MINI-SENTINEL SYSTEMATIC EVALUATION OF HEALTH OUTCOME OF INTEREST DEFINITIONS FOR STUDIES USING ADMINISTRATIVE DATA

SEIZURE, CONVULSION, EPILEPSY REPORT

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Systematic Evaluation Of Health Outcome Of Interest Definitions For Studies Using Administrative Data

Seizure, Convulsion, Epilepsy Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was to identify algorithms used to detect selected health outcomes of interest using administrative data sources and describe the performance characteristics of these algorithms as reported by the studies in which they were used. This report summarizes the process and findings of the seizure, convulsion, epilepsy algorithm review.

B. SUMMARY OF FINDINGS

We found a total of 11 validation studies for seizure, convulsion, epilepsy to include in this report. All age groups were represented. Aside from general age, very little demographic data was provided, although one study focused exclusively on the Navajo. In studies that reported gender proportions, both genders were equally represented for the most part, except for one study in veterans that was 98% male. One study mentioned the percentage of blacks (15.8%). Three studies mentioned the percentage of Hispanics (reported percentages ranged from 4.9% to 49%). The studies included in the report fell into a number of subgroups. Studies reported on both inpatient and outpatient events and incident and prevalent outcomes. PPVs ranged from 21% (for predicting incident seizures from tramadol) to 98% (for predicting the agreement between medical records and computerized minimum data sets in nursing homes). The majority of algorithms used ICD-9-CM codes, but a few included CPT-4 codes, and one used ICD-10 codes.

All algorithms included ICD-9-CM code 345.X and either 780.3 (9 studies) or 780.39 (1 study). Six of the 11 studies used 333.2 in the algorithm. In populations that included children, 779.0 was also fairly common. These latter two codes are most appropriate for identifying single seizure or seizure-like events in children, as opposed to epilepsy. Several other codes were used, but not consistently. The performance of algorithms was highly variable. However, the PPVs were generally best in studies where epilepsy diagnoses were required, whereas those that used non-specific indicators such as the presence of an electroencephalogram (EEG) or antiepileptic drug (AED) level monitoring without requiring diagnosis codes had low PPVs Using EEG or AED level monitoring would be more appropriate for case identification if sensitivity was the goal and all cases would be confirmed by medical record review, since they are not specific to seizures or epilepsy.

The study by Holden, et al. was the most comprehensive, examining several variables and concluding that the best model to identify epilepsy cases was an algorithm that contained several ICD-9-CM codes in addition to either a pharmacy fill for an antiepileptic drug or a CPT-4 code for antiepileptic drug monitoring.[11] This model had a PPV of 83.9% and a sensitivity of 81.8%. On the other hand, the study by Parko and Thurman just used ICD-9-CM codes and found a PPV of 90% for a clinical diagnosis of epilepsy or seizures, although for epilepsy per se (two or more unprovoked seizures) the PPV was 62%, leading them to suggest that a corrective factor is necessary when relying on ICD-9-CM-coded data to estimate the prevalence of epilepsy per se.[13]

The PPV of ICD-9-CM code 345.X for identifying epilepsy increased substantially as the number of diagnosis codes in a person's records increased in the Holden, et al. study.[11] The PPV was only 38.5% if one diagnosis code was present, while it increased to 100% if four diagnosis codes were present. In another study, the PPVs for 345.X exceeded 80% when the code was in the primary diagnostic position.[12] Thus, this code may perform better in the primary diagnostic position or if it occurs multiple times in records. Most studies did not report the PPV of codes separately. When examined, there was variability in the performance of codes for different types of epileptic seizures, with status epilepticus codes performing the best. Less specific codes for convulsions or seizure-like events performed variably. These codes did not perform particularly well in most studies of infants receiving vaccines, though one study found that emergency department and inpatient codes were much more reliable compared to outpatient codes. One study that used only emergency department or inpatient codes to identify seizures found a PPV of 94%.[9] This may lead to the conclusion that such studies should rely on only emergency department or inpatient diagnoses to identify seizures.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

The demographic composition of study populations appeared to be quite diverse. However, studies in adults tended to focus on epilepsy diagnoses rather than isolated seizure events. The PPV was only 21% in one study that sought to identify incident seizures among tramadol users and controls.[16] Another study of the Navajo Nation grouped seizure and epilepsy diagnoses together, so the performance of seizure-specific algorithms cannot be determined.[13] Most of the work to identify seizures examined data on very young children who received vaccines. Therefore, it is recommended that future studies attempt to develop valid algorithms to identify incident seizures in older children or adult populations.

Adding requirements for drugs or procedures to an algorithm that uses diagnostic codes would assumedly increase specificity and decrease sensitivity. It is clear from the available studies that using procedure codes for EEGs or prescription claims for drugs possibly used for epilepsy or convulsions in the absence of a diagnostic code is not recommended. These procedures and medications are not specific to epilepsy or seizure events, so a diagnosis needs to be part of any algorithm to maintain specificity. Given that many newer AEDs require no drug level monitoring, requiring an AED drug level monitoring procedure in algorithms to identify epilepsy is not recommended. This would result in lack of sensitivity of the algorithm.

Gaps in the current literature include determining which algorithms would be best for identifying any type of seizure or convulsion as opposed to epilepsy (two or more unprovoked seizures). Also, more research is needed to determine how much is gained or lost by adding antiepileptic drug fills, drug monitoring, or other codes to the algorithms, though a requirement of drug level monitoring is not recommended given that drug levels of many newer AEDs are not checked. From the available evidence the added value of drug indicators seems limited, though addition of an antiepileptic drug indicator to identify epilepsy per se may be reasonable. More research is also needed to determine the best algorithm for identifying vaccine-related seizures since in general the three studies that examined this outcome had low PPVs, and the PPVs appeared to be influenced by the location of the medical encounter, age of the patient, and timing of the event relative to vaccine administration. Based on currently available data, it may be appropriate to only include seizures diagnosed in the emergency department or inpatient setting in studies of seizures potentially related to vaccines. In addition, we only identified one study that used ICD-10 codes, so this is another area that needs more research when ICD-10 codes become more widely utilized.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that have been used to identify the HOIs using administrative data.

III. BACKGROUND

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and identify the performance characteristics of these algorithms as measured in the studies in which they were used. The data sources of interest were limited to those from the United States or Canada to increase their relevance to the Mini-Sentinel data sources, which are all from the United States. The Mini-Sentinel Protocol Core developed a preliminary list of approximately 140 potential health outcomes of interest, based on several criteria. These criteria included: 1) previous validation studies had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[1] 2) a list of designated medical events had been created from a proposed FDA rule on the safety reporting requirements for human drug and biological products,[2] 3) the Observational Medical Outcomes Partnership (OMOP)[i] had commissioned reports on algorithms used to identify the health outcome using administrative data.[3]

From the original list of 140 HOIs, the Protocol Core worked with FDA to select 20 for which reviews of algorithms would be completed. HOIs for which OMOP had already commissioned reports were purposefully excluded in order to avoid duplication of effort.

Seizure, convulsion, epilepsy was one of the 20 HOIs selected for review. This report describes the review process and findings for the seizure, convulsion, epilepsy definition algorithms.

IV. METHODS

A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed empirically that the majority of relevant articles from one set of OMOP reports (angioedema)[4,5] would

[i] For more information, visit the OMOP website.

be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, Embase searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

University of Iowa investigators compiled the search results from different databases and eliminated duplicate results using a citation manager program. The results were then output into two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

The search strategy and results for seizure, convulsion, epilepsy are detailed in the Results section. The PubMed and IDIS searches were conducted on June 24, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by two investigators to determine whether the full-text article should be reviewed. Exclusion criteria were documented sequentially (i.e., if exclusion criterion 1 was met then the other criteria were not documented). If the reviewers disagreed on whether the full-text should be reviewed, then it was selected for review. Inter-rater agreement on whether to include or exclude an abstract was calculated using a Cohen's kappa statistic. The goal was to review any administrative database study that used data from the United States or Canada and studied the HOI, as validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies.

2. Abstract Exclusion Criteria

1. Did not study the HOI.

2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.

3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-Text Review Methods

Full-text articles were reviewed independently by two investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Full-text review exclusion criteria were applied sequentially, since if fewer than 5 validation studies were identified, up to 10 of the articles excluded based on the second criterion would need to be incorporated into the final report. If there was

disagreement on whether a study should be included, the two reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator was consulted to make the final the decision.

2. Full-Text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.

2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators were surveyed to request information on any published or unpublished studies that validated an algorithm to identify an HOI in administrative data. Studies that would not be excluded by one of the aforementioned criteria were included in the final report.

E. EVIDENCE TABLE CREATION

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic-expert was consulted to review the results of the evidence table and discuss how they compare and contrast to diagnostic methods currently used in clinical practice. This included whether certain diagnostic codes used in clinical practice were missing from the algorithms, and the appropriateness of the validation definitions compared to diagnostic criteria currently used in clinical practice. A summary of this consultation was included in the results.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following tables summarize the search results obtained from PubMed and IDIS searches. The PubMed search identified 764 citations (Table 1), and the two IDIS searches identified 39 citations, 0 from the first search and 39 from the second search (Table 2). After excluding duplicates, the total number of unique citations from the combined searches was 774.

Table 1. PubMed Search Strategy and Results (764): Performed on 06/24/10

Search	Query	Results
#1	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR “Predictive Value”[tw]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1864370
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR “international statistical classification"[All] OR “international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR (“claims”[tw] AND “administrative”[tw]) OR (“data”[tw] AND “administrative”[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields] OR (TennCare [tiab]) OR (RAMQ [tiab]) OR (Cigna [tiab]) OR ((british columbia[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]))) OR (CIHI [All Fields]) OR ((manitoba[tiab]) AND ((center for health policy[all fields]) OR (population[tiab]) OR (health insurance[tiab]))) OR ((ontario[tiab]) AND ((population[tiab]) OR (OHIP[tiab]) OR (registered persons database[tiab]) OR (health insurance [tiab]) OR (ICES[All Fields]) OR (Institute for Clinical Evaluative Sciences[All Fields]))) OR ((Alberta[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]) OR (Alberta Health and Wellness[All Fields]))) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	373577

#3	Search #1 AND #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	109687
#4	("Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	2604394
#5	Search #3 NOT #4 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	69963
#6	Search "epilepsy"[All] or "seizure"[All] or "convulsion"[All] or "Epilepsy"[Mesh] OR ("Seizures"[Mesh] OR "Spasms, Infantile"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	52093
#7	Search #5 AND #6 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	764

Table 2. IDIS Search Strategy and Results (39): Performed on 06/24/10

Results = 39

Search 1: 0 Results

ADVANCED SEARCH

All Fields:

(“Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases as topic" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM" OR “TennCare” OR “RAMQ” OR “Cigna” OR “British Columbia” OR “CIHI” OR “Manitoba” OR “Ontario” OR “Alberta”)

AND **Descriptor**:

"SIDE EF NERVOUS 84" not ("CASE REPORT ADULT 0" or “FDA APPROVAL PACKAGE 155” OR “FDA BLACK BOX WARNING 165” OR “PIVOTAL STUDY 162” OR "FDA ADVISORY COMMITTEE 164" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168")

AND NOT **Author**:

"(editorial)" or "(Letter to Ed)"

AND **Abstract**:

Epilepsy or Seizure or convulsion

Years: 1990-2010

Records = 0

Search 2: 39 Results

ADVANCED SEARCH

All Fields:

(“Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR

"Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases as topic" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM" OR "TennCare" OR "RAMQ" OR "Cigna" OR "British Columbia" OR "CIHI" OR "Manitoba" OR "Ontario" OR "Alberta")

AND Disease(s):

780.3 or 345.*

AND NOT Descriptor(s):

"CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168"

AND NOT Author(s):

"(editorial)" or "(Letter to Ed)"

Years: 1990-2010

Records = 39

B. ABSTRACT REVIEWS

Of the 774 abstracts reviewed, 342 were selected for full-text review; 180 were excluded because they did not study seizure, convulsion, epilepsy, 131 were excluded because they were not administrative database studies, and 121 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of abstracts was 0.49. The primary reason for the low agreement was because of uncertainty about whether or not a study used an administrative database.

C. FULL-TEXT REVIEWS

Of the 342 full-text articles reviewed, 9 were included in the final evidence tables; 72 were excluded because the HOI identification algorithm was poorly defined, and 70 were excluded because they included no validation of the outcome definition or reporting of validity statistics. Reviewers identified 1 citation for review from full-text article references, and it was included in the final report. Reviewers excluded 192 for abstract criteria: 21 were excluded because they did not study seizure, convulsion, epilepsy, 146 were excluded because they were not administrative database studies, and 24 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 0.36. The primary reason for the low agreement was that one investigator was more liberal in selecting articles that had poorly defined algorithms or used previously validated methods.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no reports of validation studies that had been completed by their teams.

E. EVIDENCE INCLUDED IN TABLE

Of the 11 studies included in the evidence table (Table 3),[6-16] 9 were identified from the initial search strategy, 1 was identified through references of articles that underwent full-text review, and none were provided by Mini-Sentinel Investigators. One published after the literature search was conducted was identified by a reviewer of the report, and was added since it provided support for an algorithm relevant to seizure identification after vaccination.[16]

A complete list of studies with clear HOI definitions that were eligible to be selected for inclusion is available in Appendix B.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. All 11 of the publications listed in the evidence table used ICD-9-CM, ICD-10, CPT-4, or a combination of one or more of these types to identify patients with seizure, convulsion, or epilepsy. All of the studies that used ICD-9-CM codes included 345.X alone or in combination with other ICD-9-CM codes. 780.3 was used in combination with 345.X and other ICD-9-CM codes in all but one study, which used 780.39 instead of 780.3. Other common ICD-9-CM codes were 333.2 and 779.0. One study that examined computerized Minimum Data Sets also included records that had the "Seizure Disorder" item checked.[15]

Only one study validated ICD-10 epilepsy coding.[12] This study included G40.X, G41.X, R56.0, and R56.8.

Validation Criteria and Method. Nearly all studies included in the report validated administrative coding data through abstraction of medical charts. Documentation of seizure, convulsion, or epilepsy in the medical records was generally based on physician notes. One study first sent letters to the physician first to confirm epilepsy status and only consulted the medical chart if the physician did not respond or if the response needed further investigation.[10] A few studies specified criteria from medical records, but there did not appear to be any standardized criteria that were used.

One study classified seizures as simple febrile, complex febrile, or nonfebrile.[6] Another study placed patients into one of five categories: epilepsy, seizure, febrile seizure, no seizure, or missing chart.[13] One study classified seizures as neonatal seizure, febrile seizure, complex febrile seizure, afebrile seizure, symptomatic seizure, or epilepsy.[8]

Validation Algorithms. No algorithms included only a single ICD-9-CM code. All algorithms included 345.X and either 780.3 (9 studies) or 780.39 (1 study). Many studies did not specifically state whether subcodes under 780.3 (i.e., 780.3X) were included, though it is suspected that they were. Six of the 11 studies used 333.2 in the algorithm. In populations that included children, 779.0 was also fairly common. Several other codes were used, but not consistently. PPVs ranged from 21% (for predicting incident seizures from tramadol) to 98% (for predicting the agreement between medical records and computerized Minimum Data Sets in nursing homes). Some algorithms included fills or monitoring for antiepileptic drugs while some included CPT-4 codes.

Since only one study reported validation of ICD-10 codes,[12] it is difficult to comment on the validation statistics between ICD-9-CM and ICD-10 coding algorithms. They found the PPVs from three sources of data − seizure monitoring unit chart review, inpatient discharge abstract database, and emergency room database − to be 85%, 98%, and 100%, respectively.

In some studies validation statistics were based only on a subsample of the overall study population. In general, this was because medical records were not available for examination or examining all records was not feasible.

Selected Patient Populations. The studies did not restrict the study sample to patients with specific diseases other than seizure, convulsion, and epilepsy. The studies included either the entire health plan membership or all members of a specific age group.

Age of study population. Four studies examined the incidence of seizures following several childhood vaccinations, so these studies were limited to children. The tramadol-induced seizures study included only adults (mean age 44.5 years).[16] One study only included patients 65 years of age or older,[15] and one study included patients 66 years of age or older (because they wanted at least one year of Medicare data).[14] The remainder of studies included patients of all ages. One study found that the PPV for seizure events in children younger than one year of age was lower in all four settings the study evaluated than the PPV in children one year of age or older.[7] It was speculated that this may be because parents of young children are more likely to bring younger infants to medical attention for suspected seizure events that are later ruled out or that these infants are more likely to have more follow-up for seizure events. It was also stated that since PPV is a function of disease prevalence and because the incidence of all seizure disorders is highest in the second year of life then it would be expected that PPV would be highest in those age groups that are at most risk. One study examined the effects of age and ethnicity, but the only significant demographic variable they found was that patients 0-19 years old were less likely than patients 20-64 years old to have epilepsy.[11] One study calculated PPVs for adult hospital visits and children's hospital visits and found similar PPVs in both populations, except that the PPVs using epilepsy and convulsion codes (using both ICD-9-CM and ICD-10 codes) were higher in children's hospital visits (96.5% and 85.1%, respectively, for the two different coding systems) as compared to adult hospital visits (85.1% and 72.3%, respectively, for the two different coding systems).[12]

Time period of data collection. This report includes publications between 2000 and 2010. The studies included report on study populations identified between 1991 and 2008.

Incident vs prevalent outcome validation. Four studies identified incidence following different vaccines,[6-9] one study identified incidence of drug-induced seizures (following tramadol),[16] four studies identified prevalence of epilepsy or seizure,[11-13,15] one study identified incident and prevalent cases,[10] and one study that examined prescribing trends in the elderly identified new-onset cases.[14]

In general, the studies examining incidence following vaccine administration[6-8] or tramadol prescription[16] had lower PPVs (21%-65.4%), with the exception of patients seen in the emergency department following pneumococcal administration[7] (96.6%), and another study which used only emergency department or inpatient claims to identify seizures (94%).[9] Studies that examined prevalent cases[10-13,15] tended to have higher PPVs (76.9%-97.9%) with one exception[10] (32.7%). One reason for the low PPV in this study may have been that patients with just a code for EEG procedures were identified as potential cases, and that procedure may have been used to diagnose conditions other than seizure,

convulsion, epilepsy, or might have been negative for seizures. This particular method appeared to have a primary goal of sensitivity to identify any potential case for further chart review.

Inpatient vs outpatient encounter. The studies included in this report examined inpatient or outpatient encounters, or both, to identify seizure, convulsion, or epilepsy outcomes. One study examining seizures after vaccine administration calculated statistics based on setting and found the highest PPV for emergency department visits (96.6%) and the lowest PPV for outpatient visits on day 0 (1.8%), the day the vaccine was given.[7] PPV for inpatient visits was 64.0%; for outpatient visits days 1-30 post-vaccination it was 16.4%. Another study examining seizures after vaccine administration used only codes from the emergency department or inpatient setting and found a PPV of 94%,[9] much higher than that found in studies of seizures after vaccine administration that allowed outpatient codes. One study focusing on epilepsy calculated PPVs for all charts, inpatient visits, and emergency visits and found no appreciable differences,[12] suggesting that setting may be more important in identifying isolated seizure events than for identifying epilepsy.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

None of the studies that we identified excluded patients with specific comorbid conditions. Two studies mentioned exclusion criteria.[9,16] In one, patients were excluded if they had a seizure or convulsion code in 42 days prior to the vaccination under study.[9] In the other, patients who were not continuously enrolled for at least 90 days before receiving the first prescription for tramadol and for at least 60 days after receiving tramadol (an observation period of at least 151 days) were excluded.[16] This study also excluded patients with a seizure claim or with any prescription for an antiepileptic drug before the index date within the index period and pointed out that this resulted in a slightly altered ratio of nonusers to users.

H. EVIDENCE TABLE

Table 3. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
Vaccine Studies in Children				
Barlow , et al., 2001[6]	679,942 children (gender proportions not provided) enrolled in four large health maintenance organizations (HMOs) who received the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine, measles, mumps and rubella (MMR) vaccine, or no vaccine. The four HMOs were: Group Health Cooperative in Seattle, Northwest Kaiser Permanente in Portland, Kaiser Permanente of Northern California in Oakland, and Southern California Kaiser Permanente in Torrance. Children entered the cohort at birth, on the date of their enrollment in the HMOs, or at the beginning of a study site's observation period, whichever came last, and remained in the cohort until the age of seven years, disenrollment from the HMOs, or the end of the observation period, whichever came first. Data were collected from March 1991-February 1993 in the first HMO, from	Relative risk of febrile and nonfebrile seizures after receipt of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine or measles, mumps and rubella (MMR) vaccine. Incident cases of seizure were identified.	ICD-9-CM codes: 333.2 (myoclonus) 345.X (epilepsy) 779.0 (convulsions in newborn) 780.3 (convulsions) At Northwest Kaiser Permanente, additional potential cases of seizure were identified with the use of computerized data on anticonvulsant medications, referrals to neurology clinics and electroencephalographic records. Unfortunately this variation in methods to identify potential cases makes the algorithm and PPV difficult to interpret.	Group Health Cooperative and Northwest Kaiser Permanente abstracted the medical records of all children with a possible seizure to validate and classify seizure diagnoses and collect additional information. At Kaiser Permanente of Northern California all cases of seizure that occurred with 30 days of immunization and a random sample of 20% of cases of seizure in unvaccinated children within the preceding 30 days were reviewed. At Southern California Kaiser Permanente, 26% of cases of seizure were randomly selected and reviewed regardless of vaccination status. Experienced medical-record abstractors reviewed the charts using standardized chart-abstraction forms and instructions, with the final disposition of each case determined by physician investigators. The analysis of the risk of vaccination included only the first episode of seizure in each child, as confirmed by review of the medical records. Simple febrile seizures were defined as short, generalized seizures, accompanied by documented fever or a parental report of fever. Complex febrile seizures were defined as febrile seizures that occurred more than once in 24 hours and either lasted for at least 12 minutes or were accompanied by focal signs. Nonfebrile seizures were defined

	January 1991-March 1993 in the second HMO, from October 1992-September 1993 in the third HMO and from March 1991-September 1993 in the fourth HMO. No exclusion criteria were mentioned.			as seizures that were unassociated with fever and not attributable to an existing disease process. This latter group also included seizures among children with a diagnosis of epilepsy or residual seizure disorder. Seizures that were due to an underlying disease process such as infection or trauma were excluded from analysis. Using the automated data, 2,281 possible first seizures were identified. Using the random-sampling plan, 1,094 charts were selected for review. Among these children, 716 were confirmed to have had a first seizure during the study period (487 febrile seizures, 137 nonfebrile seizures, 36 infantile or neonatal spasms, and 56 seizures due to other causes e.g., infection or injury). The primary reason for nonconfirmation was the identification of an earlier seizure although no specific numbers were given. Positive predictive value (PPV) was calculated based upon data presented in the article (i.e., 1094 children were selected for chart review; of those, 716 were confirmed to have had a first seizure during the study period). **PPV = 716/1094 = 65.4%** The 716 cases included 56 that were due to other causes such as infections or injury, even though they were excluded from the final analysis. Since the main reason for not confirming a first seizure was because the child had experienced a prior seizure, the PPV can only be considered in identifying new-onset seizures. Overall, the results of this study are difficult to apply since the authors were not focusing on the algorithm or its performance characteristics in the presentation of data.
Shui , et al., 2009[7]	391,993 children (gender proportions not provided) aged 6 weeks to 23 months	Positive predictive value (PPV) of ICD-9-CM codes used to identify	Seizure visits were identified during the 0–30-day risk window following pneumococcal	Three-thousand two-hundred twenty-three visits for seizure were identified. A random sample of 1024 cases (257 ED, 236

	(inclusive) enrolled in 7 managed care organizations who received one or more doses of pneumococcal vaccine between January 1, 2000 and December 31, 2005	seizure visits in the 0-30 day period following receipt of a pneumococcal vaccine.	vaccination using the following ICD-9-CM codes: 333.2 (myoclonus) 345 (epilepsy) 779.0 (convulsions in newborn) 780.3 (convulsions) Visits were stratified by the setting of diagnosis [emergency department (ED), outpatient clinic, inpatient admission]. Outpatient visits were stratified by whether they occurred on the same day as the vaccination (day 0) or on days 1-30.	inpatient, 176 outpatient day 0, 355 outpatient days 1-30) was selected for medical record review and 859 (84%) had records available. Gender proportions from these records were 51.5% male/48.5% female, 48.7% male/51.3% female, 55.4% male/44.6% female, and 57.4% male/42.6% female for patients seen in the ED, inpatients, outpatients (days 1-30) and outpatients (day 0), respectively. Trained abstractors at each managed care organization reviewed the medical record for each visit and classified visits as: (1) no evidence of a seizure (2) probable seizure or (3) definite seizure. Definite seizures included any clinician diagnosis of seizure; probable seizures were those in which the clinician could neither exclude nor confirm a seizure. Details specified in the Brighton Collaboration definition for *generalized convulsive seizure* were also collected, as were details about family and individual history of seizures. For visits when there was no evidence of an actual seizure event, information explaining why the ICD-9-CM code was given was noted. **PPVs for true seizure events:** **All visits:** **96.6% (ED)** **64.0% (Inpatient)** **16.4% (Outpatient [days 1-30]** **1.8% (Outpatient day 0)** **By subgroup:** **-No history of seizure** **96.9% (ED)** **73.5% (Inpatient)** **24.1% (Outpatient [days 1-30]** **6.8% (Outpatient day 0)** **-ICD-9 code 780.3 only** **97.0% (ED)** **65.8% (Inpatient)** **21.5% (Outpatient [days 1- 30]** **2.4% (Outpatient day 0)** **Age:**

				-<1 year **91.6% (ED)** **59.7% (Inpatient)** **12.7% (Outpatient [days 1- 30])** **2.7% (Outpatient day 0)** **-≥1 year** **99.3% (ED)** **79.1% (Inpatient)** **25.3% (Outpatient [days 1- 30])** **0.0% (Outpatient Day 0)** In interpreting the PPVs, it is important to note that 333.2 and 779.0 accounted for very few of the codes. Thus it is difficult to generalize the PPVs to these specific codes.
Zangwill , et al., 2010[8]	Two cohorts of infants enrolled in the Southern California Kaiser Permanente Health Care Plan: Diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus (DTaP-HepB-IPV) cohort: 61,004 infants (male/female ratio 9:7) who received DTaP-HepB-IPV vaccine from April 2003-June 2005, had not reached their 9-month birthday, and had received 7-valent pneumococcal conjugate vaccine (PCV) at the same visit. Historical DTaP control cohort: A random sample of 58,251 infants (male/female ratio 8:7) who received ≥ 1 dose of DTaP, and with concomitant PCV and separate doses of hepatitis B and IPV between January 2002 and April 2003.	Incidence of seizures during the 8-day period after the primary doses of DTaP-HepB-IPV compared with the 8-day period after the primary doses of DTaP vaccine in the control cohort.	<u>ICD-9 –CM codes:</u> 333.2 (myoclonus) 345.X (epilepsy) 779.0 (convulsions in newborn) 780.3 (convulsions)	Medical visits for seizures were ascertained by trained personnel by using standardized medical chart review. The UCLA Center for Vaccine Research managed all aspects of data collection, management and analysis. Neonatal seizures were those occurring within the first 28 days of life. Febrile seizures were defined as seizures accompanied by fever and not considered to be symptomatic of an acute neurological illness; they were classified as complex febrile seizures if they lasted for more than 10 minutes or had focal features or if more than one seizure occurred within 24 hours. Afebrile seizures were those unaccompanied by fever or an acute neurological illness. Symptomatic seizures were those associated with acute neurological illness. Epilepsy was defined as recurrent seizures, at least one of which was afebrile. PPV was calculated from data provided in the study. **PPV: 16/41 = 39.0% for the DTaP-HepB-IPV cohort** **PPV: 15/51 = 29.4% for the DTaP control cohort**
Klein , et al., 2010[9]	712,507 children (gender proportions	Seizures. Specifically, the	The following codes were used to identify cases,	Charts were reviewed for all subjects with seizure codes during

	not provided) aged 12-23 months who received their first dose of at least one of three vaccines: 1) measles, mumps, rubella, and varicella (MMRV), 2) measles, mumps, rubella (MMR), 3) varicella. The study period was 2000-2008 and the population included patients covered by 7 health plans participating in the Vaccine Safety Datalink program. Charts were reviewed for 451 children. Children with a diagnosis code for epilepsy or convulsions within 42 days prior to the vaccination, in any inpatient or outpatient setting, were excluded.	first seizure or epilepsy diagnosis within 42 days after vaccination. The proportion of events that were febrile seizures was also examined.	but only if they occurred in an emergency department or inpatient setting. Outpatient codes were not used to identify cases. ICD-9 –CM codes: 345.X (epilepsy) 780.3X (convulsions)	days 0 to 42 after MMRV, all subjects with seizure codes 7 to 10 days after separately administered same-day MMR + varicella vaccination, and a random sample of subjects with seizure codes during days 0 to 6 and 11 to 42 after MMR + varicella vaccination. Seizures and febrile seizures were confirmed by chart review, with no specific criteria other than mention in the chart. 87% were febrile seizures **All codes: PPV = 94% (424/451)** **Febrile seizures only:** **Days 7-10 after vaccine: PPV = 90% (208/230)** **Days 0-6 and 11-42 after vaccine: PPV = 83% (184/221)**
Other Studies				
Frost , et al., 2000[10]	655 children and adults of all ages enrolled in the Lovelace Health Plan in New Mexico from January 1, 1995, to June 30, 1996, with an epilepsy diagnosis. 50% were male and 50% were female; 37% were Hispanic. No exclusion criteria were mentioned.	Comparison of two methods (the epilepsy-attributable cost method and the case-control cost method) for estimating the marginal cost of medical care for epilepsy. Incident and prevalent cases of epilepsy were identified.	Individuals were selected if their records contained one or more epilepsy-related diagnosis or procedure codes or a pharmacy fill for an AED. ICD-9-CM codes: 345.X (epilepsy) 780.3 (convulsions) CPT-4 codes for electroencephalogram (EEG) procedures: 95812, 95813 (EEG−monitoring) 95819, 95821 (EEG−awake/sleep) 95816, 95817 (EEG−awake/drowsy) 95822, 95823, 95827 (EEG−sleep) 95839, 95950, 95956 (EEG−monitoring) 95829 (electrocorticogram at	Letters were sent to the primary care physician to verify epilepsy status. If the physician confirmed that the patient had epilepsy, the patient was included in the case cohort. If a physician did not respond to the information request or the response needed further investigation, the patient's medical records were reviewed. PPV was calculated based upon data presented in the article (i.e., 2,474 persons met one or more criteria and were considered possible cases, and 808 patients were verified as having epilepsy). **PPV = 808/2474 = 32.7%** Given the large number of codes and medications in the algorithm, any of which could trigger a chart review, it appears that this algorithm was meant to provide a highly sensitive method of case

			surgery) 95954 (EEG−monitoring with drug/physical activation) 95955 (EEG−intraoperative) 95957 (EEG−digital analysis) 95958 (EEG−monitoring with Wada activation) 95961 (provoked seizures) CPT-4 therapeutic drug assay codes: 80154 (benzodiazepines) 80156 (carbamazepine) 80164 (dipropylacetic acid [valproic acid]) 80168 (ethosuximide) 80184 (phenobarbital) 80185, 80186 (phenytoin, total/free) 80188 (primidone) 80299 (quantitation of drug not elsewhere specified) AEDs: Atreol, Carbamazepine, Clonazepam, Clorazepate, Epitol, Ethosuximide, Ethotoin, Felbamate, Gabapentin, Lamotrigine, Mephenytoin, Mephobarbital, Methsuximide, Pharamethadione, Phenacemide, Phenytoin, Primidone, Trimethadione, Valproate, Valproic acid	finding. Thus, the low PPV is not surprising.
Holden , et al., 2005[11]	All members (any age) continuously enrolled for at least 12 months, from July 1, 1996 to June 30, 1998 (the exploratory phase) and from July 1, 1998 to June 30, 2000 (the confirmatory phase) in the Lovelace Health Plan (LHP), a component of Lovelace Health System in Albuquerque, New	Epilepsy, both prevalent and incident	A variety of algorithms were explored using combinations of the codes and pharmacy claims for AEDs listed below. The authors listed a large number of PPVs for various algorithms examined in the exploratory phase. The confirmatory phase examined whether the PPVs from phase 1 accurately predicted the prevalence of epilepsy in	A clinical review of the medical records to validate a positive case was conducted. Epilepsy cases were considered confirmed if they met four criteria: (1) a documented diagnosis of epilepsy (or seizure disorder), (2) documentation of two or more seizures, (3) seizures that occurred independent of an acute illness or injury, and (4) prescribed an AED for epilepsy. A team of four medical records abstractors led by a registered nurse with previous experience in reviewing medical

	Mexico. The exploratory (phase 1) sample included 617 patients with any of the codes or medications listed in the algorithm column. The cohort consisted of 53% females, 32% were age 65 years or older and 17% were below age 20 years. The confirmatory (phase 2) sample included 644 patients and was stratified to include various predicted probabilities of epilepsy, 51% of whom were female, 33% age 65 years or older, and 33% below age 20 years. Hispanics comprised 30% of the patients phase 1 cohort and 49% of the phase 2 cohort. Both phase 1 and 2 used random sampling of potential cases stratified by combinations of various characteristics observable in administrative data that might have changed their probability of having epilepsy. Febrile seizure cases were excluded from the study.		samples selected by algorithms with those ranges of PPVs This was generally the case, though performance of specific algorithms was not described. They also examined the combined samples of the exploratory and confirmatory phases in logistic regression models that included combinations of the codes used in the algorithms and various characteristics of subjects such as demographics, comorbidities, and specific medications. They used a cutoff of probabilities determined by the models to determine PPVs and other performance characteristics. Due to the complexity of these models, only the key points are summarized here. For complete models, please see the reference. <u>ICD-9-CM diagnosis codes:</u> *"Group A" codes:* 345.00-345.91 (epilepsy, these codes were more commonly used by neurologists to code epilepsy) *"Group B" codes:* 780.3, 780.31, 780.39 (convulsions, these codes were more commonly used by primary care providers to code epilepsy) *"Group C" codes:* 333.2 (myoclonic disorders) 779.0 (convulsions in newborns) 779.1 (cerebral irritability in newborns)	records of patients with seizure disorders collected the data. The other abstractors were certified professional coders and a fourth year nursing student experienced in reviewing medical records. ***<u>Exploratory sample results:</u>*** <u>Diagnoses only, categorized by the number of times such a diagnosis was present:</u> Group A diagnoses: 1 diagnosis: PPV=38.5% 2-3 diagnoses: PPV=69.2% 4 or more diagnoses: PPV=100% Group B diagnoses: 1 diagnosis: PPV=40.7% 2-3 diagnoses: PPV=68.8% 4 or more diagnoses: PV=78.0% Group A and B diagnoses, combined: 1 diagnosis: PPV=31.9% 2-3 diagnoses: PPV=60.0% 4 or more diagnoses: PPV=79.0% Group C diagnoses: 1 diagnosis: PPV=1.9% 2-3 diagnoses: PPV=0.4% 4 or more diagnoses: PPV=0.0% <u>Group A and B diagnoses (345 or 780.3) plus AED fills or blood level monitoring:</u> *No AED fill and no monitoring:* No diagnosis: PPV=0.8% 1 diagnosis: PPV=10.9% 2-3 diagnoses: PPV=20.7% 4 or more diagnoses: PPV=40.0% *No AED fill and but AED monitoring present:* No diagnosis: PPV=10.7% 1 diagnosis: PPV=83.3% 2-3 diagnoses: PPV=100% 4 or more diagnoses: PPV=100% *AED fill present but no AED monitoring:* No diagnosis: PPV=0% 1 diagnosis: PPV=70.0% 2-3 diagnoses: PPV=81.5% 4 or more diagnoses: PPV=88.0% *AED fill and AED monitoring both present:* No diagnosis: PPV=15.0% 1 diagnosis: PPV=69.2%

			780.02 (transient alteration of awareness) 780.2 (syncope and collapse) <u>CPT-4 codes:</u> 95812-95961 (EEG procedures) 61885, 64287, 64553, 64573 (vagus nerve stimulation procedures) 80156, 80164, 80168, 80184, 80185, 80186, 80188, 80201 (AED blood level determinations) <u>AEDs:</u> Carbamazepine, Tegretol, Epitol, Clonazepam, Klonopin, Neurongin, Lamictal, Phenobarbital, Dilantin, Phenytoin, Primidone, Mysoline, Depakene, Depakote, Valproic Acid, Topamax, Topiramate, Clorazepate, Benzodiazepines, Ethosuximide, Zarontin, Febatol, Mebaral, Acetazolamide, Gabitril	2-3 diagnoses: PPV=87.5% 4 or more diagnoses: PPV=87.5% <u>All groups of diagnoses combined with the presence of at least one AED fills or blood level monitoring code:</u> *No drug fill or monitoring code* No diagnosis: PPV=0.8% 1 diagnosis: PPV=10.9% 2-3 diagnoses: PPV=20.0% 4 or more diagnoses: PPV=40.0% *At least one drug fill or monitoring code* No diagnosis: PPV=6.3% 1 diagnosis: PPV=71.4% 2-3 diagnoses: PPV=85.4% 4 or more diagnoses: PPV=88.5% ***<u>Logistic regression models to predict epilepsy:</u>*** Data from the exploratory phase (phase 1) and the confirmatory phase (phase 2) were combined to permit refinement of logistic regression models (phase 3 of the study) and to provide more stable estimates of the parameters. A probability cutoff of 0.28 predicted by the model was used to classify people as model-defined cases or non-cases for calculating performance characteristics. Model l used diagnoses as predictor variables. Only diagnoses from groups A and B were significant predictors of epilepsy: PPV: 79.2% Sensitivity: 76.9% Specificity: 92.5% Model 2 used diagnoses and the presence of specific AEDs (determined by either prescription or blood level monitoring) entered separately in the model: PPV: 83.9% Sensitivity: 81.8% Specificity: 93.8% Model 3 used diagnoses, AEDs and diagnostic procedures (EEG or vagus nerve stimulation), neither of which added value to the algorithm except that an EEG was

				predictive of not having epilepsy: PPV: 84.1% Sensitivity: 81.2% Specificity: 94.1% The effects of age and ethnicity were also examined in all three models. Model 4: To increase the positive predictive value, an additional analysis to minimize false positives was conducted (this model added psychiatric disorders [mood disorders such as anxiety and depression] and other medical conditions [hypertension and cardiac dysrhythmia]. Age and ethnicity were dropped from the model. This model did not appreciably improve the PPV. PPV 85.3%: Sensitivity: 83.1% Specificity: 94.0% According to the authors, the best model was Model 2. Sensitivity and specificity results should be interpreted with consideration that the sample was not randomly selected. It included the exploratory cohort that had indicators of epilepsy, and the confirmatory cohort which was artificially stratified to include people with different probabilities of epilepsy.
Jette , et al., 2010[12]	Patients from all adult and pediatric acute care sites in the Calgary Health Region in Alberta, Canada were included. Charts from a seizure monitoring unit for a 2 year period were reviewed (n=127), as were other randomly selected charts of emergency room or hospital patients with codes for seizures or seizure-like conditions. The mean age of the charts reviewed varied in each database but was approximately 42	1) Validity of ICD-9-CM and ICD-10 coding for epilepsy from an emergency room (Ambulatory Care Classification System [ACCS]) database and an inpatient Discharge Abstract Database (DAD) and validity of ICD-10 coding for epilepsy from a seizure monitoring unit (SMU) database. 2) Comparison of	ICD-9-CM codes for epilepsy in the primary diagnostic position: 345.X Nonepilepsy ICD-9-CM codes in the primary diagnostic position for diagnoses that may resemble epilepsy: 346.X (migraine) 435.X (transient ischemic attack) 780.2 (syncope) 780.3X (convulsions) ICD-10 codes for epilepsy in the primary diagnostic position: G40.X, G41.X Nonepilepsy ICD-10 codes	Because all patients in the SMU underwent video-EEG (electroencephalography) monitoring, the certainty of their diagnosis was high. A total of 127 charts from the SMU were reviewed. Chart review from the SMU admissions allowed sensitivities, specificities and negative and positive predictive values to be calculated. These SMU hospitalizations were captured and coded in the DAD with ICD-10 codes. From ACCS and DAD, a random sample of records was selected; 486 records with ICD-9-CM codes and 454 with ICD-10 codes (total 940). An epileptologist and a neurology resident reviewed each

	years with a standard deviation of approximately 25 years. A total of 158 charts came from children's hospitals. ICD-9-CM time period = 2000-2001. n=486 charts were reviewed. ICD-10 time period = 2004-2005. n=454 charts were reviewed. No exclusion criteria were mentioned.	variations in coding validity between the two ICD systems and between the various hospital settings in a large Canadian hospital.	that may resemble epilepsy in the primary diagnostic position: G43.1 (classical migraine) G45.x (transient ischemic attack) R55 (syncope) R56.0, R56.8 (convulsion) The nonepilepsy codes were for conditions that may resemble epilepsy. From the nonepilepsy cases, the specificity was calculated (i.e., the proportion of nonepilepsy cases identified from the SMU charts that were recorded in the DAD as nonepilepsy cases).	chart independently. The PPV was calculated as the proportion of epilepsy cases from codes that were confirmed as having epilepsy. The NPV was calculated as the number of patients with codes for diagnoses that resemble epilepsy that were confirmed to not have epilepsy. **The following performance characteristics were determined for the ICD-10 epilepsy coding from the SMU chart review:** **Sensitivity = 99%,** **Specificity = 70%,** **PPV = 85%,** **NPV = 97%.** **The PPV and NPV for ICD-9-CM epilepsy codes from the ACCS database were, respectively, 99% and 97% and from the DAD were 98% and 99%.** When the convulsion code (780.3) was included in the case definition to determine if any of these were nonepilepsy but organic convulsions were epilepsy that was miscoded, **the PPV dropped to 84.0%**. However, the authors noted that a large number of epilepsy cases had been miscoded as convulsions. **The PPV and NPV for ICD-10 epilepsy codes from the ACCS database were, respectively, 100% and 90% and from the DAD were 98% and 99%.** When the convulsion code (R56) was included in the case definition to determine if any of these nonepilepsy but organic convulsions were epilepsy that was miscoded as epilepsy, the **PPV dropped to 75.5%.** However, the authors noted that a large number of epilepsy cases had been miscoded as convulsions. In the **ICD-9-CM charts**, the code for grand mal status (345.3) had a **PPV of 83.9%,** the code for partial epilepsy with impairment of consciousness (345.4) had a **PPV of 89.3%,** and the code for convulsions excluding epileptic convulsions and convulsions of

				newborn (780.3) had a **PPV of 45.2%**. Other codes did not perform well or were not found in the sample. In the **ICD-10 charts**, the code for grand mal status epilepticus (G41.0) had a **PPV of 100%**, the code for complex partial status epilepticus (G41.2) had a PPV of 83.3%, and the code for localization-related symptomatic epilepsy and epileptic syndromes with complex partial seizures (G40.2) had a **PPV of 77.6%**. All other epilepsy codes had PPVs of less than 40% or were not found in the sample. The code for febrile convulsions (R56.0) had a **PPV of 90.9%**, while the code for other and unspecified convulsions (R56.8) had a **PPV of 32.9%**. No differences were seen in the performance characteristics by sites (adult or children's hospitals) or visit type (ER or hospital). Overall, the PPV and NPV of epilepsy codes was quite good when all types of epilepsy are considered together. However, epilepsy was frequently miscoded by coding staff as convulsions despite being labeled as epilepsy in the charts.
Parko and Thurman, 2009[13]	All Navajo tribe members (n= 226,496; 117,255 female and 107,714 male) of any age (median age 23 years) residing in the Navajo Reservation who had at least one medical or dental encounter between October 1, 1998, and September 30, 2002. The sample for chart review was drawn from three service units (Crownpoint, Kayenta, Shiprock). These three geographic units—including more than a third of the total	Prevalence of epilepsy and seizures in the Navajo Nation.	<u>ICD-9-CM codes:</u> 345.0-345.9 (epilepsy) 333.2 (myoclonus) 779.0 (convulsions in newborn) 779.1 (cerebral irritability in newborns) 780.31 (febrile convulsions) 780.39 (other convulsions)	The analysis of the Indian Health Service data set revealed that 4,181 Navajo received an ICD-9-CM code indicating epilepsy or seizures. Within the service units of Crownpoint, Kayenta, and Shiprock, the service unit data set yielded 1,367 records indicating possible seizures or epilepsy. Medical charts were located and reviewed for 1,277 of these. Chart reviews were performed by neurologists, clinical pharmacists trained in epilepsy care, and medical students supervised by neurologists. Based on documentation in the medical chart, each patient was placed into one of five categories: (1) epilepsy with documentation of two or more unprovoked

	population of Navajo Nation—represented the range in availability of health care and specialty services. No exclusion criteria were mentioned.			seizures, (2) seizure if they had a single seizure (provoked or not) or two or more provoked seizures (e.g., alcohol withdrawal), (3) febrile seizure in a child younger than 5 years of age with seizures in the setting of fever that were labeled by caregiver as ''febrile seizure,'' (4) no seizure if there was no evidence of any seizures or epilepsy, and (5) missing if the chart was unavailable. Inter-reviewer reliability was tested for each chart reviewer on each day of chart review by independent coding of three charts by two separate reviewers. There was 100% concordance on the charts that were compared. Across all ages, coding with either 345.X or 780.3X yielded: **PPV = 90% for clinical diagnosis of epilepsy or seizures** **PPV = 62% for a clinical diagnosis of epilepsy per se (recurrent unprovoked seizures).** The authors of the study state that a corrective factor is necessary when relying on ICD-9-CM-coded data to estimate the prevalence of epilepsy per se since the PPV is much lower.
Pugh , et al., 2008[14]	The overall study (prescribing trends) included national Veteran Health Administration (VA) inpatients and outpatients ≥66 years who received at least one AED between fiscal years 2000 and 2004 and also had a diagnosis indicative of epilepsy (n = 72,358). Of these, 41,867 had chronic epilepsy, and 9,682 had new-onset epilepsy. Of the new-onset epilepsy cases, 98% were male, 78.5% were white, 15.8% were black, 4.9% were Hispanic and 9.8%	New-onset epilepsy in older veterans	Epilepsy was determined from administrative data by at least one of the ICD-9-CM codes listed below, and at least one antiepileptic drug fill. New onset cases had at least a year of prior data with no diagnosis for seizures or convulsions, and a fill for an antiepileptic drug within a year after the diagnosis. Algorithm details: ICD-9-CM codes: 345.XX (epilepsy) 780.39 (other convulsions) At least one antiepileptic drug from the VA	Two researchers abstracted electronic medical records of all patients identified as having new-onset epilepsy and who received VA care at the South Texas Veterans Health Care System (STVHCS). Diagnosis of epilepsy was confirmed if epilepsy was identified in the problem list of the chart or a description of seizures in progress notes. Raters agreed 95% of the time on epilepsy diagnosis and 98% of the time on new-onset status. Disagreements were resolved by consensus. **Of the 126 patients identified using administrative data, a diagnosis of epilepsy was confirmed in 119, giving a conservative PPV of 94%**

	were other. The study used national VA inpatient, outpatient, and pharmacy data (1998-2004), in addition to Medicare data (1999-2004). To identify these patients, the study used an adaptation of the algorithm validated by Holden. [11] For the validation review, the study included a subset of patients: all patients identified as having new-onset epilepsy and who received VA care at the South Texas Veterans Health Care System (STVHCS). The study only included patients age 66 years and older to ensure that at least one year of Medicare data were available for new onset epilepsy diagnoses.		between October 1, 1998 and September 30, 2003	**(119/126).** Three of the remaining 7 patients had diagnoses of convulsion (780.39) on multiple occasions, and one had a 345 epilepsy ICD-9-CM code in the administrative data, which improved the investigators' confidence that those three patients had epilepsy. Including the patients as being as being true positive cases, **the PPV was 98% (123/126).** If the algorithm is to be applied in VA data, it is important to note that 60% of the first seizures were documented in Medicare data, likely due to treatment in non-VA emergency departments.
Hardie , et al., 2007[15]	Elderly residents (total number, gender proportions not provided) 65 years of age or older in eleven nursing homes managed by Beverly Enterprises. Sample selection resulted in 144 residents (n = 144; 51% male, 49% female) The time period of the study was not mentioned. No exclusion criteria were mentioned.	1) The validity of the paper Minimum Data Set (MDS) by calculating the extent to which documentation of epilepsy or seizure disorder on the paper MDS agreed with a neurologist's review of the nursing home chart. 2) Agreement between the paper MDS assessment forms and their computerized counterparts.	For the paper MDS, a resident was considered to have a seizure disorder or epilepsy if: the "Seizure Disorder" item was checked or ICD-9-CM codes 345.XX or 780.3X were listed or the words "epilepsy, "seizure" or "convulsion" were listed in the text section. For the computerized MDS, the same criteria were used; however, text documenting epilepsy or seizure disorder was not available in the computerized MDS file.	Records for all elderly residents with nursing home identified epilepsy or seizure disorders were selected. Records of non-epilepsy/seizure disorder residents (without regard to antiepileptic drug use) were matched on a one-to-one basis with the epilepsy/seizure disorder residents. Records for all remaining residents without a diagnosis of seizures or epilepsy who received antiepileptic drugs were selected so that abstractors could not assume a resident's diagnostic status by their treatment. At each nursing home, abstractors searched selected residents' records for the most recent full MDS. A neurologist who was masked from knowledge of the residents' epilepsy or seizure

				disorder classification on the MDS conducted chart reviews at each nursing home. He then searched the remainder of each nursing home record for any mention of an epilepsy or seizure diagnosis and any supporting information. Overall, agreement between the documentation of epilepsy or seizure disorder on the paper version of the MDS and a neurologist's review of the nursing home record for documentation of epilepsy or seizure was 92.3% (131 agreements out of 142 paper MDS–neurologist pairs). **The PPV (likelihood the neurologist would find epilepsy or seizure, when it was documented in the paper MDS) was 87.8%** (43 agreements in 49 instances of epilepsy or seizure disorder on the paper MDS). **The NPV (likelihood the neurologist would not find epilepsy or seizure when it was not documented on the paper MDS) was 94.6%** (88 agreements in 93 instances of no epilepsy or seizure disorder on the paper MDS). Agreement between the documentation of epilepsy or seizure disorder on the paper version of the MDS and documentation of epilepsy or seizure disorder on the computerized MDS was 97.8% (137 agreements out of 140 MDS paper-computerized pairs). **The PPV (agreement with the paper MDS when epilepsy/seizure disorder was documented on the computerized MDS) was 97.9%** (47 agreements from 48 instances of epilepsy or seizure disorder on the computerized MDS), **the NPV (agreement with the paper MDS when epilepsy or seizure was not documented on the computerized MDS) was 97.8%** (90 agreements from 92 instances of no documentation of epilepsy or seizure disorder on the computerized MDS).

Gardner, , et al., 2000[16]	A cohort of 9,218 adult tramadol users and 37,232 concurrent nonusers (mean age 44.5 years; 31.1% male, 68.9% female) from 12 UnitedHealth Group-affiliated health plans between April 1, 1995, and December 31, 1996. The users cohort consisted of all those whose pharmacy records indicated a first prescription for tramadol (index date) between April 1, 1995, and December 31, 1996, and who were continuously enrolled for at least 90 days before receiving the first prescription and for at least 60 days after receiving it (index period). The nonusers cohort consisted of a stratified random sample of all members continuously enrolled for a concurrent time period who had a drug benefit but no prescription claim for tramadol, matched individually and without replacement in a 4:1 ratio to tramadol users by age group, gender, time span of enrollment, and health plan. The index date of the user was assigned to the nonuser within each matched set. Wherever possible, the set of users-nonusers was followed for 60 days after the date of the last prescription for tramadol. Thus, the	The rate and risk of incident tramadol-associated seizures.	A case-control study was performed. Cases and controls (noncases) were selected from within the tramadol users cohort. A presumptive seizure case was any person whose hospital or physician visit claims files included any of the following primary or secondary codes on or after the index date, but not in the 90 days before the index date: ICD-9-CM diagnosis codes: 780.3 (convulsions) 345.0-345.9 (epilepsy) 333.2 (progressive myoclonus) ICD-9-CM procedure codes: 89.13-89.15, 89.19 (neurologic examination, EEG, other nonoperative neurologic functions tests, or video and radiotelemetered EEG monitoring) CPT-4 codes: 95950, 95951 (8-channel EEG) 95953, 95954 (16-channel EEG) 95956 (EEG recording and interpretation by channel) 95961, 95962 (functional cortical mapping) Presumptive non-cases were selected randomly after antiepileptic drug users were excluded. Non-cases were eligible if they had no evidence within the index period of any code listed above.	Medical record information was obtained to confirm case status. Case status was confirmed by determining the claims-identified seizure event occurring after (and not before) the index date as documented in the medical record and also confirmed by an independent neurologist who reviewed the medical records. Noncases were confirmed if they had no notation of a seizure event after (or before) the index date in their medical records. In the case-control study, medical records abstractions were completed for 51% (38/74) of cases and 55% (101/183) of noncases. PPV was calculated based upon data presented in the article (i.e., 8 cases were identified as having epilepsy out of the 38 records that were abstracted). **PPV = 8/38 = 21%** NPV was calculated based upon data presented in the article (i.e., of 101 medical records abstracted for claims noncases, 99 were confirmed as not having had a seizure after taking tramadol) **NPV = 99/101 = 98%**

	observation period varied among individuals but was the same for each matched set of users-nonusers, a minimum of 151 days. Subjects in either cohort who did not meet at least the 151-day criteria were excluded. In addition, any member with a seizure claim or with any prescription for an antiepileptic drug (AED) before the index date within the index period was excluded.			

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Epilepsy and seizures are difficult to study for many reasons, including variability in age of onset, demographics, and risk factors. Epilepsy has multiple causes, and is not a single disease entity. Not all seizures derive from epilepsy. The associated billing codes reflect this conundrum; while the 345.X codes are relatively specific for epilepsy, a recently diagnosed patient - especially after a single unprovoked seizure - may be coded under 780.3 or 780.39 until supportive data is obtained or further seizures occur.

The algorithms used in the reviewed articles vary according to the study aims, population, dataset(s) used, and statistical methods. For example, studies of incident seizures following vaccination in children properly use a wider range of billing codes (including 333.2, 779.X and 780.3X), whereas those studies focused on the prevalence of epilepsy use codes 345.x and 780.3X. When used, final adjudication of case-inclusion is performed by a neurologist, but mention is often not explicitly made whether the neurologist has sub-specialty training in epilepsy (which might affect the validity of the measure).

The ICD-9 billing codes used in the reviewed studies are complete (and in some cases, perhaps overly broad). Study of ICD-10 codes would require greater application of this billing system in clinical practice. Use of electroencephalography (EEG) and anti-epileptic drug (AED) level procedure codes, and AED prescription data, are of low specificity and sensitivity. For example, EEG is not universally applied to the diagnosis of a single seizure, either provoked or unprovoked. EEG, on the other hand, is used to diagnose conditions other than seizures and epilepsy (e.g., coma). Many AEDs are prescribed for non-epilepsy indications, both on- and off-label. Plasma levels of newer generation AEDs (those released to the U.S. market after 1993) are obtained less often than those of older generation AEDs.

Diagnostic criteria for epilepsy, seizures and convulsions have not significantly changed in recent decades, but may vary between practitioner (primary care vs neurology vs epilepsy specialists) and site (outpatient, emergency department, and inpatient). Epilepsy and seizures are primarily clinically diagnosed conditions, and a pathognomonic diagnostic test does not exist.

Future studies should consider the inclusion of laboratory codes (including those for prolonged EEG with video; 95956) applicable to the study hypothesis. Caution should be used, however, in recognition of potential changes in practice patterns driven in part by third-party payer reimbursement and the impact of current and future health care law. For example, the reimbursement for prolonged EEG recording is being restricted in length of days under certain circumstances. This might potentially affect case ascertainment. There is also a trend, at least within the epilepsy specialist community, to perform less "routine" testing of AED levels. If AED prescription fill data is used in future studies of epilepsy, it might be more specific and sensitive to focus on AEDs used almost exclusively for epilepsy, such as levetiracetam.

In summary, the reviewed studies provide a lattice-like framework for future studies, with foundational information but many holes to fill. Designing broadly generalizable studies will be difficult based on the present state of the literature, billing codes, and medical practice. Variables to consider include the nature of the study population, the desired balance in sensitivity and specificity, the structure of available databases, coding and billing practices, future development of new AEDs and changes in prescribing patterns, and application of diagnostic tests.

Future studies of incident seizures or epilepsy in association with the use of pharmacological, biological, or device therapies should consider:

- Case ascertainment methods that employ databases applicable to the research hypothesis, with case numbers to provide adequate power given the often-low risk of such exposures.
- Use of diagnostic codes appropriate to the question, e.g., 345.X for epilepsy, 780.3 and 780.39 for seizures/convulsions, perhaps 333.2 and 779.0 and 779.1 in children. Codes 780.02 and 780.2 are likely to be insufficiently specific.
- When applicable, final case-inclusion adjudication performed by a neurologist with epilepsy training or experience.
- The changing landscape of medical practice and therapeutic indications and use. A study could potentially be conducted that would lack applicability or generalizability by the time it was published.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

The studies we identified included a broad range of settings, age groups, and algorithms. PPVs ranged from 21% (for predicting incident seizures from tramadol) to 98% (for predicting the agreement between medical records and computerized Minimum Data Sets in nursing homes). For these reasons, it is difficult to draw any strong conclusions. However, the PPVs were generally best in studies in which epilepsy diagnoses were required, whereas those that used non-specific indicators such as the presence of an EEG or AED drug level monitoring without requiring diagnosis codes had low PPVs. The latter sets of codes would be more appropriate for case identification if sensitivity was the goal and all cases would be confirmed by medical record review. Studies examining the sensitivity of algorithms focused exclusively on epilepsy, as opposed to isolated seizure events. Sensitivity ranged from 70% to 99%.

All algorithms included 345.X and either 780.3 (10 studies) or 780.39 (1 study). Six of the 11 studies used 333.2. In populations that included children, 779.0 was also fairly common. Several other codes were used, but not consistently.

The study by Holden, et al. was the most comprehensive, examining several variables and concluding that the best model to identify epilepsy cases was an algorithm that contained several ICD-9-CM codes in addition to either a pharmacy fill for an antiepileptic drug or a CPT-4 code for antiepileptic drug monitoring.[11] This model had a PPV of 83.9% and a sensitivity of 81.8%. On the other hand, the study by Parko and Thurman just used ICD-9-CM codes and found a PPV of 90% for a clinical diagnosis of epilepsy or seizures, although for epilepsy per se (two or more unprovoked seizures) the PPV was 62%, leading them to suggest that a corrective factor is necessary when relying on ICD-9-CM-coded data to estimate the prevalence of epilepsy per se.[13]

The PPV of ICD-9-CM code 345.X for identifying epilepsy increased substantially as the number of diagnosis codes in a person's records increased in the Holden , et al.study.[11] The PPV was only 38.5% if one diagnosis code was present, while it increased to 100% if four diagnosis codes were present. In another study the PPVs for 345.X exceeded 80% when the code was in the primary diagnostic position.[12] Thus, this code may perform better in the primary diagnostic position or if it occurs multiple times in records. Most studies did not report the PPV of codes separately. When examined, there was variability in the performance of codes for different types of epileptic seizures, with status epilepticus codes performing the best. Less specific codes for convulsions or seizure-like events performed variably. These codes did not perform particularly well in most studies of infants receiving vaccines, though one study found that emergency department and inpatient codes were much more reliable compared to outpatient codes.[7] One study that used only emergency department or inpatient codes to identify seizures found a PPV of 94%.[9] This may lead to the conclusion that such studies should rely on only emergency department or inpatient diagnoses to identify seizures. Adding requirements for drugs or procedures to an algorithm that uses diagnostic codes would assumedly increase specificity and decrease sensitivity. It is clear from the available studies that using procedure codes for EEGs or prescription claims for drugs possibly used for epilepsy or convulsions in the absence of a diagnostic code is not recommended. These procedures and medications are not specific to epilepsy or seizure events, so a diagnosis needs to be part of any algorithm to maintain specificity. Given that many newer AEDs require no drug level monitoring, requiring an AED drug level monitoring procedure in algorithms to identify epilepsy is not recommended. This would result in lack of sensitivity of the algorithm.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

The demographic composition of study populations appeared to be quite diverse. However, studies in adults tended to focus on epilepsy diagnoses rather than isolated seizure events, so the performance of seizure-specific algorithms cannot be determined. Most of the work to identify seizures examined data on very young children who received vaccines. Therefore, it is recommended that future studies might attempt to develop valid algorithms to identify incident seizures in older children or adult populations.

Other gaps in the current literature include determining which algorithms would be best for identifying any type of seizure or convulsion as opposed to epilepsy (two or more unprovoked seizures). It may also be important to determine the validity of epilepsy codes based on diagnostic position, or re-explore the importance of the number of times that the code occurs given the variability in PPVs among studies and only one study examining this factor. Also, more research is needed to determine how much is gained or

lost by adding antiepileptic drug fills, drug monitoring, or other codes to the algorithms, though a requirement of drug level monitoring is not recommended given that drug levels of many newer AEDs are not checked. From the available evidence the added value of drug indicators seems limited, though addition of an antiepileptic drug indicator to identify epilepsy per se may be reasonable. More research is also needed to determine the best algorithm for identifying vaccine-related seizures since in general the three studies that examined this outcome had low PPVs, and the PPVs appeared to be influenced by the location of the medical encounter, age of the patient, and timing of the event relative to vaccine administration. It may be that only emergency department and inpatient codes should be utilized in such studies, given the apparent poor performance of outpatient codes for this purpose. In addition, we only identified one study that used ICD-10 codes, so this is another area that needs more research when ICD-10 codes become more widely utilized.

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VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLE

Barlow WE, Davis RL, Glasser JW, , et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med*. 2001; 345(9): 656-661.

BACKGROUND: The administration of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with adverse neurologic events, including seizures. We studied the relation between these vaccinations and the risk of a first seizure, subsequent seizures, and neurodevelopmental disability in children. METHODS: This cohort study was conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures. We calculated the relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities. RESULTS: Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42). Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). Neither vaccination was associated with an increased risk of nonfebrile seizures. Analyses of automated data alone gave results similar to the analyses of the data from medical-record reviews. The number of febrile seizures attributable to the administration of DTP and MMR vaccines was estimated to be 6 to 9 and 25 to 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities. CONCLUSIONS: There are significantly elevated risks of febrile seizures on the day of receipt of DTP vaccine and 8 to 14 days after the receipt of MMR vaccine, but these risks do not appear to be associated with any long-term, adverse consequences.

Frost FJ, Hurley JS, Petersen HV, Gunter MJ, Gause D. A comparison of two methods for estimating the health care costs of epilepsy. *Epilepsia*. 2000; 41(8): 1020-1026.

PURPOSE: Previous studies have estimated medical care costs of epilepsy by applying unit costs to estimated utilization or by summing costs for (a) ambulatory care and hospitalizations coded as epilepsy and (b) procedures and drugs specifically associated with the diagnosis or treatment of epilepsy. These methods may underestimate the cost of medical care for epilepsy. Two methods for estimating the medical care costs of epilepsy ("epilepsy-attributable cost method" and "case-control cost method") were compared. METHODS: The study population was 655 individuals with an epilepsy diagnosis enrolled in a managed care plan in the southwestern United States. The epilepsy-attributable costs were determined by summing costs for inpatient and outpatient encounters coded as epilepsy, procedures for the diagnosis or treatment of epilepsy, and drugs used to treat epilepsy. The case-control method determined costs by calculating the difference in total costs between cases and 1,965 age- and gender-matched controls. RESULTS: The case-control epilepsy costs were $2,923 per case compared with epilepsy-attributable costs of $1,335 per case. The case-control method found statistically significant differences in costs between cases and controls for inpatient care, prescription drugs, and 8 of 11 categories of outpatient care. The largest contributors to the discrepancy between estimates were inpatient care, emergency department care, laboratory tests, and "other specialist" care. CONCLUSIONS: Epilepsy-attributable costs accounted for only 46%

of the total difference in costs between epilepsy cases and controls. Persons with epilepsy use more medical services than controls, but a substantial portion of this care is not coded to epilepsy.

Gardner JS, Blough D, Drinkard CR, , et al. Tramadol and seizures: A surveillance study in a managed care population. *Pharmacotherapy*. 2000; 20(12): 1423-1431.

STUDY OBJECTIVE: To investigate the occurrence of tramadol-associated seizures. DESIGN: Retrospective cohort and case-control studies. SETTING: UnitedHealth Group-affiliated independent practice model health plans, from different regions of the United States, contracting with large networks of physicians. INTERVENTION: Analysis of administrative data from a large U.S. managed care population. PATIENTS: A cohort of 9218 adult tramadol users and 37,232 concurrent nonusers. MEASUREMENTS AND MAIN RESULTS: Fewer than 1% of users (80) had a presumed incident seizure claim after the first tramadol prescription. Risk of seizure claim was increased 2- to 6-fold among users adjusted for selected comorbidities and concomitant drugs. Risk was highest among those aged 25-54 years, those with more than four tramadol prescriptions, and those with history of alcohol abuse, stroke, or head injury. A case-control study among users was conducted to validate incident seizure outcomes from medical records. Only eight cases were confirmed, and all had cofactors associated with increased seizure risk. CONCLUSION: In a general population, risk of seizure may be associated with long-term therapy with tramadol or the presence of cofactors, or confined to a small sensitive population subset.

Hardie NA, Garrard J, Gross CR, , et al. The validity of epilepsy or seizure documentation in nursing homes. *Epilepsy Res*. 2007; 74(2-3): 171-175.

Recent studies have reported that epilepsy and seizures are common in nursing homes. Prevalence has been reported to range from 5 to 9% and antiepileptic drug (AED) use is even more common. Most of these studies have relied on various forms of nursing home records, but the validity of this source data, while assumed, has not been verified. This study evaluated the degree of agreement between the Minimum Data Set (MDS), both paper and electronic versions, and actual medical records available at the nursing home. Records of 144 residents were evaluated; agreement between paper and electronic versions of the MDS was 97.8%. Agreement between the paper version of the MDS and neurologists review of the nursing home record was 92.3%. However, the criteria for diagnosing epilepsy or seizure were not well documented. Nevertheless, the agreement among nursing home records, paper MDS and electronic MDS is great enough to allow the electronic MDS to be used as a research tool, but more investigation of the actual criteria used by nursing home physicians in diagnosing epilepsy and seizures is necessary.

Holden EW, Grossman E, Nguyen HT, , et al. Developing a computer algorithm to identify epilepsy cases in managed care organizations. *Dis Manag*. 2005; 8(1): 1-14.

The goal of this study was to develop an algorithm for detecting epilepsy cases in managed care organizations (MCOs). A data set of potential epilepsy cases was constructed from an MCO's administrative data system for all health plan members continuously enrolled in the MCO for at least 1 year within the study period of July 1, 1996 through June 30, 1998. Epilepsy status was determined using medical record review for a sample of 617 cases. The best algorithm for detecting epilepsy cases was developed by examining combinations of diagnosis, diagnostic procedures, and medication use. The best algorithm derived in the exploratory phase was then applied to a new set of data from the same MCO covering the period of July 1, 1998 through June 30, 2000. A stratified sample based on ethnicity and age was drawn from the preliminary algorithm-identified epilepsy cases and non-cases. Medical record review was completed for 644 cases to determine the accuracy

of the algorithm. Data from both phases were combined to permit refinement of logistic regression models and to provide more stable estimates of the parameters. The best model used diagnoses and antiepileptic drugs as predictors and had a positive predictive value of 84% (sensitivity 82%, specificity 94%). The best model correctly classified 90% of the cases. A stable algorithm that can be used to identify epilepsy patients within MCOs was developed. Implications for use of the algorithm in other health care settings are discussed.

Jette N, Reid AY, Quan H, Hill MD, Wiebe S. How accurate is ICD coding for epilepsy? *Epilepsia*. 2010; 51(1): 62-69.

PURPOSE: Assess the validity of ICD-9-CM and ICD-10 epilepsy coding from an emergency visit (ER) and a hospital discharge abstract database (DAD). METHODS: Two separate sources of patient records were reviewed and validated. (1) Charts of patients admitted to our seizure monitoring unit over 2 years (n = 127, ICD-10 coded records) were reviewed. Sensitivity (Sn), specificity (Sp), and positive and negative predictive values (PPV and NPV) were calculated. (2) Random sample of charts for patients seen in the ER or admitted to hospital under any services, and whose charts were coded with epilepsy or an epilepsy-like condition, were reviewed. Two time-periods were selected to allow validation of both ICD-9-CM (n = 486) and ICD-10 coded (n = 454) records. Only PPV and NPV were calculated for these records. All charts were reviewed by two physicians to confirm the presence/absence of epilepsy and compare to administrative coding. RESULTS: Sample 1: Sn, Sp, PPV, and NPV of ICD-10 epilepsy coding from the seizure monitoring unit (SMU) chart review were 99%, 70%, 85%, and 97% respectively. Sample 2: The PPV and NPV for ICD-9-CM coding from the ER database were, respectively, 99% and 97% and from the DAD were 98% and 99%. The PPV and NPV for ICD-10 coding from the ER database were, respectively, 100% and 90% and from the DAD were 98% and 99%. The epilepsy subtypes grand mal status and partial epilepsy with complex partial seizures both had PPVs >75% (ICD-9-CM and ICD-10 data). DISCUSSION: Administrative emergency and hospital discharge data have high epilepsy coding validity overall in our health region.

Klein NP, Fireman B, Yih WK, , et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010; 126: e1-e8.

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine. METHODS: Using 2000-2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses. RESULTS: MMRV vaccine recipients (83,107) were compared with recipients of MMR + varicella vaccines (376,354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43-2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10,000 doses (95% confidence interval: 2.6-5.6). CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of

separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines.

Parko K, Thurman DJ. Prevalence of epilepsy and seizures in the Navajo nation 1998-2002. *Epilepsia*. 2009; 50(10): 2180-2185.

PURPOSE: To determine the prevalence of epilepsy and seizures in the Navajo. METHODS: We studied 226,496 Navajo residing in the Navajo Reservation who had at least one medical encounter between October 1, 1998 and September 30, 2002. We ascertained and confirmed cases in two phases. First, we identified patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes signifying epilepsy or seizures using Indian Health Service (IHS) administrative data. Second, we reviewed medical charts of a geographic subpopulation of identified patients to confirm diagnoses and assess the positive predictive value of the ICD-9-CM codes in identifying patients with active epilepsy. RESULTS: Two percent of Navajo receiving IHS care were found to have an ICD-9-CM code consistent with epilepsy or seizures. Based on confirmed cases, the crude prevalence for the occurrence of any seizure (including febrile seizures and recurrent seizures that may have been provoked) in the geographic subpopulation was 13.5 per 1,000 and the crude prevalence of active epilepsy was 9.2 per 1,000. Prevalence was higher among males, children under 5 years of age, and older adults. DISCUSSION: The estimated prevalence of active epilepsy in the Navajo Nation is above the upper limit of the range of reported estimates from other comparable studies of U.S. communities.

Pugh MJ, Van Cott AC, Cramer JA, , et al. Trends in antiepileptic drug prescribing for older patients with new-onset epilepsy: 2000-2004. *Neurology*. 2008; 70(22 Pt 2): 2171-2178.

BACKGROUND: Newer antiepileptic drugs (AEDs) have been shown to be equally efficacious as older seizure medications but with fewer neurotoxic and systemic side effects in the elderly. A growing body of clinical recommendations based on systematic literature review and expert opinion advocate the use of the newer agents and avoidance of phenobarbital and phenytoin. This study sought to determine if changes in practice occurred between 2000 and 2004--a time during which evidence and recommendations became increasingly available. METHODS: National data from the Veterans Health Administration (VA; inpatient, outpatient, pharmacy) from 1998 to 2004 and Medicare data (1999-2004) were used to identify patients 66 years and older with new-onset epilepsy. Initial AED was the first AED received from the VA. AEDs were categorized into four groups: phenobarbital, phenytoin, standard (carbamazepine, valproate), and new (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate). RESULTS: We found a small reduction in use of phenytoin (70.6% to 66.1%) and phenobarbital (3.2% to 1.9%). Use of new AEDs increased significantly from 12.9% to 19.8%, due primarily to use of lamotrigine, levetiracetam, and topiramate. CONCLUSIONS: Despite a growing list of clinical recommendations and guidelines, phenytoin was the most commonly used antiepileptic drug, and there was little change in its use for elderly patients over 5 years. Research further exploring physician and health care system factors associated with change (or lack thereof) will provide better insight into the impact of clinical recommendations on practice.

Shui IM, Shi P, Dutta-Linn MM, , et al. Predictive value of seizure ICD-9 codes for vaccine safety research. *Vaccine*. 2009; 27(39): 5307-5312.

Post-licensure vaccine safety studies often monitor for seizures using automated screening of ICD-9 codes. This study assessed the positive predictive value (PPV) of ICD-9 codes used to identify seizure

visits in children aged 6 weeks to 23 months who were enrolled in seven managed care organizations during January 2000 to December 2005. ICD-9 codes were used to identify visits for seizures in the 0-30-day period following receipt of a pneumococcal vaccine. Visits were stratified by setting of diagnosis (emergency department (ED), outpatient, and inpatient). Review of medical records confirmed whether the visit represented a true acute seizure event. 3233 visits for seizures were identified; 1024 were randomly selected for medical record review and 859 (84%) had records available. The PPV of ICD-9 codes was highest in the ED setting (97%), followed by the inpatient setting (64%). In the outpatient setting, computerized codes for seizures had very low PPV: 16% on days 1-30 following vaccination and 2% for visits on the same day of vaccination. An estimated 77% of true seizures identified were from the ED or inpatient settings. In conclusion, when using ICD-9 codes to identify seizure outcomes, restricting to the ED and inpatient settings of diagnosis may result in less biased preliminary analyses and more efficient vaccine safety studies.

Zangwill KM, Eriksen E, Lee M, , et al. A population-based, postlicensure evaluation of the safety of a combination diphtheria, tetanus, acellular pertussis, hepatitis B, and inactivated poliovirus vaccine in a large managed care organization. *Pediatrics*. 2008; 122(6): e1179-85.

BACKGROUND: Prelicensure studies of diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus vaccine suggested that there were higher rates of fever after its administration than when its component antigens were given separately. METHODS: We conducted an open, controlled, cohort study to evaluate selected potential adverse events after receipt of diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine in the Southern California Kaiser Permanente Health Care Plan. From April 2003 through June 2005, we identified 61,004 infants who received >or=1 dose of vaccine (120000 total doses). This group was compared with a previous cohort of 58,251 age-, gender-, and medical center-matched infants (116,637 doses) who received diphtheria, tetanus, acellular pertussis vaccine and separate doses of hepatitis B and inactivated poliovirus vaccines from January 2002 through March 2003. We compared the incidence of seizures, medically attended events that were associated with fever, and other selected adverse outcomes. RESULTS: We identified 16 infants (8 with fever) who had a seizure in the diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus cohort and 15 infants (6 with fever) among control subjects in the 8-day period after receipt of any dose of vaccine. The incidence of all seizures or seizures associated with fever was not significantly different between cohorts. The incidence of medically attended events that were associated with fever in the 4-day period after any dose of vaccine was also similar in both cohorts. As well, no significant differences between the diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and control cohorts, were noted in the incidence of allergic reactions within 48 hours of any dose of vaccine, outpatient visits within 21 days, hospitalizations within 21 days, or death within 1 year. CONCLUSIONS: We did not observe a statistically significant increase in any of several clinically important safety events after diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccination compared with a historical cohort who received separate component vaccines.

B. APPENDIX B: LIST OF CITATIONS SELECTED FOR FULL-TEXT REVIEW BUT NOT INCLUDED, BY REASONS FOR EXCLUSION

1. Studies Excluded Due to Poorly Defined Algorithms

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C. APPENDIX C: LIST AND DEFINITIONS OF ICD OR PROCEDURAL CODES INCLUDED IN ALGORITHMS

Type of Code	Code	Description
ICD-9-CM	89.13	Neurologic examination
ICD-9-CM	89.14	Electroencephalogram
ICD-9-CM	89.15	Nonoperative neurologic function test
ICD-9-CM	89.19	Video or radiotelemetered electroencephalogram monitoring
ICD-9-CM	333.2	Myoclonus
ICD-9-CM	**345.X**	**Epilepsy**
ICD-9-CM	345.0	Generalized nonconvulsive epilepsy
ICD-9-CM	345.00	Generalized nonconvulsive epilepsy without intractable epilepsy
ICD-9-CM	345.1	Generalized convulsive epilepsy
ICD-9-CM	345.2	Petit mal status epileptic
ICD-9-CM	345.3	Grand mal status
ICD-9-CM	345.4	Partial epilepsy, with impairment of consciousness
ICD-9-CM	345.5	Partial epilepsy, without mention of impairment of consciousness
ICD-9-CM	345.6	Infantile spasms
ICD-9-CM	345.7	Epilepsia partialis continua
ICD-9-CM	345.8	Other forms of epilepsy
ICD-9-CM	345.9	Epilepsy, unspecified
ICD-9-CM	345.91	Epilepsy unspecified with intractable epilepsy
ICD-9-CM	346.X	Migraine
ICD-9-CM	435.X	Transient ischemic attack
ICD-9-CM	779.0	Convulsions in newborn
ICD-9-CM	779.1	Cerebral irritability in newborns
ICD-9-CM	780.02	Transient alteration of awareness
ICD-9-CM	780.2	Syncope and collapse
ICD-9-CM	780.3	Convulsion
ICD-9-CM	780.31	Febrile convulsion

ICD-9-CM	780.32	Complex convulsion
ICD-9-CM	780.39	Other convulsion
ICD-10	**G40.X**	**Epilepsy**
ICD-10	G40.0	Localization-related idiopathic epilepsy and epileptic syndromes
ICD-10	G40.1	Localization-related symptomatic epilepsy and epileptic syndromes with simple partial seizures
ICD-10	G40.2	Localization-related symptomatic epilepsy and epileptic syndromes with complex partial seizures
ICD-10	G40.3	Generalized idiopathic epilepsy
ICD-10	G40.4	Other generalized epilepsy
ICD-10	G40.5	Special epileptic syndromes
ICD-10	G40.6	Grand mal seizures, unspecified
ICD-10	G40.7	Petit mal, unspecified
ICD-10	G40.8	Other epilepsy
ICD-10	G40.9	Epilepsy unspecific
ICD-10	**G41.X**	**Status epilepticus**
ICD-10	G41.0	Grand mal status epilepticus
ICD-10	G41.1	Petit mal status epilepticus
ICD-10	G41.2	Complex partial status epilepticus
ICD-10	G41.8	Other status epilepticus
ICD-10	G41.9	Status epilepticus, unspecified
ICD-10	G43.1	Classical migraine
ICD-10	G45.X	Transient ischemic attack
ICD-10	R55	Syncope
ICD-10	R56.0	Febrile convulsion
ICD-10	R56.8	Other and unspecified convulsion
CPT-4	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
CPT-4	64287	Vagus nerve stimulation
CPT-4	64553	Percutaneous implantation of neurostimulator electrodes; cranial nerve

CPT-4	64573	Incision for implantation of neurostimulator electrodes; cranial nerve
CPT-4	80154	Therapeutic drug assay - benzodiazepines
CPT-4	80156	Therapeutic drug assay - carbamazepine
CPT-4	80164	Therapeutic drug assay - dipropylacetic acid (valproic acid)
CPT-4	80168	Therapeutic drug assay - ethosuximide
CPT-4	80184	Therapeutic drug assay - phenobarbital
CPT-4	80185	Therapeutic drug assay – phenytoin, total
CPT-4	80186	Therapeutic drug assay – phenytoin, free
CPT-4	80188	Therapeutic drug assay - primidone
CPT-4	80299	Therapeutic drug assay - quantitation of drug not elsewhere specified
CPT-4	95823	Electroencephalogram recording with physical/pharmacologic activation
CPT-4	95827	Electroencephalogram; all night recording
CPT-4	95829	Electrocorticogram recording at surgery
CPT-4	95839	Electroencephalogram monitoring
CPT-4	95950	Monitoring for identification and lateralization of cerebral seizure focus by attached electrodes; electroencephalographic (e.g., 8 channel EEG) and video recording and interpretation, each 24 hours
CPT-4	95951	8-channel electroencephalogram
CPT-4	95953	16-channel electroencephalogram
CPT-4	95954	Electroencephalogram monitoring/giving drugs
CPT-4	95955	Electroencephalogram during surgery
CPT-4	95956	Monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, electroencephalographic (EEG) recording and interpretation, each 24 hours
CPT-4	95957	Digital analysis of electroencephalogram (EEG)
CPT-4	95958	Electroencephalogram monitoring/function test
CPT-4	95961	Electrode stimulation, brain
CPT-4	95962	Functional cortical mapping