An Open Science Community Approach to Observational Research: Lessons from the Observational Health Data Sciences and Informatics (OHDSI) collaborative

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Janssen Research and Development
Columbia University Medical Center
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Atypical Antipsychotic Drugs and the Risk for Acute Kidney Injury and Other Adverse Outcomes in Older Adults

A Population-Based Cohort Study

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**Background:** Several adverse outcomes attributed to atypical antipsychotic drugs, specifically quetiapine, risperidone, and olanzapine, are known to cause acute kidney injury (AKI). Such outcomes include hypotension, acute urinary retention, and the neuroleptic malignant syndrome or rhabdomyolysis.

**Objective:** To investigate the risk for AKI and other adverse outcomes associated with use of atypical antipsychotic drugs versus nonuse.

**Design:** Population-based cohort study.

**Setting:** Ontario, Canada, from 2003 to 2012.

**Patients:** Adults aged 65 years or older who received a new outpatient prescription for an oral atypical antipsychotic drug (n = 97,777) matched 1:1 with those who did not receive such a prescription.

**Measurements:** The primary outcome was hospitalization with AKI (assessed by using a hospital diagnosis code and, in a subpopulation, serum creatinine levels) within 90 days of prescription for atypical antipsychotic drugs.

**Results:** Atypical antipsychotic drug use versus nonuse was associated with a higher risk for hospitalization with AKI (relative risk [RR], 1.73 [95% CI, 1.55 to 1.92]). This association was consistent when AKI was assessed in a subpopulation for which information on serum creatinine levels was available (5.46% vs. 3.34%; RR, 1.70 [CI, 1.22 to 2.38]; absolute risk increase, 2.12% [CI, 0.80% to 3.43%]). Drug use was also associated with hypotension (RR, 1.91 [CI, 1.60 to 2.28]), acute urinary retention (RR, 1.98 [CI, 1.63 to 2.40]), and all-cause mortality (RR, 2.39 [CI, 2.28 to 2.50]).

**Limitation:** Only older adults were included in the study.

**Conclusion:** Atypical antipsychotic drug use is associated with an increased risk for AKI and other adverse outcomes that may explain the observed association with AKI. The findings support current safety concerns about the use of these drugs in older adults.

**Primary Funding Source:** Academic Medical Organization of Southwestern Ontario.


For author affiliations, see end of text.
### Table 1. 90-Day Risk for Hospitalization With AKI and Other Adverse Outcomes and All-Cause Mortality in Antipsychotic Drug Recipients and Nonrecipients After the Index Date

<table>
<thead>
<tr>
<th>Variable</th>
<th>Drug Recipients (n = 97,777)</th>
<th>Nonrecipients (n = 97,777)</th>
<th>Relative Risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>1002 (1.02)</td>
<td>602 (0.62)</td>
<td>1.73 (1.55–1.92)</td>
</tr>
<tr>
<td>Other adverse outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>384 (0.39)</td>
<td>215 (0.22)</td>
<td>1.91 (1.60–2.28)</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>329 (0.34)</td>
<td>170 (0.17)</td>
<td>1.98 (1.63–2.40)</td>
</tr>
<tr>
<td>The neuroleptic malignant syndrome or rhabdomyolysis</td>
<td>99 (0.10)</td>
<td>69 (0.07)</td>
<td>1.36 (0.96–1.92)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1692 (1.73)</td>
<td>1137 (1.16)</td>
<td>1.50 (1.39–1.62)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>652 (0.67)</td>
<td>492 (0.50)</td>
<td>1.36 (1.20–1.53)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>214 (0.22)</td>
<td>151 (0.15)</td>
<td>1.47 (1.18–1.82)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6666 (6.82)</td>
<td>2985 (3.05)</td>
<td>2.39 (2.28–2.50)</td>
</tr>
</tbody>
</table>

How many people believe this ‘signal’ is real?

Hwang et al, AIM, 2014
<table>
<thead>
<tr>
<th>90-Day hospitalization event</th>
<th>Model</th>
<th>Exposure events, n (%)</th>
<th>Comparator events, n (%)</th>
<th>OR</th>
<th>95% CI</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>Hwang effect estimate</td>
<td>1002 (1.02)</td>
<td>602 (0.62)</td>
<td>1.73</td>
<td>1.55–1.92</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>1043 (1.07)</td>
<td>717 (0.74)</td>
<td>1.45</td>
<td>1.32–1.60</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Hwang effect estimate</td>
<td>384 (0.39)</td>
<td>215 (0.22)</td>
<td>1.91</td>
<td>1.60–2.28</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>686 (0.73)</td>
<td>420 (0.45)</td>
<td>1.63</td>
<td>1.45–1.85</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>Hwang effect estimate</td>
<td>329 (0.34)</td>
<td>170 (0.17)</td>
<td>1.98</td>
<td>1.63–2.40</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>322 (0.34)</td>
<td>197 (0.21)</td>
<td>1.63</td>
<td>1.37–1.95</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Neuroleptic malignant</td>
<td>Hwang effect estimate</td>
<td>99 (0.10)</td>
<td>69 (0.07)</td>
<td>1.36</td>
<td>0.96–1.62</td>
<td>NS</td>
</tr>
<tr>
<td>syndrome or rhabdomyolysis</td>
<td>Replication</td>
<td>89 (0.09)</td>
<td>33 (0.03)</td>
<td>2.70</td>
<td>1.83–4.08</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Hwang effect estimate</td>
<td>1692 (1.73)</td>
<td>1137 (1.16)</td>
<td>1.50</td>
<td>1.39–1.62</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>1623 (1.85)</td>
<td>1061 (1.21)</td>
<td>1.53</td>
<td>1.42–1.65</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Hwang effect estimate</td>
<td>652 (0.67)</td>
<td>492 (0.50)</td>
<td>1.36</td>
<td>1.20–1.53</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>431 (0.46)</td>
<td>365 (0.39)</td>
<td>1.18</td>
<td>1.03–1.36</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>Hwang effect estimate</td>
<td>214 (0.22)</td>
<td>151 (0.15)</td>
<td>1.47</td>
<td>1.18–1.82</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Replication</td>
<td>189 (0.20)</td>
<td>153 (0.16)</td>
<td>1.24</td>
<td>0.999–10.53</td>
<td>0.05</td>
</tr>
<tr>
<td>Death (in-hospital)</td>
<td>Hwang effect estimate</td>
<td>6666 (6.82)</td>
<td>2985 (3.05)</td>
<td>2.39</td>
<td>2.28–2.50</td>
<td>NS</td>
</tr>
</tbody>
</table>

How about now?
How does this new ‘signal’ on a different outcome (fracture) impact your thinking on the original outcome (AKI)?
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis</th>
<th>Exposure Events, n (%)</th>
<th>Comparator Events, n (%)</th>
<th>OR</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip, pelvic, humerus, or radius fracture</td>
<td>Fraser et al¹</td>
<td>2462 (2.5)</td>
<td>161 (1.7)</td>
<td>1.51</td>
<td>1.41–1.60</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Emulation</td>
<td>1271 (1.48)</td>
<td>853 (1.00)</td>
<td>1.49</td>
<td>1.37–1.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Fraser et al¹</td>
<td>1459 (1.5)</td>
<td>883 (0.9)</td>
<td>1.67</td>
<td>1.53–1.81</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Emulation</td>
<td>858 (0.94)</td>
<td>539 (0.59)</td>
<td>1.59</td>
<td>1.43–1.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any fracture</td>
<td>Fraser et al¹</td>
<td>6886 (7.0)</td>
<td>5429 (5.5)</td>
<td>1.29</td>
<td>1.24–1.34</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Emulation</td>
<td>1892 (2.52)</td>
<td>1437 (1.91)</td>
<td>1.32</td>
<td>1.23–1.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospitalization for fall</td>
<td>Fraser et al¹</td>
<td>4314 (4.4)</td>
<td>2858 (2.9)</td>
<td>1.54</td>
<td>1.47–1.61</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Emulation</td>
<td>133 (0.14)</td>
<td>92 (0.10)</td>
<td>1.45</td>
<td>1.11–1.89</td>
<td>0.01</td>
</tr>
</tbody>
</table>
What if we applied the same study design to outcomes we know shouldn’t be associated with exposure?

Example candidate negative control outcomes:
• Contact dermatitis
• Foot deformity
• Iron deficiency anemia
• Osteoarthritis
• Tuberculosis testing
How does these new ‘signals’ on different outcomes (negative controls) impact your thinking on the original outcome (AKI)?
If I mix together the estimates of the ‘AKI-related effects’ with the ‘negative control outcomes’, can you figure out which is which?
Study design, alternative comparator: new user of different drug

Target cohort
- >180d of prior observation
- 180d for baseline covariates in PS and matching
- >180d of no antipsychotic use
- No prior evidence of ESRD or AKI
- >=1 mental health visit in prior 90d

Comparator cohort
- >180d of prior observation
- 180d for baseline covariates in PS and matching
- >180d of no antipsychotic use
- No prior evidence of ESRD or AKI
- >=1 mental health visit in prior 90d

Oral antipsychotic dispensing
- >90d of follow-up observation
- >=90d time-at-risk to observe outcome

No concomitant antipsychotics; no hospital discharge +/- 2d from index

Random index date
- New use of different drug
- >=1 drug in 90d prior to index

No hospital discharge +/- 2d from index

Random index date
- >=1 drug in 90d prior to index

>=90d time-at-risk to observe outcome

No hospital discharge +/- 2d from index

No prior evidence of ESRD or AKI
- No concomitant antipsychotics; no hospital discharge +/- 2d from index

Random index date
- >=1 drug in 90d prior to index

>=90d time-at-risk to observe outcome

No hospital discharge +/- 2d from index

No prior evidence of ESRD or AKI
- No concomitant antipsychotics; no hospital discharge +/- 2d from index

Random index date
- >=1 drug in 90d prior to index

>=90d time-at-risk to observe outcome

No hospital discharge +/- 2d from index
Atypical Antipsychotics and the Risks of Acute Kidney Injury and Related Outcomes Among Older Adults: A Replication Analysis and an Evaluation of Adapted Confounding Control Strategies

Patrick B. Ryan¹ · Martijn J. Schuemie¹ · Darmendra Ramcharran¹ · Paul E. Stang¹
A caricature of the patient journey
Each observational database is just an (incomplete) compilation of patient journeys.
Questions asked across the patient journey

- Which treatment did patients choose after diagnosis?
- Which patients chose which treatments?
- How many patients experienced the outcome after treatment?
- Does one treatment cause the outcome more than an alternative?
- Does treatment cause outcome?
- What is the probability I will develop the disease?
- What is the probability I will experience the outcome?
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?
Complementary evidence to inform the patient journey

Clinical characterization: What happened to them?

Patient-level prediction: What will happen to me?

Observation

Inference

Population-level effect estimation: What are the causal effects?

Causal inference
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
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
OHDSI Collaborators:
- >140 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:
- >50 databases
- >660 million patients
One common data model to support multiple use cases

- Person
- Observation_period
- Specimen
- Death
- 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
- Cohort
- Cohort_attribute
- Condition_era
- Drug_era
- Dose_era
- Source_to_concept_map
- Concept
- Vocabulary
- Domain
- Concept_class
- Concept_relationship
- Relationship
- Concept_synonym
- Concept_ancestor
- Standardized derived elements
- Standardized meta-data
- CDM_source
- Standardized vocabularies
- Attribute_definition
Complementary evidence to inform the patient journey

Clinical characterization: What happened to them?

Patient-level prediction: What will happen to me?

Population-level effect estimation: What are the causal effects?

Observation

Inference

Causal inference
How *should* patients with major depressive disorder be treated?

**Treating Major Depressive Disorder**

**A Quick Reference Guide**

**Pharmacotherapy**

- The effectiveness of antidepressant medications is generally comparable between and within classes of medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Therefore, choose a medication largely based on the following:
  - Patient preference
  - Nature of prior response to medication
  - Safety, tolerability, and anticipated side effects
  - Co-occurring psychiatric or general medical conditions
  - Pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions; consult the full guideline or a current drug database)
    - Cost
      - For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal.
      - In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

*Based on* Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition, originally published in October 2010. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available.
How are patients with major depressive disorder ACTUALLY treated?

Hripcsak et al, PNAS, 2016
<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Description</th>
<th>Size (M)</th>
</tr>
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<tbody>
<tr>
<td>AUSOM</td>
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<td>South Korea; inpatient hospital EHR</td>
<td>2</td>
</tr>
<tr>
<td>CCAE</td>
<td>MarketScan Commercial Claims and Encounters</td>
<td>US private-payer claims</td>
<td>119</td>
</tr>
<tr>
<td>CPRD</td>
<td>UK Clinical Practice Research Datalink</td>
<td>UK; EHR from general practice</td>
<td>11</td>
</tr>
<tr>
<td>CUMC</td>
<td>Columbia University Medical Center</td>
<td>US; inpatient EHR</td>
<td>4</td>
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<tr>
<td>GE</td>
<td>GE Centricity</td>
<td>US; outpatient EHR</td>
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</tr>
<tr>
<td>INPC</td>
<td>Regenstrief Institute, Indiana Network for Patient Care</td>
<td>US; integrated health exchange</td>
<td>15</td>
</tr>
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<td>JMDC</td>
<td>Japan Medical Data Center</td>
<td>Japan; private-payer claims</td>
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<td>MDCD</td>
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<td>MDCR</td>
<td>MarketScan Medicare Supplemental and Coordination of Benefits</td>
<td>US; private and public-payer claims</td>
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<td>OPTUM</td>
<td>Optum ClinFormatics</td>
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<td>Stanford Translational Research Integrated Database Environment</td>
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<tr>
<td>HKU</td>
<td>Hong Kong University</td>
<td>Hong Kong; EHR</td>
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</tr>
</tbody>
</table>
Treatment pathway study design

• >250,000,000 patient records used across OHDSI network
• >=4 years continuous observation
• >=3 years continuous treatment from first treatment
• N=264,841 qualifying patients with depression

Hripcsak et al, PNAS, 2016
How are patients with major depressive disorder ACTUALLY treated?

- Substantial variation in treatment practice across data sources, health systems, geographies, and over time
- Consistent heterogeneity in treatment choice as no source showed one preferred first-line treatment
- 11% of depressed patients followed a treatment pathway that was shared with no one else in any of the databases

Hripcsak et al, PNAS, 2016
One standardized approach can be applied to multiple clinical areas

Hripcsak et al, PNAS, 2016
Complementary evidence to inform the patient journey

Clinical characterization: What happened to them?

Patient-level prediction: What will happen to me?

Population-level effect estimation: What are the causal effects?

Inference

Causal inference

Observation
Demo the current state of population-level effect estimation in the literature

https://schuemie.shinyapps.io/ShinyApp/
Observational research results in literature

85% of exposure-outcome pairs have $p < 0.05$

What’s going wrong?  
• Observational study bias  
• Publication bias  
• P-hacking

29,982 estimates  
11,758 papers
Observational research in depression

1,935 estimates
What if we considered all outcomes?

Duloxetine vs. Sertraline for these 22 outcomes:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver injury</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Constipation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>Open-angle glaucoma</td>
</tr>
<tr>
<td>Delirium</td>
<td>Seizure</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Stroke</td>
</tr>
<tr>
<td>Fracture</td>
<td>Suicide and suicidal ideation</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Ventricular arrhythmia and sudden cardiac death</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Vertigo</td>
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</table>
What if we consider all treatments?

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Atypical</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Drug</td>
<td>Atypical</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Procedure</td>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>Procedure</td>
<td>Psychotherapy</td>
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</tr>
<tr>
<td>Drug</td>
<td>SARI</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Drug</td>
<td>SNRI</td>
<td>Desvenlafaxine</td>
</tr>
<tr>
<td>Drug</td>
<td>SNRI</td>
<td>duloxetine</td>
</tr>
<tr>
<td>Drug</td>
<td>SNRI</td>
<td>venlafaxine</td>
</tr>
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<td>SSRI</td>
<td>Citalopram</td>
</tr>
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<td>SSRI</td>
<td>Escitalopram</td>
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<td>Fluoxetine</td>
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<td>Paroxetine</td>
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<td>SSRI</td>
<td>Sertraline</td>
</tr>
<tr>
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<td>SSRI</td>
<td>vilazodone</td>
</tr>
<tr>
<td>Drug</td>
<td>TCA</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Drug</td>
<td>TCA</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Drug</td>
<td>TCA</td>
<td>Nortriptyline</td>
</tr>
</tbody>
</table>
Large-scale estimation for depression

- 17 treatments
- $17 \times 16 = 272$ comparisons
- 22 outcomes
- $272 \times 22 = 5,984$ effect size estimates
- 4 databases so far (Truven CCAE, Truven MDCD, Truven MDCR, Optum)
- $4 \times 5,984 = 23,936$ estimates

NOT DATA MINING - Each analysis following best practice in causal inference
Estimates are in line with expectations

11% of exposure-outcome pairs have calibrated p < 0.05

In literature, 85% have p < 0.05
Evidence Generation
- Write and share protocol
- Open source study code
- Use validated software
- Replicate across databases

Evidence Evaluation
- Produce standard diagnostics
- Include negative controls
- Create positive controls
- Calibrate confidence interval and p-value

Evidence Dissemination
- Don’t provide only the effect estimate
- Also share protocol, study code, diagnostics and evaluation
- Produce evidence at scale
OHDSI in Action:
Levetiracetam and Angioedema

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, Yurii Khoma, Yonghui Wu, Hua Xu, Nigam H. Shah, Juan M. Banda, and Martijn J. Schuemie

Epilepsia, **(5):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.

Dr. Jon Duke is Director of the Center for Health Analytics and Informatics at the Georgia Tech Research Institute.
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)
Clinical reviews from Epilepsia recognize value in observational research

• No substantive revisions needed on first submission!
• Editor:
  – Your paper has been reviewed by our referees, and the manuscript has been recommended as acceptable if certain relatively limited revisions are made
• Reviewer: 1
  – Well conducted study with an impressing data material that you were able to combine these databases. This is an important contribution to improved pharmacovigilance.
  – Phenytoin should also be mentioned in the title
  – Pharmacovigilance is a key word; should also be in the abstract and conclusion
  – Kaplan Meyer plots should be moved from supplementary to main text
• Reviewer: 2
  – Using a large international health care data network comprising more than 600 million enrolled patients, 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. This brief report is concise and well written.
  – Include references that further describe the 10 clinical datasets
  – Briefly mention some broad categories of baseline confounders from the propensity model
  – Propensity score matching has some risk of bias. Not suggesting any revision to the methods, but wonder if the potential limitations warrant a brief mention
  – Potential misclassifications could be mentioned as a minor limitation. I don’t think this mention is essential
Complementary evidence to inform the patient journey

Clinical characterization: What happened to them?

Patient-level prediction: What will happen to me?

Inference

Population-level effect estimation: What are the causal effects?

Causal inference
Populations can be used to accurately predict outcomes for individuals

<table>
<thead>
<tr>
<th>AMI</th>
<th>Acute Liver Injury</th>
<th>Alzheira</th>
<th>Constipation</th>
<th>Decreased libido</th>
<th>Diarrhea</th>
<th>Hypothyroidism</th>
<th>Nausea</th>
<th>Stroke</th>
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AUC

- 1.00
- 0.90
- 0.80
- 0.70
- 0.60
- 0.50
To go forward, we must go back

“What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”

- Strength
- Consistency
- Temporality
- Plausibility
- Experiment
- Coherence
- Biological gradient
- Specificity
- Analogy

Introducing HOMER

• Health Outcomes and Medical Effectiveness Research (HOMER) system

• Live, interactive evidence exploration system with fully functional implementations of all of the components of Sir Bradford Hill’s viewpoints for risk identification and assessment, plus some additional components designed by the OMOP team
HOMER implementation of Hill’s viewpoints

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

Ryan OMOP Symposium 2013
Building the LHC of observational research?
Join the journey

• Discussion / questions / comments

ryan@ohdsi.org