Large-scale analysis to transform the evidence generation process: lessons from the Observational Health Data Sciences and Informatics (OHDSI) collaborative

Patrick Ryan, PhD
Janssen Research and Development
Columbia University Medical Center
18 September 2017
Introducing OHDSI

• The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics

• OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University

http://ohdsi.org
OHDSI’s mission

To improve health, by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

http://ohdsi.org
OHDSI: an open science community

OHDSI Collaborators:
• >200 researchers in academia, industry, government, health systems
• >20 countries
• Multi-disciplinary expertise: epidemiology, statistics, medical informatics, computer science, machine learning, clinical sciences

Databases converted to OMOP CDM within OHDSI Community:
• >60 databases
• >660 million patients

European OHDSI Symposium
Bridging Europe
23-24th March 2018, Rotterdam, The Netherlands
Common data model to structure observational data and enable standardized analytics

- **Person**
  - Observation_period
  - Specimen
  - Death

- **Standardized clinical data**
  - Visit_occurrence
  - Procedure_occurrence
  - Drug_exposure
  - Device_exposure
  - Condition_occurrence
  - Measurement
  - Note
  - Observation
  - Fact_relationship

- **Standardized health system data**
  - Location
  - Care_site
  - Provider
  - Payer_plan_period
  - Cost

- **Standardized meta-data**
  - CDM_source

- **Standardized derived elements**
  - Cohort
  - Cohort_attribute
  - Condition_era
  - Drug_era
  - Dose_era

- **Standardized vocabularies**
  - Concept
  - Vocabulary
  - Domain
  - Concept_class
  - Concept_relationship
  - Relationship
  - Concept_synonym
  - Concept_ancestor
  - Source_to_concept_map
  - Drug_strength
  - Cohort_definition
  - Attribute_definition
Common data model to enable standardized analytics

Source 1 raw data
- Electronic health records
  - VA
  - PEDSNet
  - CPRD

Source 2 raw data
- Administrative claims
  - Optum
  - Truven
  - IMS

Source 3 raw data
- Clinical data
  - SEER
  - NHANES
  - BTRIS

Transformation to OMOP common data model

Source 1 CDM

Source 2 CDM

Source 3 CDM

Open-source analysis code

Open evidence
What is OHDSI’s strategy to deliver reliable evidence?

• **Methodological research**
  - Develop new approaches to observational data analysis
  - Evaluate the performance of new and existing methods
  - Establish empirically-based scientific best practices

• **Open-source analytics development**
  - Design tools for data transformation and standardization
  - Implement statistical methods for large-scale analytics
  - Build interactive visualization for evidence exploration

• **Clinical evidence generation**
  - Identify clinically-relevant questions that require real-world evidence
  - Execute research studies by applying scientific best practices through open-source tools across the OHDSI international data network
  - Promote open-science strategies for transparent study design and evidence dissemination
Classifying questions across the patient journey

- **Clinical characterization:** What happened to them?
  - What treatment did they choose after diagnosis?
  - Which patients chose which treatments?
  - How many patients experienced the outcome after treatment?

- **Patient-level prediction:** What will happen to me?
  - What is the probability that I will develop the disease?
  - What is the probability that I will experience the outcome?

- **Population-level effect estimation:** What are the causal effects?
  - Does treatment cause outcome?
  - Does one treatment cause the outcome more than an alternative?
“Now what is the message there? The message is that there are no "knowns." There are things we know that we know. There are known unknowns. That is to say there are things that we now know we don't know. But there are also unknown unknowns. There are things we do not know we don't know. So when we do the best we can and we pull all this information together, and we then say well that's basically what we see as the situation, that is really only the known knowns and the known unknowns. And each year, we discover a few more of those unknown unknowns.

It sounds like a riddle. It isn't a riddle. It is a very serious, important matter.

There's another way to phrase that and that is that the absence of evidence is not evidence of absence. It is basically saying the same thing in a different way. Simply because you do not have evidence that something exists does not mean that you have evidence that it doesn't exist.”
“Things we know that we know”

• What we think we know:
  – ACE inhibitors cause angioedema

• What we want to know:
  – Clinical characterization: Incidence of angioedema in patients exposed to ACE inhibitors
  – Population-level effect estimation:
    • Safety surveillance: Strength of association with ACE inhibitor vs. counterfactual
    • Comparative effectiveness: Strength of association with ACE inhibitor, relative to alternative treatments
  – Patient-level prediction: Probability that a patient will experience event, given baseline characteristics
ANGIOEDEMA: Angioedema has been reported in patients receiving lisinopril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with lisinopril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)
What’s the published evidence?

Incidence rate estimate predicated on 2 assumptions:
- Observed data represents a random sample of a target population
- Estimator in unbiased, so no systematic error

<table>
<thead>
<tr>
<th>Publication</th>
<th>Person-years</th>
<th>Events</th>
<th>Incidence (per 1000 person-years)</th>
<th>95% CI (Incidence rate per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller Hypertension 2008</td>
<td>179,088</td>
<td>352</td>
<td>1.97 (1.76-2.17)</td>
<td></td>
</tr>
<tr>
<td>Makani Am J Cardiol. 2012</td>
<td>185,067</td>
<td>394</td>
<td>3.00 (2.80-3.20)</td>
<td></td>
</tr>
<tr>
<td>Toh AIM 2012</td>
<td>753,105</td>
<td>3,301</td>
<td>4.38 (4.23-4.53)</td>
<td></td>
</tr>
</tbody>
</table>
How does it get distilled to clinicians?

The overall incidence of angioedema related to ACE inhibitors has been estimated between 0.1 percent and 0.7 percent. However, the lower end of this range may overlap with the background rate of angioedema in the general population. In the TRANSCEND trial of ACE inhibitor-intolerant individuals given an angiotensin II receptor blocker (ARB) or placebo, rates of angioedema were 0.07 and 0.1 percent in the ARB and placebo groups, respectively.
Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houotn, PharmD; Mary Ross Southworth, Pha Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey Azadeh Shoaii, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, Pharm

Background: Although certain drugs that target the renin-angiotensin-aldosterone system are linked to an increased risk for angioedema, data on their absolute and comparative risks are limited. We assessed the risk for angioedema associated with the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and the direct renin inhibitor aliskiren.

Methods: We conducted a retrospective, observational, inception cohort study of patients 18 years or older from 17 health plans participating in the Mini-Sentinel program who had initiated the use of an ACEI (n = 1845 138), an ARB (n = 467 313), aliskiren (n = 4867), or a β-blocker (n = 1 592 278) between January 1, 2001, and December 31, 2010. We calculated the cumulative incidence and incidence rate of angioedema during a maximal 365-day follow-up period. Using β-blockers as a reference and a propensity score approach, we estimated the hazard ratios of angioedema separately for ACEIs, ARBs, and aliskiren, adjusting for age, sex, history of allergic reactions, diabetes mellitus, heart failure, or ischemic heart disease, and the use of prescription nonsteroidal anti-inflammatory drugs.

Results: A total of 4511 angioedema ACEIs, 288 for ARBs, 7 for aliskiren, and 19 for others) were observed during the follow-up cumulative incidences per 1000 persons CI, 1.73-1.85) cases for ACEIs, 0.62 (95% CI, 0.69) cases for ARBs, 1.44 (95% CI, 0.58-2.96) cases for aliskiren, and 0.58 (95% CI, 0.50-2.61) cases for β-blockers. The incidence rates per 1000 person-years were 4.38 (95% CI, 4.24-4.54) cases for ACEIs, 1.66 (95% CI, 1.47-1.86) cases for ARBs, 4.67 (95% CI, 1.88-9.03) cases for aliskiren, and 1.67 (95% CI, 1.56-1.78) cases for β-blockers. Compared with the use of β-blockers, the adjusted hazard ratios were 3.04 (95% CI, 2.81-3.27) for ACEIs, 1.16 (95% CI, 1.00-1.34) for ARBs, and 2.85 (95% CI, 1.34-6.04) for aliskiren.

Conclusions: Compared with β-blockers, ACEIs or aliskiren was associated with an approximately 3-fold higher risk for angioedema, although the number of exposed events for aliskiren was small. The risk for angioedema was lower with ARBs than with ACEIs or aliskiren.

Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association

JJ Gagne\(^1\), X Han\(^2\), S Hennessy\(^2\), CE Leonard\(^2\), EA Chrischilles\(^3\), RM Carnahan\(^3\), SV Wang\(^1\), C Fuller\(^4\), A Iyer\(^4\), H Katcoff\(^3\), TS Woodworth\(^4\), P Archdeacon\(^5\), TE Meyer\(^6\), S Schneeweiss\(^1\) and S Toh\(^4\)

The US Food and Drug Administration’s Sentinel system has developed the capability to conduct active safety surveillance of marketed medical products in a large network of electronic healthcare databases. We assessed the extent to which the newly developed, semiautomated Sentinel Propensity Score Matching (PSM) tool could produce the same results as a customized protocol-driven assessment, which found an adjusted hazard ratio (HR) of 3.04 (95% confidence interval [CI], 2.81–3.27) comparing angioedema in patients initiating angiotensin-converting enzyme (ACE) inhibitors vs. beta-blockers. Using data from 13 Data Partners between 1 January 2008, and 30 September 2013, the PSM tool identified 2,211,215 eligible ACE inhibitor and 1,673,682 eligible beta-blocker initiators. The tool produced an HR of 3.14 (95% CI, 2.86–3.44). This comparison provides initial evidence that Sentinel analytic tools can produce findings similar to those produced by a highly customized protocol-driven assessment.

<table>
<thead>
<tr>
<th>Table 3 Results by analysis type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Unmatched Analysis (Data Partner-adjusted only)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
</tbody>
</table>
Comparing incidence rate estimates between Sentinel analyses

Overlap coefficient = 19%
“Known unknowns”
“Known unknowns” #1: Do PPIs increase risk of death?

ABSTRACT
Objective Proton pump inhibitors (PPIs) are widely used, and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown. We aimed to examine the association between PPI use and risk of all-cause mortality.

Design Longitudinal observational cohort study
Setting US Department of Veterans Affairs Medical Centers
Primary cohort patients with peptic ulcer disease (n=349,312); additional cohort patients with osteoporotic fractures (n=3,288,092) and PPI users (n=397,030).

Main outcome measures
Results Over a median follow-up of 5.1 (IQR 3.4–6.37), PPI use was associated with an increased risk of death compared with H2 blockers (HR 1.16, CI 1.13 to 1.20) and no PPI use. H2 blocker use was associated with a decreased risk of death compared with no PPI use (HR 1.06, CI 1.03 to 1.09). The relationship between PPI use and risk of death was modified by age, sex, and comorbid conditions.

Conclusions The results suggest a potential association between PPI use and increased risk of death.
“Known unknowns” #1: Do PPIs increase risk of death?

Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans

Yan Xie,1 Benjamin Bowe,1 Tingting Li,1,2 Hong Xian,1,3 Yan Yan,1,4 Ziyad Al-Aly1,2,5,6

ABSTRACT
Objective Proton pump inhibitors (PPIs) have been widely used to treat gastrointestinal conditions. However, the effect of PPI use on long-term outcomes is not well understood.

Design A longitudinal observational cohort study of veterans in the United States.

Setting The US Department of Veterans Affairs.

Participants Primary cohort was veterans aged 65 years or older with a prescription for a PPI during the study period (n=54,931) and a comparison cohort matched on age, sex, and index date (n=54,931).

Main outcome measures Risk of death.

Results Over a median follow-up of 5.7 years (IQR 5.1–6.3), PPI use was associated with increased risk of death compared with H2 blockers (HR 1.25, CI 1.23 to 1.26). Risk of death associated with PPI use was higher in analyses adjusted for high-dimensional propensity score (HR 1.16, CI 1.13 to 1.18) in two-stage residual inclusion estimation (HR 1.21, CI 1.18 to 1.24) in a 1:1 time-dependent propensity score–matched cohort (HR 1.34, CI 1.29 to 1.39). The risk of death was increased when considering PPI use versus no PPI (HR 1.15, CI 1.14 to 1.15), and PPI use versus no PPI and no H2 blockers (HR 1.23, CI 1.22 to 1.24).

Conclusions The results suggest excess risk of death associated with PPI use among participants without gastrointestinal conditions. PPI use versus H2 blockers (HR 1.24, CI 1.21 to 1.27), PPI use versus no PPI (HR 1.19, CI 1.18 to 1.20) and PPI use versus no PPI and no H2 blockers (HR 1.23, CI 1.22 to 1.24). Risk of death associated with PPI use was increased among participants without gastrointestinal conditions. PPI use versus H2 blockers (HR 1.24, CI 1.21 to 1.27), PPI use versus no PPI (HR 1.19, CI 1.18 to 1.20) and PPI use versus no PPI and no H2 blockers (HR 1.23, CI 1.22 to 1.24). Among new PPI users, there was a graded association between the duration of exposure and the risk of death.

A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis.1,9 Recent studies established an association between exposure to PPI and risk of chronic kidney disease (CKD), kidney disease progression, and end-stage renal disease.1,2 Several observational analyses have shown that PPI use was associated with increased risk of both incident and recurrent Clostridium difficile infections.12 Several observational analyses have shown that PPI use was also associated with increased risk of osteoporotic fractures, including hip and
“Known unknowns” #1: Do PPIs increase risk of death?

- Sensitivity analyses yield non-overlapping confidence intervals
- What ‘interval’ would you need to see to adequately represent the uncertainty?
Some heartburn drugs linked with higher risk of death

Heartburn drugs tied to increased risk of early death, study says

By Susan Scutti, CNN
Updated 2:59 PM ET, Tue July 4, 2017

Proton pump inhibitors, used by millions, observational study suggests.

Drugs

People taking heartburn drugs could have higher risk of death, study claims

Research suggests people on proton pump inhibitors are more likely to die than those taking different antacid or none at all.
“Known unknowns” #2: Levetiracetam and Angioedema

FDA is evaluating the need for regulatory action.

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

<table>
<thead>
<tr>
<th>Product Name: Trade (Active Ingredient) or Product Class</th>
<th>Potential Signal of a Serious New Safety Information</th>
<th>Risk / Additional Information (as of March 31, 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium gluconate injection</td>
<td>Potential for wrong drug error</td>
<td>The container labels for calcium gluconate were revised to better differentiate the product from sterile water for injection. Calcium gluconate labeling</td>
</tr>
<tr>
<td>Epinephrine auto-injectors</td>
<td>Clostridium perfringens infection</td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Epipen (epinephrine) injection</td>
<td>Lacerations and embedded needles</td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Epipen Jr (epinephrine) injection</td>
<td></td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Harvoni (ledipasvir/sofosbuvir) tablet</td>
<td>Rhabdomyolysis</td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Olysio (simeprevir) capsule</td>
<td></td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Sovaddi (sofosbuvir) tablet</td>
<td></td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Iodinated contrast agents (numerous products)</td>
<td>Malignancy</td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
<tr>
<td>Keppra (levetiracetam) tablet, oral solution, injection</td>
<td>Angioedema</td>
<td>FDA is evaluating the need for regulatory action.</td>
</tr>
</tbody>
</table>

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm491645.htm
**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.
Open-source code development

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

• New user comparative cohort design
  – T: levetiracetam
  – C: phenytoin
  – O: incident angioedema

• Time at risk defined in two ways: 1) per protocol and 2) intent to treat

• Model: Propensity score-matched Cox proportional hazards

• 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 and evaluated heterogeneity between databases
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

_Epilepsia_ **(*):1–6, 2017
doi: 10.1111/epi.13828

**SUMMARY**

Recent adverse event reports have raised the question of increased angioedema risk associated with exposure to levetiracetam. To help address this question, the Observational Health Data Sciences and Informatics research network conducted a retrospective observational new-user cohort study of seizure patients exposed to levetiracetam (n = 276,665) across 10 databases. With phenytoin users (n = 74,682) as a comparator group, propensity score-matching was conducted and hazard ratios computed for angioedema events by per-protocol and intent-to-treat analyses. Angioedema events were rare in both the levetiracetam and phenytoin groups (54 vs. 71 in per-protocol and 248 vs. 435 in intent-to-treat). No significant increase in angioedema risk with levetiracetam was seen in any individual database (hazard ratios ranging from 0.43 to 1.31). Meta-analysis showed a summary hazard ratio of 0.72 (95% confidence interval [CI] 0.39–1.31) and 0.64 (95% CI 0.52–0.79) for the per-protocol and intent-to-treat analyses, respectively. The results suggest that levetiracetam has the same or lower risk for angioedema than phenytoin, which does not currently carry a labeled warning for angioedema. Further studies are warranted to evaluate angioedema risk across all antiepileptic drugs.
Illustrating the value of a global network study

- >55,000 patients exposed across 10 sites
- Quantify observed incidence of event for public health impact
- Population-level effect estimation provides strength and consistency toward causality assessment (which couldn’t have been done by any one site alone)

### Table 1. Angioedema events in propensity score-matched levetiracetam and phenytoin exposed patients using per-protocol analysis and intent-to-treat analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients</th>
<th>Days treated</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMS P-Plus</td>
<td>6,893</td>
<td>351,090</td>
<td>2</td>
</tr>
<tr>
<td>Optum Clinformatics</td>
<td>10,819</td>
<td>3,150,504</td>
<td>14</td>
</tr>
<tr>
<td>Truven CCAE</td>
<td>13,088</td>
<td>3,549,812</td>
<td>13</td>
</tr>
<tr>
<td>Truven MDCD</td>
<td>8,227</td>
<td>1,883,518</td>
<td>15</td>
</tr>
<tr>
<td>Truven MDCR</td>
<td>4,592</td>
<td>1,400,797</td>
<td>8</td>
</tr>
<tr>
<td>IMS Ambulatory</td>
<td>8,762</td>
<td>618,757</td>
<td>1</td>
</tr>
<tr>
<td>Cerner Health Facts (UT)</td>
<td>5,584</td>
<td>54,852</td>
<td>1</td>
</tr>
<tr>
<td>Columbia</td>
<td>501</td>
<td>111,307</td>
<td>0</td>
</tr>
<tr>
<td>IMS French EMR</td>
<td>7</td>
<td>552</td>
<td>0</td>
</tr>
<tr>
<td>Stanford EMR</td>
<td>404</td>
<td>12,313</td>
<td>0</td>
</tr>
<tr>
<td>IMS P-Plus</td>
<td>18,213</td>
<td>16,233,093</td>
<td>78</td>
</tr>
<tr>
<td>Optum Clinformatics</td>
<td>10,890</td>
<td>9,101,161</td>
<td>31</td>
</tr>
<tr>
<td>Truven CCAE</td>
<td>13,434</td>
<td>11,347,801</td>
<td>41</td>
</tr>
<tr>
<td>Truven MDCD</td>
<td>8,536</td>
<td>7,328,658</td>
<td>41</td>
</tr>
<tr>
<td>Truven MDCR</td>
<td>4,656</td>
<td>4,317,982</td>
<td>15</td>
</tr>
<tr>
<td>IMS Ambulatory</td>
<td>8,762</td>
<td>9,978,497</td>
<td>19</td>
</tr>
<tr>
<td>Cerner Health Facts (UT)</td>
<td>9,094</td>
<td>5,842,344</td>
<td>22</td>
</tr>
<tr>
<td>Columbia</td>
<td>553</td>
<td>523,215</td>
<td>1</td>
</tr>
<tr>
<td>IMS French EMR</td>
<td>7</td>
<td>5,542</td>
<td>0</td>
</tr>
<tr>
<td>Stanford EMR</td>
<td>404</td>
<td>342,136</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol</td>
<td></td>
</tr>
<tr>
<td>IMS Ambulatory</td>
<td>0.00 (0.00-1.10)</td>
</tr>
<tr>
<td>IMS P-Plus</td>
<td>1.41 (0.05-36.73)</td>
</tr>
<tr>
<td>Optum</td>
<td>0.69 (0.18-2.34)</td>
</tr>
<tr>
<td>Truven CCAE</td>
<td>0.59 (0.15-1.93)</td>
</tr>
<tr>
<td>Truven MDCD</td>
<td>0.65 (0.20-1.91)</td>
</tr>
<tr>
<td>Truven MDCR</td>
<td>0.96 (0.28-3.11)</td>
</tr>
<tr>
<td>Summary</td>
<td>0.72 (0.39-1.31)</td>
</tr>
</tbody>
</table>

| Intent-to-Treat         |                       |
|-------------------------|                       |
| IMS Ambulatory          | 0.65 (0.31-1.31)      |
| IMS P-Plus              | 0.61 (0.42-0.87)      |
| Optum                   | 0.73 (0.39-1.33)      |
| Truven CCAE             | 0.87 (0.49-1.52)      |
| Truven MDCD             | 0.43 (0.25-0.72)      |
| Truven MDCR             | 0.54 (0.23-1.18)      |
| UT EMR                  | 0.95 (0.46-1.94)      |
| Summary                 | 0.64 (0.52-0.79)      |
“those unknown unknowns”

A framing of a goal for a ‘risk identification’ system:

- Known unknowns
  - known effects
  - known non-effects

Unknown unknowns
Existing evidence in published literature

- Depression
- Seizures
- Myocardial Infarction
- Renal Insufficiency
- Thrombocytopenia
- Drug Eruptions
- Neutropenia
- Pancreatitis
- Chemical and Drug Induced...
- Anaphylaxis
- Confusion
- Gastrointestinal Hemorrhage
- Peripheral Nervous System...
- Bipolar Disorder
- Rhabdomyolysis
- Long QT Syndrome
- Venous Thrombosis
- Suicide
- Anemia, Hemolytic
- Pancytopenia
- Anemia, Aplastic
- Amnesia
- Dyskinesias

CO_OCCURRENCE W/ QUALIFIERS
CO-OCCURRENCE
BROAD
HOMER implementation of Hill’s viewpoints

- Consistency
- Temporality
- Strength
- Plausibility
- Experiment
- Analogy
- Biological gradient
- Specificity
- Comparative effectiveness
- Coherence
- Predictive modeling

Ryan OMOP Symposium 2013
Potential uses of a public ‘big data’ evidence generation system

- Clinical characterization: descriptive summary to put real-world context around treatment utilization
  - Demographics
  - Prior conditions
  - Prior health service utilization (drugs, procedures, measurements)
- Outcome incidence: descriptive summary of frequency that outcomes occur during or after exposure
- Population-level effect estimation
  - Monitor known risks
  - Search for event known to be on label to estimate incidence and magnitude of effect
  - Compare risk of known effect between alternative treatments
  - Search for effects for potential risk
  - Explore outcomes that show increased effects across databases
  - Explore outcomes that are ‘high incidence’ and ‘high seriousness’
Questions?

Join the journey!
http://ohdsi.org

OHDSI Symposium 2017
18 October 2017
Bethesda, MD, USA

ryan@ohdsi.org