Levetiracetam and Risk of Angioedema in patients with Seizure Disorder

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The authors declare the following disclosures: Drs. Ryan and Schuemie are employees of Janssen Research & Development.

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# List of abbreviations

ATC Anatomic Therapeutic Chemical

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

MedDRA Medical Dictionary for Regulatory Activities

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PRR Proportional Reporting Ratio

PS Propensity Scores

# 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 raisedby 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.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 18 April 2016 | Jon Duke | Initial draft |
| 0.2 | 30 April 2016 | Jon Duke | Added negative controls and updates exclusion criteria |
| 0.3 | 2 May 2016 | Jon Duke | Updated negative controls |
| 0.4 | 3 May 2016 | Jon Duke | Additional edits to negative controls |
| 0.5 | 17 May 2016 | Martijn Schuemie | Updated Methods section |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis |  |
| End of analysis |  |
| Posting of results |  |
| Submission of manuscript |  |

# Rationale and Background

The US Food and Drug Administration provides [quarterly reports of potential safety signals](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM082196) generated through analysis of the FDA Adverse Event Reporting System (FAERS) data. In regards to these signals, the FDA states:

The appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a ***potential safety issue***, but it does not mean that FDA has identified a causal relationship between the drug and the listed risk. If after further evaluation the FDA determines that the drug is associated with the risk, it may take a variety of actions, including requiring changes to the labeling of the drug, requiring development of a Risk Evaluation and Mitigation Strategy (REMS), or gathering additional data to better characterize the risk.

One goal of OHDSI is to provide timely and transparent data on topics of relevance to the public health, including potential drug safety issues. For this study, we seek to generate evidence regarding one of the potential safety issues raised by the FDA in their most recent quarterly report ([Oct-Dec 2015](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm491645.htm)). The drug-outcome pair to be analyzed is Keppra (levetiracetam) and angioedema.

In the study described here we will utilize the OHDSI CohortMethod package to assess the associated risk between the aforementioned drug and outcome pair. We aim to disseminate the network study results as rapidly as possible to serve as a data point for the FDA in making its decisions regarding these potential drug safety issues.

## Research Questions

**Levetiracetam** **and Angioedema**

Levetiracetam is a commonly used anti-epileptic medication that was approved in 1999. Angioedema is a rapid swelling of the face, mouth, tongue, and throat that can appear both in a hereditary and a drug-induced form.1 Sometimes accompanied by limb or intestinal swelling, angioedema can be fatal if associated with severe respiratory compromise. Some anti-seizure medications carry a labeled warning for angioedema2 (eg., lamotrigine), but no such warning currently exists for levetiracetam. While angioedema is rare, given its severity, the FDA is currently assessing whether users of levetiracetam may be at increased risk.

For our comparator drug, we will be using Dilantin (phenytoin sodium), a commonly prescribed anti-epileptic medication that has been on the market since 1953 and does not currently carry a warning for angioedema.

Primary hypothesis

* When comparing the risk of angioedema between levetiracetam and phenytoin sodium using a fully adjusted model, the hazard ratio will be unequal to 1.

## Objectives

Primary objective

* Assess the adjusted hazard ratio for use of levetiracetam vs phenytoin sodium on risk of angioedema

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational, new-user cohort study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘new-user’ we mean we will only analyze the first exposure of a subject to the drugs of interest. By ‘cohort study’ we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

The treatment cohort will be new users of levetiracetam. The comparator cohort will be new users of phenytoin sodium. For both groups we restrict to people with seizure disorder, one of the main indications for the drugs of interest. The outcome of is Angioedema. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts.

Adjustment for baseline confounders will be done using propensity scores. First, a propensity model will be fitted and used to create propensity scores (PS). These PS will be used to match the treatment and comparator cohorts, and the proportional hazards outcome models will be conditioned on the matched sets of strata respectively.

The time of risk will be defined as all time on the drug (so-called per-protocol), and will end at the end of exposure or end of observation, whichever is first. Multiple prescriptions will be considered continuous exposure with a maximum gap of 30 days.

Negative control outcomes (outcomes not believed to be caused by either levetiracetam or phenytoin sodium) will also be included. The hazard ratios computed for these negative controls will be used to evaluate residual bias and compute calibrated p-values for the outcomes of interest [[1](#_ENREF_1)].

### Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first exposure to levetiracetam or phenytoin)

* Exposure to levetiracetam or phenytoin
* At least 183 days of observation time prior to the index date
* A diagnose of seizure disorder on or preceding the index date
* No diagnosis of the outcome of interest preceding the index date

### Additional analysis details

The propensity model will be fitted using L1 regularized logistic regression. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

Variable-ratio propensity score matching will be performed using greedy matching [[2](#_ENREF_2)]. A caliper of 0.25 times the standard deviation of the propensity score distribution will be used.

The outcome model will be fitted using a Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets.

Secondary analyses:

* No PS model, a simple outcome model with only the treatment as predictor.
* Using a PS model and perform 1-on-1 matching. The outcome model will be condition on the matched sets, but will only contain the treatment as predictor. This is included to allow plotting of the Kaplan-Meier curve, which is not possible when using variable ratio matching.
* Variable ratio matching on the PS. The outcome model will include all covariates that were also included in the propensity model, and will be fitted using a L1 regularized conditional Cox regression with prior. The regularization hyperparameter will be selected be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable (i.e. those representing the hazard ratio of interest).
* All analyses will be repeated using an intent-to-treat risk window definition, which starts on treatment initiation, and ends when observation ends.

## Variables

### Exposures

#### Levetiracetam

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient levetiracetam

Inclusion rules based on the index date:

* At least 183 days of observation time prior to the index date
* A diagnosis of seizure disorder on or preceding the index date
* No diagnose of angioedema preceding the index date

#### Phenytoin Sodium

Index rule defining the index date:

* First exposure to a drug containing any phenytoin sodium

Inclusion rules based on the index date:

* At least 183 days of observation time prior to the index date
* A diagnosis of seizure disorder on or preceding the index date
* No diagnosis of angioedema preceding the index date

### Outcomes

#### Angioedema

Index rule defining the index date:

* Any occurrence of an angioedema diagnosis code

Inclusion rules based on the index date:

* Cannot have an angioedema diagnosis code prior to the index date.

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnosis code)
* Condition era (one or more variables per diagnosis code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative controls

Negative controls were selected using the following criteria:

* No evidence found in literature on clinical trials using the method proposed by Avillach [[3](#_ENREF_3)].
* No evidence found in literature using the method used in SemMedDB [[4](#_ENREF_4)].
* No evidence found in the structured product label (US and EU) for the outcome or associated outcomes
* FAERS Proportional Reporting Ratio (PRR) needed to be less than 2.
* Sufficient exposure in a US healthcare database (Over 10,000 occurrence of the diagnoses code in the Truven CCAE database).

Negative controls were defined as any of the following diagnoses:

|  |
| --- |
| Acute renal failure syndrome |
| Anal finding |
| Aortic aneurysm |
| Aortic valve disorder |
| Appendicitis |
| Arthritis of elbow |
| Arthropathy associated with another disorder |
| Arthropathy of knee joint |
| Ascites |
| Aseptic necrosis of bone |
| Astigmatism |
| Atelectasis |
| Atopic dermatitis |
| Bacterial intestinal infectious disease |
| Barrett's esophagus |
| Benign neoplasm of endocrine gland |
| Blepharitis |
| Bronchopneumonia |
| Burn |
| Bursitis |
| Candidiasis of mouth |
| Candidiasis of urogenital site |
| Condyloma acuminatum |
| Coxsackie virus disease |
| Croup |
| Cystic disease of kidney |
| Cystitis |
| Deficiency of macronutrients |
| Dental caries |
| Duodenitis |
| Dyspareunia |
| Dysplasia of cervix |
| Dyspnea |
| Dysthymia |
| Dysuria |
| Effusion of joint |
| Endocarditis |
| Enthesopathy of elbow region |
| Fibrocystic disease of breast |
| Gastroesophageal reflux disease |
| Hemorrhoids |
| Hypermetropia |
| Hyperplasia of prostate |
| Hypokalemia |
| Impetigo |
| Infectious disorder of kidney |
| Infestation by Sarcoptes scabiei var hominis |
| Inflammatory disease of female pelvic organs AND/OR tissues |
| Inflammatory disease of the uterus |
| Inflammatory disorder of breast |
| Ingrowing nail |
| Injury of abdomen |
| Intervertebral disc disorder |
| Intracranial injury |
| Iridocyclitis |
| Irritable bowel syndrome |
| Late effects of cerebrovascular disease |
| Leukorrhea |
| Lipoma |
| Malignant neoplasm of thorax |
| Mitral valve disorder |
| Mononeuropathy of upper limb |
| Non-toxic uninodular goiter |
| Open-angle glaucoma |
| Osteomyelitis |
| Otitis externa |
| Otorrhea |
| Paraplegia |
| Paronychia |
| Paroxysmal tachycardia |
| Peripheral venous insufficiency |
| Plantar fasciitis |
| Pleurisy |
| Pneumococcal infectious disease |
| Pneumonia due to Gram negative bacteria |
| Pneumothorax |
| Presbyopia |
| Primary malignant neoplasm of respiratory tract |
| Prolapse of female genital organs |
| Prostatitis |
| Pyelonephritis |
| Respiratory arrest |
| Retinopathy |
| Rosacea |
| Sciatica |
| Seborrheic keratosis |
| Secondary malignant neoplastic disease |
| Sialoadenitis |
| Staphylococcal infectious disease |
| Symbolic dysfunction |
| Temporomandibular joint disorder |
| Tetraplegia |
| Thyrotoxicosis |
| Tietze's disease |
| Tinea pedis |
| Torticollis |
| Tricuspid valve disorder |
| Urge incontinence of urine |
| Viral hepatitis |
| Viral pneumonia |

### Other variables

Seizure disorder will be identified using the concept for seizure disorder (4029498) and any of its descendants in the OMOP Vocabulary.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* Truven MarketScan Commercial Claims and Encounters (CCAE)
* Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)
* Truven MarketScan Multi-state Medicaid (MDCD)
* Optum ClinFormatics (Optum)
* Clinical Practice Research Datalink (CPRD)
* Indiana Network for Patient Care
* Columbia University Medical Center
* Others….

Truven MarketScan Commercial Claims and Encounters (CCAE)

CCAE is an administrative health claims database for active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans). As of 30November2014, CCAE contained 117m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in CCAE include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming CCAE into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_ccae/dashboard>.

Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database.. As of 30November2014, MDCR contained 9m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in MDCR include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCR into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcr/dashboard>.

Truven MarketScan Multi-state Medicaid (MDCD)

MDCD is an administrative health claims database for the pooled healthcare experience of Medicaid enrollees from multiple states. As of 30November2014, MDCD contained 16m patients with patient-level observations from Jan2006 through Dec2012. Source codes used in MDCD include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcd/dashboard>.

Optum ClinFormatics (Optum)

Optum is an administrative health claims database for members of United Healthcare, who enrolled in commercial plans (including ASO, 36.31M), Medicaid (prior to July 2010, 1.25M) and Legacy Medicare Choice (prior to January 2006, 0.36M) with both medical and prescription drug coverage. As of 30November2014, Optum contained 38m patients with patient-level observations from Oct2005 through Dec2013. Source codes used in Optum include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming Optum into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/optum/dashboard>.

Clinical Practice Research Datalink (CPRD)

CPRD is an anonymized longitudinal electronic health records from primary care practices in UK. Patient management system with many aspects of patient care covered, including diagnoses, prescriptions, signs and symptoms, procedures, labs, lifestyle factors, clinical and administrative/social data. As of 30November2014, CPRD contained 11m patients with patient-level observations from Jan1988 through Nov2013. Source codes used in CPRD include: conditions- Read; drugs: Multilex; procedures: OPCS.

The ETL specification for transforming CPRD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/cprd/dashboard>.

Indiana Network for Patient Care (INPC)

The INPC is a 22-year-old health information exchange operated in Indiana. The health information exchange data repository carries over 6 billion pieces of clinical data, including over 118 million text reports, for approximately 27.5 million different patient registrations, for approximately 13.4 million unique patients derived from over 100 hospitals. All clinical data is standardized, and laboratory test results are mapped to a set of common test codes (LOINC) with standard units of measure for patient care, public health, and research purposes.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Regenstrief at <https://nlp01.regenstrief.org/Achilles>

## Sample Size and Study Power

No power calculations have been performed.

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching [[5](#_ENREF_5)]. Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.
* The outcome of interest, angioedema, is rare and typically captured only in inpatient settings, so we may have insufficient numbers of patients to generate reliable evidence on this drug-outcome association.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

1. Bertazzoni G, Spina MT, Scarpellini MG, Buccelletti F, De Simone M, Gregori M, Valeriano V, Pugliese FR, Ruggieri MP, Magnanti M, Susi B. Drug-induced angioedema: experience of Italian emergency departments. Internal and emergency medicine. 2014 Jun 1;9(4):455-62.

2. Elias A, Madhusoodanan S, Pudukkadan D, Antony JT. Angioedema and maculopapular eruptions associated with carbamazepine administration. CNS spectrums. 2006 May 1;11(05):352-4.