PostgreSQL, Amazon RedShift, or Microsoft APS.
- R version 3.2.2 or newer
- On Windows: RTools
- Java
- 100 GB of free disk space

Recommended

- 8 CPU cores or more
- 32 GB of memory or more

How to run

OHDSI Risk of Os

1. Make sure that you have Java installed, and on Windows make sure that RTools is installed. See the OHDSI Wiki for help on setting up your R environment

2. In R, use the following code to install the study package and its dependencies:

Run at Sites
OHDSI Network Studies

Results

![Standardized difference of mean](image1)

<table>
<thead>
<tr>
<th>Source</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS Ambulatory</td>
<td>0.65 (0.31-1.31)</td>
</tr>
<tr>
<td>IMS P-Plus</td>
<td>0.61 (0.42-0.87)</td>
</tr>
<tr>
<td>Optum</td>
<td>0.73 (0.39-1.33)</td>
</tr>
<tr>
<td>Truven CCAE</td>
<td>0.87 (0.49-1.52)</td>
</tr>
<tr>
<td>Truven MDCD</td>
<td>0.43 (0.25-0.72)</td>
</tr>
<tr>
<td>Truven MDCR</td>
<td>0.54 (0.23-1.18)</td>
</tr>
<tr>
<td>UT EMR</td>
<td>0.95 (0.46-1.94)</td>
</tr>
<tr>
<td>Summary</td>
<td>0.64 (0.52-0.79)</td>
</tr>
</tbody>
</table>

![Kaplan-Meier Plot](image2)
Risk of Osteoporosis Associated with Aspirin Use: Findings of the Observational Health Data Sciences and Informatics Research Network

1 Observational Health Data Sciences and Informatics (OHDSI) Consortium
2 Georgia Institute of Technology
3 Janssen Research and Development
4 University of California Los Angeles
5 Columbia University
6 Quintiles-IMS
7 University of Texas Health Science Center at Houston
8 Stanford University

Draft Paper!
OHDSI Network Studies

ORIGINAL ARTICLE

Risk of Osteoporosis with Aspirin Use: Findings of the OHDSI Network

Disseminate!
OHDSI Network Studies

All it takes is an **Idea** to get started.
FDA Highlights a Potential Risk

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) between October - December 2015

| Keppra (levetiracetam) tablet, oral solution, injection | Angioedema | FDA is evaluating the need for regulatory action. |
## What is Levetiracetam?

### Anticonvulsants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Modern approach</th>
<th>Other indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>$Na^+$ channel blocker: binds inactive $Na$ channel, extend inactivation</td>
<td>simple partial, complex partial, secondary generalized (narrow)</td>
<td>bipolar disorder, trigeminal neuralgia</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>$Na^+$ channel blocker: complex actions</td>
<td>simple partial, complex partial, secondary generalized (narrow)</td>
<td>n/a</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>$Na^+$ channel blocker: selective for excitatory neuron NT like glutamate</td>
<td>all seizure types (broad spectrum)</td>
<td>bipolar disorder; antidepressant effects</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>$Ca^{2+}$ channel blocker ($\alpha$ subunit, T type, thalamic)</td>
<td>absence seizures (narrow spectrum)</td>
<td>n/a; just first line for absence seizures</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>$GABA$ antagonist: augments $GABA$ receptor (Cl channel)</td>
<td>simple partial, complex partial, secondary generalized (narrow)</td>
<td>Tremors (similar to primidone for essential tremor)</td>
</tr>
<tr>
<td>Valproate</td>
<td>many; blocks Na, enhance $GABA$, block Ca</td>
<td>all seizure types (broad spectrum)</td>
<td>Migraine prophylaxis, bipolar disorder</td>
</tr>
<tr>
<td>Topiramate</td>
<td>many; blocks Na, enhance $GABA$, block glutamate (NMDA) receptor</td>
<td>all seizure types (broad spectrum)</td>
<td>Migraine prophylaxis</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>unknown or partially known mechanism</td>
<td>simple partial, complex partial, secondary generalized (narrow)</td>
<td>Neuropathic pain, chronic pain</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>unknown or partially known mechanism</td>
<td>simple partial, complex partial, secondary generalized (narrow)</td>
<td>Neuropathic pain; fibromyalgia</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>unknown or partially known mechanism</td>
<td>all seizure types (broad spectrum)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Counts of unique patients by 1st index drug (N = 713,576)

- Levitiracetam
- Lamotrigine
- Phenytoin
- Topiramate
- Valproate
- Oxcarbazepine
- Carbamazepine
- Lacosamide
- Phenobarbital
- Zonisamide
- Primidone
- Clobazam
- Rufinamide
- Ethosuximide
- Felbamate
- Ezogabine
- Tiagabine
- Methsuximide
- Ethotoin
- VGBATRIN
What is Angioedema?
Why is it hard to study?

• Angioedema is very rare
• Hereditary form incidence 1/50000
• Drug-induced angioedema is more common but still rare as we have seen (reported rates with ACE-inhibitors ranging from 2 to 7/1000 person-years)
• Perfect opportunity for a network study!

OHDSI Springs into Action!
Protocol Development

• Transparent protocol development

3 Abstract
This study aims to evaluate angioedema risk in seizure disorder patients exposed to Keppra (levetiracetam) compared with those exposed to phenytoin sodium. A potential link between levetiracetam and angioedema has been recently raised by the Food and Drug Administration in their review of spontaneous reporting data. In this study, we will analyze data from a distributed network using the OHDSI CohortMethod package.

4 Amendments and Updates

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>18 April 2016</td>
<td>Jon Duke</td>
<td>Initial draft</td>
</tr>
<tr>
<td>0.2</td>
<td>30 April 2016</td>
<td>Jon Duke</td>
<td>Added negative controls and updates exclusion criteria</td>
</tr>
<tr>
<td>0.3</td>
<td>2 May 2016</td>
<td>Jon Duke</td>
<td>Updated negative controls</td>
</tr>
<tr>
<td>0.4</td>
<td>3 May 2016</td>
<td>Jon Duke</td>
<td>Additional edits to negative controls</td>
</tr>
<tr>
<td>0.5</td>
<td>17 May 2016</td>
<td>Martijn Schuemie</td>
<td>Updated Methods section</td>
</tr>
</tbody>
</table>
Levetiracetam and Risk of Angioedema in patients with Seizure Disorder

**Objective:** To assess the risk between exposure to Keppra (levetiracetam) and angioedema.

**Rationale:** The Food and Drug Administration (FDA) has recently announced that they are evaluating the need for regulatory action regarding a potential association between exposure to the anti-seizure drug Keppra and angioedema. OHDSI seeks to support evidence generation for questions of importance to FDA and other stakeholders seeking to protect and promote the public's health.

**Project Lead(s):** Jon Duke, Patrick Ryan, Marc Suchard, George Hripcsak, [?Adler], Christian Reich, Yuriy Khoma, Marie-Sophie Schwalm, Yonghui Hu, [Stanford- Juan?], Martijn Schuemie.

**Coordinating Institution(s):** Regenstrief Institute / Georgia Tech

**Participating Institution(s):** Regenstrief Institute, Georgia Tech, Janssen Research and Development, Columbia University, University of California Los Angeles, University of Texas Houston, Stanford University, QuintilesIMS.

**Full Protocol:** Keppra and Angioedema Risk Protocol

**Initial Proposal Date:** 5/3/2016

**Launch Date:** 5/18/2016

**Receive Results for Analysis Date:** 7/15/2016

**Study Closure Date:** 12/1/2016 (Study closed)

**Results Submission:** Via the OHDSI Sharing module embedded in study or via Email.
Code Development

- Leveraged OHDSI CohortMethod R package
- Code tested at 2 sites prior to study start
- All code posted on GitHub
Study Overview

• Retrospective observational new-user cohort study
• Inclusion: Exposure to levetiracetam or phenytoin with prior diagnosis of **seizure disorder**
  – Phenytoin selected because common first-line anti-seizure treatment, no labeled warning for angioedema after 60 yrs on market, PRR <1 for phenytoin and angioedema in FAERS
• Outcome: diagnosis of **angioedema** during the time at risk (per protocol and intent-to-treat)
• Exclusion: <6 months continuous observation prior to exposure, previous dx of angioedema
Study Overview

• PS-matched treatment and comparator cohorts using variable ratio matching
• Cox proportional hazard models to assess HRs
• To identify residual bias, calculated HRs for 100 negative controls in order to compute calibrated p-values for angioedema in each dataset
• Performed meta-analysis if low heterogeneity between databases ($I^2 < .25$) and min residual bias
• Set a nominal type 1 error rate of 5% without adjusting for multiple testing
Study Announced

• Once protocol was completed and the code tested, study was announced on forums

**OHDSI Study: Levetiracetam and Risk of Angioedema in patients with Seizure Disorder**

jon_duke

Good afternoon OHDSI researchers!

We are pleased to announce the official start of the Keppra and Angioedema study! See full details on the wiki including study rationale, protocol, and code.

So far we have participation from UCLA, Columbia University, Regenstrief, and Janssen. We would be delighted for you to join!

If you have any questions, please respond via this thread.

Thanks,

Jon, Martijn, Marc, Patrick, George

• 50 viewed protocol, 25 viewed the code, and 7 sites ran the code on 10 databases (5 claims / 5 EHR)
Cohorts

• Per protocol: 59,367 levetiracetam users matched with 74,550 phenytoin users
  – cumulative follow-up of 11,199,152 and 10,597,206 days respectively

• Intent to treat: 75,056 levetiracetam users matched with 95,598 phenytoin users
  – cumulative observation periods of 80,164,173 and 96,182,651 days respectively
## Per Protocol Results

### Table: Per Protocol Results

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients</th>
<th>Days Treated</th>
<th>Events</th>
<th>Patients</th>
<th>Days Treated</th>
<th>Events</th>
<th>Hazard Ratio (CI)</th>
<th>p-value (calibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS P-Plus</td>
<td>6,893</td>
<td>351,090</td>
<td>2</td>
<td>7,745</td>
<td>398,827</td>
<td>2</td>
<td>1.41 (0.05 - 36.73)</td>
<td>0.83 (0.79)</td>
</tr>
<tr>
<td>Optum</td>
<td>10,819</td>
<td>3,150,504</td>
<td>14</td>
<td>14,115</td>
<td>3,030,739</td>
<td>19</td>
<td>0.69 (0.18 - 2.34)</td>
<td>0.57 (0.62)</td>
</tr>
<tr>
<td>Truven CCAE</td>
<td>13,088</td>
<td>3,549,812</td>
<td>13</td>
<td>16,234</td>
<td>2,962,530</td>
<td>14</td>
<td>0.59 (0.15 - 1.93)</td>
<td>0.41 (0.45)</td>
</tr>
<tr>
<td>Truven MDCD</td>
<td>8,227</td>
<td>1,883,518</td>
<td>15</td>
<td>9,969</td>
<td>1,666,857</td>
<td>19</td>
<td>0.65 (0.20 - 1.91)</td>
<td>0.45 (0.55)</td>
</tr>
<tr>
<td>Truven MDCR</td>
<td>4,592</td>
<td>1,400,797</td>
<td>8</td>
<td>6,433</td>
<td>1,564,355</td>
<td>14</td>
<td>0.96 (0.28 - 3.11)</td>
<td>0.94 (0.94)</td>
</tr>
<tr>
<td>IMS Ambulatory</td>
<td>8,762</td>
<td>618,757</td>
<td>1</td>
<td>10,732</td>
<td>730,158</td>
<td>3</td>
<td>0.00 (0.00 - 1.41)</td>
<td>0.23 (0.23)</td>
</tr>
<tr>
<td>Cerner Health Facts (UT)</td>
<td>5,584</td>
<td>54,852</td>
<td>1</td>
<td>7,624</td>
<td>93,543</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Columbia</td>
<td>501</td>
<td>111,307</td>
<td>0</td>
<td>603</td>
<td>68,251</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>IMS French_EMR</td>
<td>7</td>
<td>552</td>
<td>0</td>
<td>37</td>
<td>2,463</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Stanford EMR</td>
<td>404</td>
<td>12,313</td>
<td>0</td>
<td>460</td>
<td>13,525</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### Graph: Hazard Ratio (95% CI)

- **IMS Ambulatory**: 0.00 (0.00-1.10)
- **IMS P-Plus**: 1.41 (0.05-36.73)
- **Optum**: 0.69 (0.18-2.34)
- **Truven CCAE**: 0.59 (0.15-1.93)
- **Truven MDCD**: 0.65 (0.20-1.91)
- **Truven MDCR**: 0.96 (0.28-3.11)
- **Summary**: 0.72 (0.39-1.31)
# Intent to Treat Results

<table>
<thead>
<tr>
<th>Source</th>
<th>Levetiracetam</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Days Treated</td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMS P-Plus</td>
<td>18,213</td>
<td>16,233,093</td>
</tr>
<tr>
<td>Optum</td>
<td>10,890</td>
<td>9,101,161</td>
</tr>
<tr>
<td>Truven_CCAE</td>
<td>13,434</td>
<td>11,347,801</td>
</tr>
<tr>
<td>Truven_MDCD</td>
<td>8,536</td>
<td>7,328,658</td>
</tr>
<tr>
<td>Truven_MDCR</td>
<td>4,656</td>
<td>4,317,982</td>
</tr>
<tr>
<td>IMS Ambulatory</td>
<td>8,762</td>
<td>9,978,497</td>
</tr>
<tr>
<td>Cerner Health Facts (UT)</td>
<td>9,094</td>
<td>5,842,344</td>
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<tr>
<td>Columbia</td>
<td>553</td>
<td>523,215</td>
</tr>
<tr>
<td>IMS French_EMR</td>
<td>7</td>
<td>5,542</td>
</tr>
<tr>
<td>Stanford EMR</td>
<td>404</td>
<td>342,136</td>
</tr>
</tbody>
</table>

## Hazard Ratio Plots

![Hazard Ratio Plot](image)
Summary

• No evidence of increased angioedema risk with levetiracetam use compared with phenytoin use

• Results were consistent across datasets including both claims and EHR data

• Further analysis of phenytoin angioedema risk and risk across all anti-epileptic drugs is warranted
“Using a large international health care data network, the authors have measured angioedema risk in patients exposed to levetiracetam and compared this to the risk patients exposed to phenytoin. The study is focused, appears well designed, and provides new insight that should be of interest to clinicians and regulators.”

“Well conducted study with an impressive data material that you were able to combine these databases. This is an important contribution to improved pharmacovigilance.”
Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network

*†Jon D. Duke, *‡§Patrick B. Ryan, *¶Marc A. Suchard, *§George Hripcsak, *§Peng Jin, *#Christian Reich, *#Marie-Sophie Schwalm, ***††Yuriy Khoma, *‡‡Yonghui Wu, *‡‡Hua Xu, *§§Nigam H. Shah, *§§Juan M. Banda, and *‡Martijn J. Schuemie