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A systematic approach to using regression modelling and ‘big data’ to derive a meaningful clinical decision rule for epilepsy

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A systematic approach to using regression modelling and ‘big data’ to derive a meaningful clinical decision rule for epilepsy

by

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Abstract

Introduction: clinical decision rules (CDRs) have been developed in a number of medical fields resulting in improved patient outcomes, quality of care, and health economics.

Aims: to identify all CDRs developed for epilepsy and to derive one that guides the prescription of the antiepileptic drug (AED), levetiracetam, according to its risk of a psychiatric adverse effect.

Methods: a systematic review and meta-analysis was first performed to determine the state of the literature with respect to CDRs in epilepsy. The Health Improvement Network (THIN) electronic medical records register was used to identify patients with epilepsy by employing a modified validated case definition with a 5-year washout. Analyses were restricted to patients receiving AED monotherapy and the association between levetiracetam use and psychiatric adverse effects was explored Cox proportional hazards regression with time-varying covariates. Finally, logistic regression with parameter regularisation and k=5 fold cross validation was used to derive the CDR that predicts the development of psychiatric adverse effects following levetiracetam prescription.

Results: the systematic review identified four epilepsy-specific CDRs, none of which guided AED prescription. A total of 9595 presumed incident cases of epilepsy (85.7 cases per 100,000 persons) were identified in THIN. Both carbamazepine (hazard ratio [HR]: 0.84, 95% confidence interval [95% CI]: 0.73–0.97; p = 0.02) and lamotrigine (HR: 0.83, 95% CI: 0.70–0.99; p = 0.03) were associated with reduced hazards of a psychiatric sign, symptom, or disorder

compared to no AED treatment. Levetiracetam was not associated with psychiatric adverse effects but the analyses were underpowered (n=202; 3%). All patients receiving levetiracetam (1173/7400; 16%) were included for CDR derivation. Prediction variables were incorporated into multiple logistic regression models with parameter regularisation. Odds of reporting a psychiatric complaint were elevated for females and those with a pre-exposure history of depression, anxiety, recreational drug use, or higher social deprivation. The prediction model performed well (area under the curve [AUC] 0.68; 95% confidence interval 0.58-0.79 after stratified k=5 fold cross-validation). Using a cut-off threshold 0.1, the CDR had a specificity of 83%.

Conclusion: If externally validated and properly implemented, this CDR could be used to guide prescription in clinical practice.

Keywords: epilepsy, levetiracetam, psychiatric adverse effects, prediction modelling, clinical decision rules

Preface

For fulfilment of this manuscript-based thesis, it is noted that:

Chapter 2: A systematic review of clinical decision rules for epilepsy has been published in its current form (Josephson CB, Sandy S, Jette N, Sajobi TT, Marshall D, and Wiebe S. A systematic review of clinical decision rules for epilepsy. Epilepsy Behav 2016;57:69-76)[1] with C. Josephson as first author. Permissions were received from the journal and all co-authors.

Chapter 3: Prescription trends and psychiatric symptoms following first receipt of one of seven common antiepileptic drugs in general practice has been published in its current form (Josephson CB, Engbers JDT, Jette N, Patten S., Sajobi T., Marshall D., Lowerison M., and Wiebe S. Prescription trends and psychiatric symptoms following first receipt of one of seven common antiepileptic drugs in general practice. Epilepsy Behav 2018;84:49-55.:10.1016/j.yebeh.2018.1004.1012.)[2] with C. Josephson as first author. Permissions were received from the journal and all co-authors.

This thesis is original, containing published and unpublished, independent work by the author, C. Josephson. The analyses performed in Chapters 2-4 were covered both through the University of Calgary's Conjoint Health Research Ethics Board (REB15-0203) and the CSD Medical Research's Scientific Review Committee in December 2015 (SRC Reference number 15THIN087).

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List of Symbols, Abbreviations, & Nomenclature

AED	Antiepileptic drugs
AMR	Acceptable mortality reporting
AUC	Area under receiver operating characteristic curve
CDR	Clinical decision rules
cEEG	Continuous electroencephalography
CI	Confidence interval
C-statistic	Concordance statistic
CT	Computed tomography
EEG	Electroencephalogram
EMR	Electronic medical records
FLEP Scale	Frontal lobe epilepsies and parasomnias scale
GP	General practice/general practitioners
HR	Hazard ratio
IQR	Interquartile range
MRI	Magnetic resonance imaging
NREM	Non-rapid eye movement sleep
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
REM	Rapid eye movement sleep
SAIL	Secure Anonymised Information Linkage Database
THIN	The Health Improvement Network Database
UK	United Kingdom

Chapter 1: Introduction

1.1 Epilepsy

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain[3]. Seizures can be focal (originating in networks limited to one hemisphere of the brain) or generalised (arising within and rapidly engaging networks in both hemispheres)[4].

Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition[3]. The International League Against Epilepsy's clinical definition of epilepsy requires two unprovoked seizures separated by more than 24 hours, one unprovoked seizure with a future 10 year risk of recurrence equal to that of someone with epilepsy (60%; the risk is determined by clinical history, physical examination, and diagnostic tests), or the diagnosis of an epilepsy syndrome[5].

Epilepsy is a common condition effecting people of all ages, gender, and socioeconomic status. It is the third most common neurological cause of years lived with disability in the world[6] with approximately 190,000 Canadians (prevalence of 0.6%)[7, 8] and 2.2 million Americans suffering from active epilepsy

at any given time[9]. The annual cost of epilepsy in the United States was estimated at $12.5 billion in 2000[10].

Despite its prevalence, epilepsy can be very challenging to diagnose. Syncope (fainting), cardiac arrhythmias, and psychogenic non-epileptic attacks are among many conditions that commonly involve episodic loss of consciousness, altered awareness, or convulsions and can therefore be mistaken as seizures[11]. Indeed, up to 20-31% of patients presenting with suspected epilepsy may be ultimately misdiagnosed with another condition[12-14]. An accurate diagnosis is crucial; it improves patient outcome, avoids exposing patients to potentially harmful treatment, and promotes efficient use of health care resources. The number of ancillary tests available to assist in the diagnosis of epilepsy continues to grow. Each investigation carries its own set of advantages and disadvantages and all have inherent costs that are becoming ever more relevant in health care settings that are increasingly constrained by limited resources. Therefore, while an accurate diagnosis is necessary, and desirable, an evidence-based approach to selecting those most likely to benefit from these tests is crucial to optimise the rational provision of finite resources.

Many patients with epilepsy, once diagnosed, can be successfully treated with anti-epileptic drugs (AEDs)[16]. However, the number of medications has expanded rapidly with over 20 AEDs now available. Even those who are well controlled on AEDs may suffer significant adverse effects that lower quality of life. The spectrum of adverse effects can range from somnolence, cognitive

slowing, dizziness and vertigo, tremor, and weight gain, to metabolic disturbances such as electrolyte imbalances and ultimately to serious, life-threatening conditions such as anaphylaxis, hepatotoxicity, pancreatitis, and agranulocytosis. Up to 30-40% of patients will continue to have seizures despite optimal medical management[16]. Surgery is of proven efficacy in appropriately selected patients with drug-resistant epilepsy[17-19], however, pre-surgical evaluations can be complicated and costly and not all patients benefit from an operative approach.

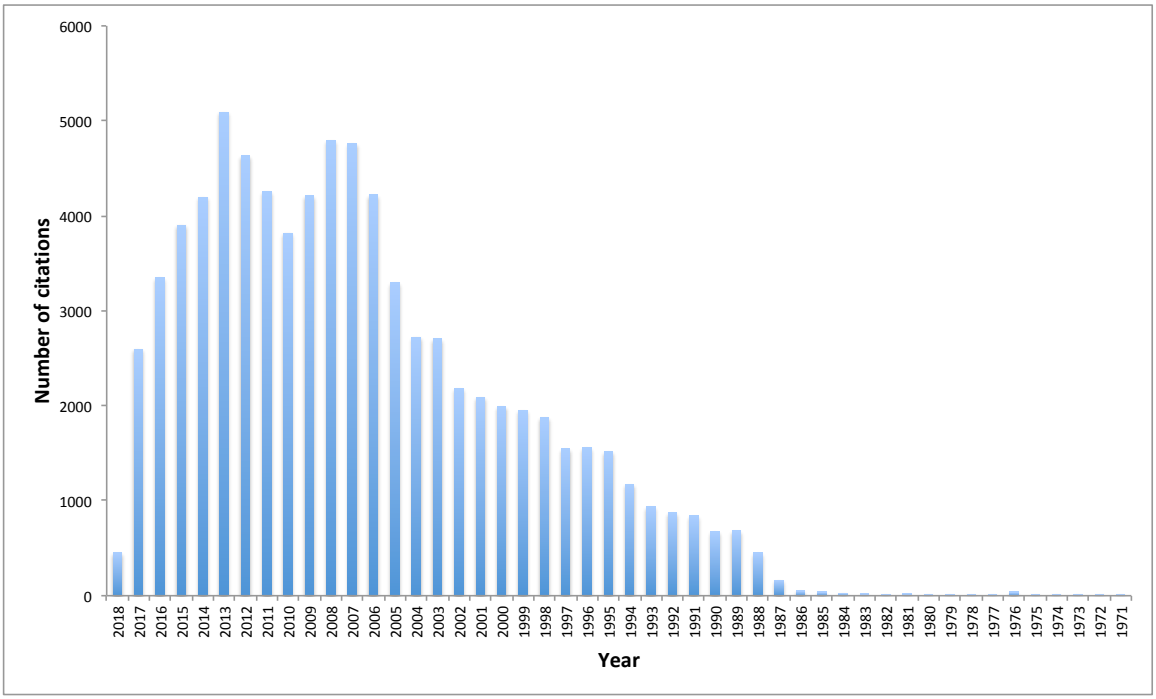
The growing diagnostic and therapeutic options can be overwhelming for physicians and costly for the health care system. For instance, there is evidence that electroencephalograms (EEGs) are over-utilised by non-specialists[20] while proper selection of patients for magnetic resonance imaging (MRI) would promote cost-effective care as up to 31% of people with epilepsy lack an obvious epileptogenic lesion on imaging[21].

1.2 Clinical decision rules

Discovering ideal approaches and the ideal candidate to undergo diagnostic and therapeutic interventions is important in improving adherence and in reducing patient risk. Clinical decision rules (CDRs) represent a means by which one can achieve these goals. A CDR is used to quantify the individual contribution made by multiple components of a patient's history, physical exam, laboratory, and imaging results, towards the probability of a certain diagnosis or response to

treatment[22]. They have been empirically demonstrated to reduce inefficient provision of resources and prevent unnecessary exposure to risk when applied appropriately in the proper clinical setting[23]. Clinical decision rules have proliferated over the last 20 years. The number of scientific articles addressing clinical decision rules more than doubled between 1995 and 2005[24]. Likewise, a search of Pubmed.gov on April 10, 2018 (https://www.ncbi.nlm.nih.gov/pubmed/?term=clinical+decision+rule%E2%80%99+or+%E2%80%98clinical+prediction+rule%E2%80%99) revealed a peak of 5,484 publications in 2013 when searching for 'clinical decision rule' or 'clinical prediction rule', whilst the yield was 3,500 articles 2016 compared to 1,993 in 2000 (Figure 1). Rules have mainly been derived for acute clinical conditions encountered in emergency medicine[25-27], internal medicine[28, 29], and surgery[30, 31].

Figure 1. Number of citations pertaining to 'clinical decision rules' or 'clinical prediction rules' in Pubmed.gov from 1971 to present.



Clinical decision rules are complex tools that combine two or more items of patient data to predict a specific clinical outcome[32]. These tools are conventionally defined as incorporating at least three variables derived from original research[33]. These rules are not simply survival analyses or prognostic models. CDRs on the other hand, take prognostic models a step further by appending a rule to the algorithm. For instance, using logistic regression, one can calculate the odds of an outcome of interest. Predictive variables are identified, assigned weights, and then amalgamated into a final model that is used to calculate the odds of an outcome of interest[22]. Odds can be converted to risk[34], and then one can compare the predicted outcome to observed outcomes. The next step is finding a risk threshold that balances sensitivity (true positives/[true positives + false negatives], a measure of the proportion of patients with the outcome who are correctly identified by the rule) and specificity (true negatives/[true negatives + false positives]; a measure of the proportion of patients without the outcome who are correctly identified by the rule). Usually the optimal threshold is the one that either balances sensitivity and specificity, or promotes one measure over the other depending on the intention of the test (e.g. a screening test often favours sensitivity over specificity). The resultant rule is such that anyone whose risk (as computed through the regression model) is above the threshold will be considered at high risk of developing the outcome of interest and therefore the intervention is either given (if it is protective) or withheld (if it is deleterious). This helps clinicians actually make bedside decisions about diagnostic or therapeutic courses of action.

1.3 Stages of clinical decision rule development

A rigorous three-stage design is required to generate accurate and reliable CDRs[22]. The initial stage is a *derivation study* in which the rule is constructed by exploring the predictive value of pre-specified variables in a population of interest. A derivation study constitutes a preliminary analysis and therefore represents level IV evidence (CDRs that have been derived but not validated)[22]. The second stage consists of *validation studies* where the CDR is tested either on only one narrow prospective sample (level III evidence) or in one large prospective study that includes a broad spectrum of patients (level II evidence). This is intended to prospectively assess the rule's accuracy, reliability, and potential impact in independent populations. The third stage involves *implementation studies* in which the rule's 'real-life' impact on patient management and health care resource utilization is empirically established[22]. This provides level I evidence since it consists of prospective validation in a different population and at least one impact analysis. For instance, before-after randomised controlled studies have been used to evaluate the reduction in X-ray use following staff training for the Ottawa Knee Rule[31]. This involved two intervention sites compared with two control sites that simply performed routine practice. Implementation of the rule resulted in a 26% relative reduction of radiography use in the intervention site compared to a 1% reduction in the control group ($p<0.001$). The rule had a sensitivity of 1.0 (95% confidence interval [95%CI] 0.94-1.0; correctly identified all patients with a knee fracture in this

study). Interrater reliability was excellent (kappa = 0.91; 95%CI 0.82-1.0). Patients not undergoing radiography had shorter hospital times (85 *versus* 119 minutes) and use of the rule was associated with lower direct health care costs ($80 versus $183). Comparable results were achieved when evaluating the Ottawa Ankle Rule through similar methodology[35, 36].

1.4 Derivation of clinical decision rules

The primary methods used to derive CDRs include univariable analyses, multiple linear and logistic regression, nomograms, and recursive partitioning analysis)[37]. A univariable analysis is conducted by identifying factors that are statistically related to the outcome of interest. These factors are then assigned a 'weighted' score and each item is tabulated together to calculate an overall output used to make a decision regarding whether a specific diagnostic test or therapeutic intervention should be pursued. Although univariable models are simple to design, they are limited by the inclusion of potentially non-independent risk factors and the arbitrary allocation of weights[37].

Multiple linear or logistic regression modelling and nomograms adopt similar mechanisms but has the advantage of less arbitrary weighting and is better equipped to identify and exclude non-independent risk factors[31, 38]. Most rules typically are created using logistic regression analysis though nomograms have the advantage of being simpler to use with more intuitive means of conveying the relative contribution of interval data in clinical settings[31]. These models are the

most frequently encountered in the medical literature with many having been successfully validated and implemented[35, 36]. For example, logistic regression has been used to derive a rule for acute appendicitis[38]. First, using univariable comparisons, features that differed significantly ($p<0.001$) between those with and without appendicitis were identified. Following this, backward stepwise elimination logistic regression was used to develop the model whereby all retained beta coefficients were divided by the lowest beta coefficient value and rounding results. The model was then evaluated using various thresholds and the one that maximised negative likelihood ratio and negative predictive value was selected to define the rule. The authors settled on a threshold of 5 under which the model demonstrated excellent discrimination (area under the receiver operating characteristic curve = 0.87) with a sensitivity of 98.1% (95%CI 90.1-99.9%), a negative predictive value of 97.5% (95%CI 86.8-99.9%) and a negative likelihood ratio of 0.058 (95%CI 0.008-0.411) in an independent validation set[38].

1.5 Regression modelling and CDR derivation

Conventional regression and machine learning are intimately connected approaches to outcome prediction. If the interest of the clinician is prognosis as conveyed by effect sizes (hazard or odds ratios) or statistical significance, then data modelling approaches may be preferred. If they are interested in decision rules (prediction and accuracy), and less concerned about interpretability compared to model performance, then the application of machine learning (algorithm modelling) becomes more appealing[39]. For example, two statistical

models may have equivalent goodness-of-fit measures. This can complicate attempts at defining expository relationships. The machine learning approach is more flexible in that it disregards the need to explain how independent variables explain dependent variables. Its aim is not to discover a model that best explains the data; rather simply to create accurate decision tools[40].

Regression modelling models have been assimilated into machine learning as a means of predicting known classes of outcomes. In particular, regression-based data modelling and supervised machine learning share similar methodology with frequently only subtle differences in application. For conventional regression, the investigator makes assumptions about the raw data (e.g. normal distributions of values; linear versus non-linear associations), selects a model, fits the parameters of the selected model, and then determines how well the final model represents what is observed in the general population ('goodness-of-fit')[40]. Alternatively, machine learning frequently makes no assumptions about data and rather is concerned with algorithmic modelling; finding a mathematical relationship that maximises prediction (classification) of an outcome based on input variables (features).

Regression-based techniques for prediction modelling employ stochastic gradient descent by randomly assigning parameter coefficient values and calculating error (observed – predicted value) in an iterative fashion. The aim is to minimise the cost function (error). To do this, the gradient in error is computed with respect to

each set of assigned parameters. For instance, one could begin by assigning all parameters a coefficient value of '0'. Using the calculated error gradient, parameter coefficient values are slightly adjusted and error is recalculated. This continues until the final model, the one associated with the lowest error, is reached[41]. Finally, stratified k-fold cross-validation techniques can be used to assess generalizability[42]. This technique randomly divides a dataset of size *n* into *k* subsets of which each has a sample size of roughly *n/k*. A training set is established by amalgamating *k*-1 sets and the remaining subset is reserved for testing model performance. This is repeated *k* times, so that each subset comprises the test set once, and the combined value of the prediction error is the cross-validated estimate of performance[42].

Thus, for the purpose of the proposed studies in this dissertation, the focus will be remain on regression-based prediction modelling whereby the outcome (classifier) is labelled (known) for each patient. Choice of this model is predicated on the fact that the problem is one of classification. Hence, regression can be used to determine the odds of an outcome that can then be converted to a probability. A decision boundary can be established thus forming a decision rule. Furthermore, a supervised approach is best suited to addressing this issue whereby the outcomes are known in advance of the analysis and each patient is assigned the class (outcome positive or negative). Here, one can directly evaluate model performance by comparing the predicted to actual class of each patient using the aforementioned methodology[43, 44].

1.6 Application of 'big data' to CDR development

Although many CDRs have been derived, very few have been properly validated and implemented[24]. Validation and implementation studies are crucial since derived models often do not perform as well in independent populations. This may be because the model was inadequately developed, the model 'overfits' the source population, or there were major differences between the population in which the model was derived and the population in which validation was attempted. Properly validated and implemented CDRs, accomplished through randomised cluster or controlled trial design, can offer enhanced, patient-centred, cost-effective care[23, 35, 36]. Current CDRs are derived using prospective datasets amalgamated for the express purpose of developing the specific tool. This can be cumbersome, resource intensive, and ultimately time-prohibitive. Using 'big data' is a means of mitigating these limitations. This is particularly relevant to machine learning problems where an 'n *versus* p problem' (a large number of feature [i.e. independent] variables coupled with a comparably low cohort size) can be encountered[45]. Big data may be able to mitigate this limitation by providing sufficient statistical power to abide by the '10:1 outcomes to predictors' rule of thumb[46] though extrapolation of such power calculations to machine learning has yet to be comprehensively explored.

'Big data' is conventionally defined in the literature as comprising five "V's": volume, velocity, variety, veracity, and value[47]. Volume refers to the enormity of

the data; in many cases it can contain anywhere from terabytes (10^{12}) to zetabytes (10^{21}) of information. Velocity is the speed of data creation, streaming, and aggregation that requires large bandwidths. Data variety is an indication of the 'richness' of the data (e.g. quantitative variables in addition to text, image, and audio files). Veracity is a measure of the accuracy of the data. In order to produce valid tools for the real-world application, the data used to derive the model must be representative of the intended population. Otherwise, the tool will yield spurious results when deployed. Finally, value refers to the usefulness of data in making logical, high probability decisions[48]

The exact size of 'big data' remains a nebulous concept. With respect to health research, one could consider electronic large datasets collected during the course of routine clinical care. These can comprise anything from large electronic medical records (EMR) data, administrative health records data, repositories of genomic data, raw electroencephalography or neuroimaging source data, and wearable mobile heath applications data[47]. Although pure EMR data may not constitute terabytes worth of information, they can be considered 'big' due to their variety and considerable volume[49]. Alternatively, these data can be collected prospectively (e.g. through genetic studies) but this often involves enormous resource expenditure. Thus, the process is typically achieved passively by using data generated through pre-existing hardware in the form of health records data or mobile applications. Use of readily available 'big data' is ultimately advantageous if they are of a sufficient volume and variety to permit the

discovery of new insights in an expedited fashion that cannot be appreciated from smaller datasets.

Use of these datasets has the potential to permit concurrent derivation and some aspects of validation, including cross-validation, that should allow for the rapid development of prototype rules. This should quickly advance these models to external validation and implementation stages. Currently, prediction models using ‘big data’ are in their nascent stage with none appending a formal rule for clinical direction. However, it is becoming increasingly evident that ‘big data’ can be exploited to develop high quality, cost-effective CDRs designed to improve care particular patients such as those with epilepsy. The use of ‘big data’ may be particularly pertinent for epilepsy since it is a disorder that traditionally lacks the statistical power that is available for more common conditions.

1.7 Levetiracetam and the need for a CDR

Levetiracetam is an AED that has gained significant popularity in recent years. This is likely due to ease of use, broad spectrum, patient tolerability during rapid up-titration, a lack of significant interactions with other medications, and a putative lack of major adverse effects. It was approved as adjunctive therapy for focal and generalised epilepsy by the European Medicines Agency in 2000 and by Health Canada in 2003. The original trials suggested that the overall proportion of adverse events was similar between those taking levetiracetam and those assigned to placebo. However, closer inspection of specific categories of

adverse events demonstrated rates of depression and anxiety that were approximately double that seen in the placebo arm (~4% *versus* ~2%)[50].

Post-marketing analysis raised additional concerns that the potential psychiatric adverse effects of levetiracetam may be even higher than those reported from the original trials. Retrospective analyses in the post-approval period indicate that the proportions may be as high as 31% who exhibit behavioural abnormalities, 29% irritability, 10% aggression, and 5% hallucinations[51]. Case reports have described symptoms that include acute mania[52]; delirium[53]; psychosis[54, 55]; aggressive behaviour[56]; and suicidal ideation[57] putatively related to levetiracetam use. These studies were small, however, and most constitute single centre experiences.

There is very limited information available on the predictors of psychiatric adverse events with levetiracetam. Febrile seizures, status epilepticus, and psychiatric comorbidities are associated with increased odds of developing psychiatric adverse effects from levetiracetam[58]. Co-administration of lamotrigine may lower the odds but these data are restricted to a retrospective analysis of data from a single tertiary care referral centre[58].

Levetiracetam is an effective and well-tolerated AED with its most serious concern being that of a psychiatric adverse effect. If one can avoid the psychiatric adverse effect, this could arguably be the drug of choice for many

patients. Hence, generating a rule predicating its use on the risk of developing a psychiatric adverse event could be extremely impactful and represents an ideal proof of principle scenario to explore the utility of CDRs in epilepsy. This medication is widely used by general practitioners (GPs), emergency medicine physicians, neurologists and epileptologists. Thus, this particular CDR, should it be feasible, has the potential to be relevant to all practitioners, from primary care physicians to specialists. Eventual validation and implementation of this CDR will permit judicious use of this medication thus promoting the efficient provision of optimal, evidence-based, patient-centred health care.

1.8 Summary

Epilepsy is a common disease that can have a significant impact on a patient's quality of life. Epilepsy can be difficult to diagnosis as there are many conditions that can mimic seizures. In addition, epilepsy is associated with specific co-morbidities. Thus, aside from the disease itself, there are a myriad of other diagnostic conditions that must be factored into any evaluation of a patient with epilepsy. To further complicate management, there has been a proliferation of therapeutic options for people with epilepsy. It is therefore becoming increasingly difficult to make clinically efficient and cost-effective diagnostic and therapeutic decisions. Clinical decision rules have been empirically demonstrated to improve patient care and promote judicious use of limited resources. The usefulness of CDRs for epilepsy has yet to be rigorously explored. They have the potential to substantially improve care and thus studies regarding their application to epilepsy

are warranted. A logical place to start will be deriving a rule for the use of levetiracetam based on its potential risk of causing psychiatric adverse effects based on individual patient factors. Specialists and non-specialists routinely use levetiracetam for the treatment of epilepsy. Many are unaware of the risks associated with this medication and thus it represents an ideal clinical conundrum that could be resolved with a validated CDR that guides its use in people with epilepsy.

1.9 Study aims and hypotheses

Aim 1 was to systematically review the literature to determine what CDRs have been developed for epilepsy. For this aim, the hypotheses were:

1) That CDRs exist for epilepsy and can be identified and analysed in a formal systematic review and meta-analysis of the literature using standard methodology.
2) That no CDRs have been developed for epilepsy using sources of 'big data'.
3) That no CDR exists for the use of levetiracetam according to risk of psychiatric adverse effects.

Aim 2 was to attempt to derive a CDR for the use of levetiracetam in patients with epilepsy using 'big data' based on their predicted risk of a psychiatric adverse event. For this aim, the hypothesis was:

1) That a CDR can be derived using 'big data' in the form of a large repository of electronic medical records data. If successful, future studies can be performed to validating and implement the rule.

1.10 Study objectives

1) To determine what CDRs exist for epilepsy.
2) To explore whether 'big data' have been used to derive CDRs for epilepsy.
3) To determine which methods were used to derive CDRs?
4) To examine the association between AED use and psychiatric signs, symptoms, and disorders in the THIN database.
5) To determine which clinical variables predict successful derivation of epilepsy-specific CDRs and can these variables be useful for our proposed CDR for levetiracetam in patients with epilepsy according to their risk of psychiatric adverse effects.
6) To derive a rule that discriminates between those who will and those who will not develop a psychiatric adverse effect following a prescription for levetiracetam. A threshold emphasising specificity is preferred to minimise false positive misattribution. Although this may be achieved at the expense of potentially increasing false negatives, it is still desirable since the relative impact of denying a patient a potentially effective AED, based on a spurious impression of risk, is arguably more deleterious than exposing them to a reversible adverse event. The THIN database was chosen because it is a large EMR database containing information on 5% of the United Kingdom (UK) general

practice population that is representative of the general UK population[15]. It is anticipated that the general practice in the UK is similar to that in Canada given the similarities in demographics and health care systems.

Chapter 2: A systematic review of clinical decision rules for epilepsy

2.1 Publication

This chapter has been published in *Epilepsy & Behavior*[1] and permission for use has been provided by all co-authors.

2.2 Abstract

Clinical decision rules (CDRs) have been empirically demonstrated to improve patient satisfaction and enhance cost-effective care. The use of CDRs has not yet been robustly explored for epilepsy. We performed a systematic review of MEDLINE (from 1946) and Embase (from 1947) using Medical Subject Headings and keywords related to CDRs and epilepsy. We included original research of any language deriving, validating, or implementing a CDR using standardised definitions. Study quality was determined using a modified version of previously published criteria. A bivariate model was used to meta-analyse studies undergoing sequential derivation and validation studies. Of 2445 unique articles, 5 were determined to be relevant to this review. Three were derivation studies (three diagnostic and one therapeutic), one validation study, and one combined derivation and validation study. No implementation studies were identified. Study quality varied but was primarily of a moderate level. Two CDRs were validated and thus able to be meta-analysed. Although initial measures of accuracy were high (sensitivity ~80% or above), they tended to diminish significantly in the validation studies. The pooled estimates of sensitivity and specificity both

exhibited wide 95% confidence and prediction intervals that may limit their utility in routine practice. Despite the advances in therapeutic and diagnostic interventions for epilepsy, few CDRs have been developed to guide their use. Future CDRs should address common clinical scenarios such as efficient use of diagnostic tools and optimal clinical treatment decisions. CDR development should be a priority in epilepsy given their potential for advancing efficient, evidence-based, patient-centred health care.

2.3 Introduction

Epilepsy is the second most common neurological condition seen in primary practice worldwide[59] with an approximate lifetime prevalence of 5.8 per 1000 population in the developed world and between 10.3 per 1000 to 15.4 per 1000 in developing countries[60]. Despite its prevalence, epilepsy can be very challenging to diagnose and treat. As such, it is not surprising that the annual cost of epilepsy in the United States was estimated at $12.5 billion in 2000[10]. An accurate diagnosis and appropriate approach to treatment is crucial; it improves patient outcome, avoids exposing patients to potentially harmful treatment, and promotes efficient use of health care resources.

The growing diagnostic and therapeutic options can be overwhelming for physicians and costly for the health care system. For instance, there is evidence that EEGs are over-used by non-specialists[20] while appropriate selection of patients for MRI would promote cost-effective care since up to 31% of people with epilepsy lack an obvious epileptogenic lesion on imaging[21]. The list of AEDs

is also growing and choosing the correct one for each patient can be challenging[61].

Clinical decision rules are a way in which we can achieve these diagnostic and therapeutic goals. A CDR is used to quantify the individual contribution that multiple components of a patient's history, physical exam, laboratory, and/or imaging results make towards the likelihood of a certain diagnosis or response to treatment[22]. They have been empirically demonstrated to reduce inefficient provision of resources and prevent unnecessary exposure to risk when applied appropriately in the right clinical setting[23]. These rules offer advantages over simple decision analyses and clinical guidelines in that they empirically identify a discrete, unique course of action.

The role of CDRs in epilepsy has yet to be explored. The purpose of this study was to systematically review the literature to critically appraise the use of CDRs in epilepsy.

2.4 Methods

2.4.1 Definitions

We defined a CDR as incorporating at least three variables from the history, physical examination, and/or diagnostic tests that provide a probability of an outcome and suggests a single diagnostic or therapeutic course of action[33]. These rules must not simply be survival analyses or prognostic models but must

incorporate a decision rule that is used to empirically identify a unique course of action according to a patient's particular attributes.

2.4.2 Search strategy and selection criteria

The review was performed in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[62]. Methods of the analysis and inclusion criteria were specified in advance and documented in an unpublished protocol.

We searched Medline (from 1946) and Embase (from 1947) using a comprehensive search strategy that incorporated Medical Subject Heading (MeSH) and text words for CDRs (Appendix 1; most recent search date July 2015). We also reviewed relevant studies identified in the reference sections of included articles.

We included studies containing original research, irrespective of patient age, language, or location, which derived a CDR. Decision analyses and practice guidelines were excluded from this review since they do not provide a discrete, single course of action. Rather, they evaluate many potential decision nodes factoring in a variety costs and benefits. Thus, many potential options are available to the physician. CDRs, on the other hand, provide a score that offers an explicit, singular course of action for a distinct and highly specific clinical question thus removing a level of uncertainty.

2.4.3 Study selection and data collection

Two authors (Dr. Colin Bruce Josephson and Dr. Sherry Sandy) performed the literature search and screened study titles and abstracts. Both authors screened each abstract and eligible articles were selected for full review. Full texts were reviewed in duplicate by the same authors to identify those that met eligibility criteria. Any disagreement was resolved by reaching consensus through discussion and included a senior author (Dr. Nathalie Jette and/or Dr. Samuel Wiebe) where necessary.

2.4.4 Data extraction

Variables extracted included year of publication, the country in which the study was conducted, inclusion criteria, participant recruitment (prospective, retrospective, both, or an administrative database), study setting (tertiary, secondary, or primary care) and the number of participants. The study design (whether it was a derivation, validation, or implementation study) and the study aim (diagnostic, therapeutic, or prognostic) were also documented.

A standardised mechanism for evaluating study quality is currently being developed (http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines-under-development/#3). In the absence of such a tool, we adapted previously proposed criteria[22, 33] and applied them to all included studies (Appendix 2). QUADAS-2 criteria[63] were also included

because the process for establishing risk categories for individual patients closely approximates studies of diagnostic quality. Study quality was evaluated and tabulated for all included studies; studies were not excluded according to their overall quality level.

Attempts were made to determine if study variables were identified *a priori.* The number of variables each study examined, including those that were not statistically significant, was tabulated. The type of statistical model used to derive the rule was documented along with the overall strength of prediction.

We followed the CDRs forward to determine if they underwent validation or implementation analyses through hand searching reference lists of included studies and through Google Scholar. When evaluating validation studies, we recorded whether additional variables were examined in an effort to refine the rule. We recorded the overall predictive strength of the rule in the new population, tabulated accuracy of use of the rule and measures of interobserver agreement.

2.4.5 Statistical analysis

We performed meta-analyses using RevMan5.2.3[64] and Stata version 13.0[65]. The bivariate meta-analytic method[66] was used to pool the study-specific sensitivity and specificity values since CDRs are designed using discrete thresholds[33]. We assessed statistical heterogeneity between studies within the

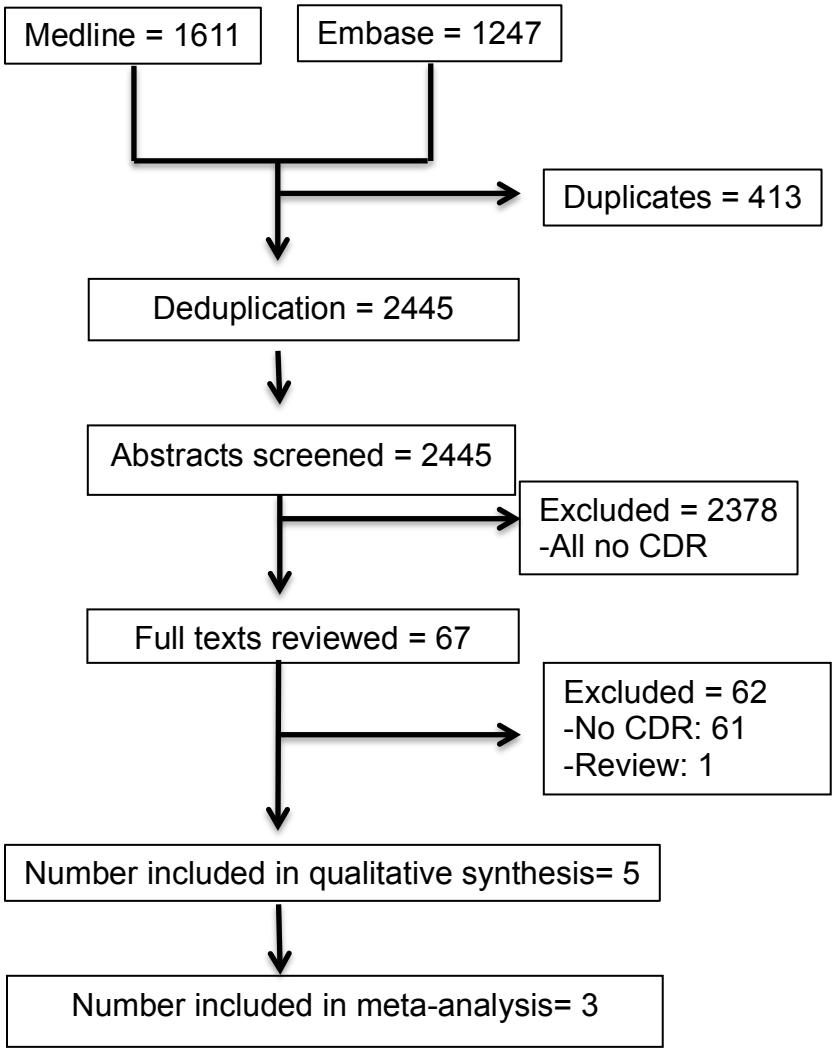
bivariate model (by evaluating the prediction regions)[67] and explored publication bias using visual inspection of a funnel plot.

2.5 Results

2.5.1 Literature search

A Medline and Embase search in July 2015 yielded 2858 articles of which 2445 were determined to be unique after de-duplication. We excluded 2355 after initial abstract review and a further 23 after consensus review. These were all excluded on the basis of being review articles or because there was no appended CDR. Sixty two additional studies were excluded after full-text review leaving 5 studies (three derivation, one combined derivation and validation, and one validation) for the systematic review (Figure 2)[68-72]. All studies were derived in high-income countries (2 in Europe, 2 in the North America, and 1 in Australia).

Figure 2. PRISMA flow diagram for the systematic review and meta-analysis of clinical decision rules in epilepsy



2.5.2 Derived CDRs

The Frontal Lobe Epilepsies and Parasomnias scale (FLEP) scale[70, 72] was derived from a pilot study of 18 cases by selecting variables from a literature search and clinical experience[72]. It was designed to guide diagnosis and treatment of patients with undifferentiated nocturnal events. No details are provided on this population or on how the model was assembled. Weights were arbitrarily applied to each variable following study of the pilot population. Ultimately, it was subsequently studied in a population of 62 patients both retrospectively and prospectively to determine diagnostic accuracy. This score was further validated in an independent population from Italy that comprised 71 patients[70]. Ultimately, it was able to discern nocturnal frontal lobe epilepsy from sleep disorders with a moderate sensitivity (0.714) and high specificity (1.00) in the follow-up validation study[70].

The continuous EEG (cEEG) decision rule[71] was designed to identify critically ill children without epilepsy who will experience seizures during their inpatient admission. It was initially derived using a database (n = 336) from 11 centres in the United States and was subsequently validated in a population of 222 patients from a single tertiary care centre in Philadelphia. A multiple logistic regression model, based on the results of univariable analyses, was used to derive the rule that would guide the use of continuous EEG monitoring in this patient population. Specifically, it can be used to determine those critically ill children who will likely have seizures and therefore require cEEG monitoring.

A third study described the use of computed tomography (CT) scanning in children with epilepsy. Four predictors of an abnormal CT scan were identified thus facilitating the creation of an *ad hoc* CDR. The presence of any of an inherited or congenital disease, focal motor finding, onset of seizures in the first 6 months of life, or developmental delay was associated with elevated odds of an abnormal CT scan. Thus, identification of any of these characteristics in a child with epilepsy was associated with an accuracy of 79% of having an abnormal CT scan. The associated sensitivity was 89% with a corresponding specificity of 74% and a negative predictive value of 94%. Hence, the authors suggested that the absence of all of these features should lead a physician to refrain from ordering a CT scan due to the low yield.

The final study developed a CDR for the safe discontinuation of AEDs in children following one year of continuous treatment[68]. Using univariable comparisons followed by multiple logistic regression, a predictive model was developed that incorporated seizure type, age of seizure onset, and the presence of EEG abnormalities. The model demonstrated close correlation between the predicted probabilities and the prognostic scores ($r = -0.88$; $p < 0.001$) thus permitting the development of an associated CDR. The authors were able to construct a rule wherein children scoring above specific thresholds were able to safely discontinue AED therapy following one year of continuous treatment with low risk of seizure recurrence.

2.5.3 Study characteristics and quality of derivation studies

An overview of all identified rules is displayed in Table 1. Study quality varied substantially (Table 2). Most (3/4) studies clearly stated the clinical question and all addressed an important clinical scenario. The study site and population acquisition (single or multicentre; primary, secondary, tertiary or population based sampling) were adequately described in all studies. The majority (3/4) identified participants in an unbiased fashion and selected prognostic factors *a priori*. The statistical approaches to deriving the rule were only adequately described in one half of studies. Most studies (3/4) clearly defined the outcome of the rule. However, no study evaluated the reproducibility (intra- and interrater reliability) of identifying the predictive variables in a blinded fashion. Likewise, only one study analysed the reproducibility in applying the rule in the fashion that was initially intended by the authors. Pre- and post-test probabilities were not evaluated by any study. Finally, only two scores were validated while none underwent implementation studies.

Table 1. Overview of clinical decision rules derived for epilepsy. Only derivation and validation studies were identified for epilepsy. No implementation studies were identified

Rule	Number of participants	Purpose	Phase of development	Result
FLEP scale[70, 72]	133	Diagnostic	Validation	For diagnosing NFLE: Sn 0.95 (95%CI 0.57 to 1.00) Sp 0.98 (95%CI 0.88 to 1.00)
cEEG rule[71]	588	Diagnostic	Validation	For diagnosing electrographic seizures: Sn 0.69 (95%CI 0.58 to 0.78) Sp 0.77 (95%CI 0.71 to 0.81)
CT head rule[69]	88	Diagnostic	Derivation	For having an abnormal CT scan: Sn: 0.89 Sp: 0.74
AED discontinuation[68]	161	Treatment	Derivation	For seizure recurrence at one year: No sensitivity or specificity reported

Abbreviations: 95%CI = 95% confidence interval; cEEG = continuous EEG; CT = computed tomography; NFLE = nocturnal frontal lobe epilepsy; Sn = sensitivity; Sp = specificity

Table 2. Qualitative evaluation of all identified derivation studies using a modified version of published quality assessment criteria[22, 33].

Study quality	AED discontinuation	FLEP Scale	CT head rule	cEEG rule
Is the clinical question clearly stated	■	■	□	■
Is the clinical question important	■	■	■	■
Was the study site described	■	■	■	■
Were patients selected in an unbiased fashion?	■	□	■	■
Were prognostic factors defined *a priori*	■	■	■	□
Were prognostic factors assessed in a blinded fashion?	■	□	□	□
Was the outcome explicitly defined?	■	■	■	■
Was the outcome blindly assessed?	■	■	□	■
Were the statistical techniques appropriate and described adequately?	■	□	□	■
Were all patients accounted for at the end of follow-up?	■	■	■	■
Did all patients undergo testing at the same stage of their care process?	■	■	■	■
Were important clinical characteristics defined?	■	□	■	□
Were the results of the rule adequately defined?	■	■	□	■
Was reproducibility of predictive variables evaluated?	□	□	□	□
Was reproducibility of the rule evaluated?	□	■	□	□
Is the clinically sensible?	■	■	■	■
Is the rule easy to use?	■	■	■	□
Is a course of action described?	■	■	■	■
Is the probability of the disease described?	■	■	■	■
Was the rule validated?	□	■	□	■
Did the rule undergo implementation studies?	□	□	□	□

Legend: ■=criterion met; □=criterion unclear or not met

2.5.4 Meta-analysis of validated scores

Two studies comprising 133 participants evaluated the FLEP scale[70, 72]. The first study[20] was a mixture of a derivation and validation study while the second[18] was performed to validate the score. The initial study reported a sensitivity of 1.00 (95%CI 0.86 to 1.00) and a specificity of 0.90 (95%CI 0.73 to 0.97)[72]. The diagnostic accuracy was not as robust in the validation study with a sensitivity of 0.71 (95%CI 0.47 to 0.95) and a specificity of 1.00 (no 95%CI reported; Figures 3 and 4)[70]. Of note, the high specificity may be related to pre-selection of an enriched population including patients with known nocturnal frontal lobe epilepsy, NREM parasomnias, and REM sleep behaviour disorders based on video-EEG polysomnography. In this study, no patients with a NREM parasomnia or REM sleep behaviour disorder were misdiagnosed with nocturnal frontal lobe epilepsy (0% false positive rate).

Figure 3. Coupled forest plot of the sensitivity and specificity of the Frontal Lobe Epilepsies and Parasomnias (FLEP) scale.

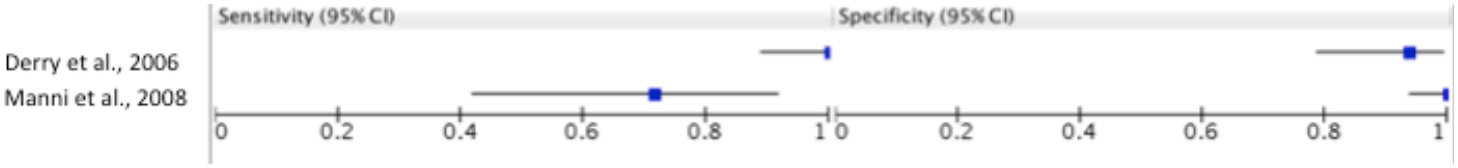
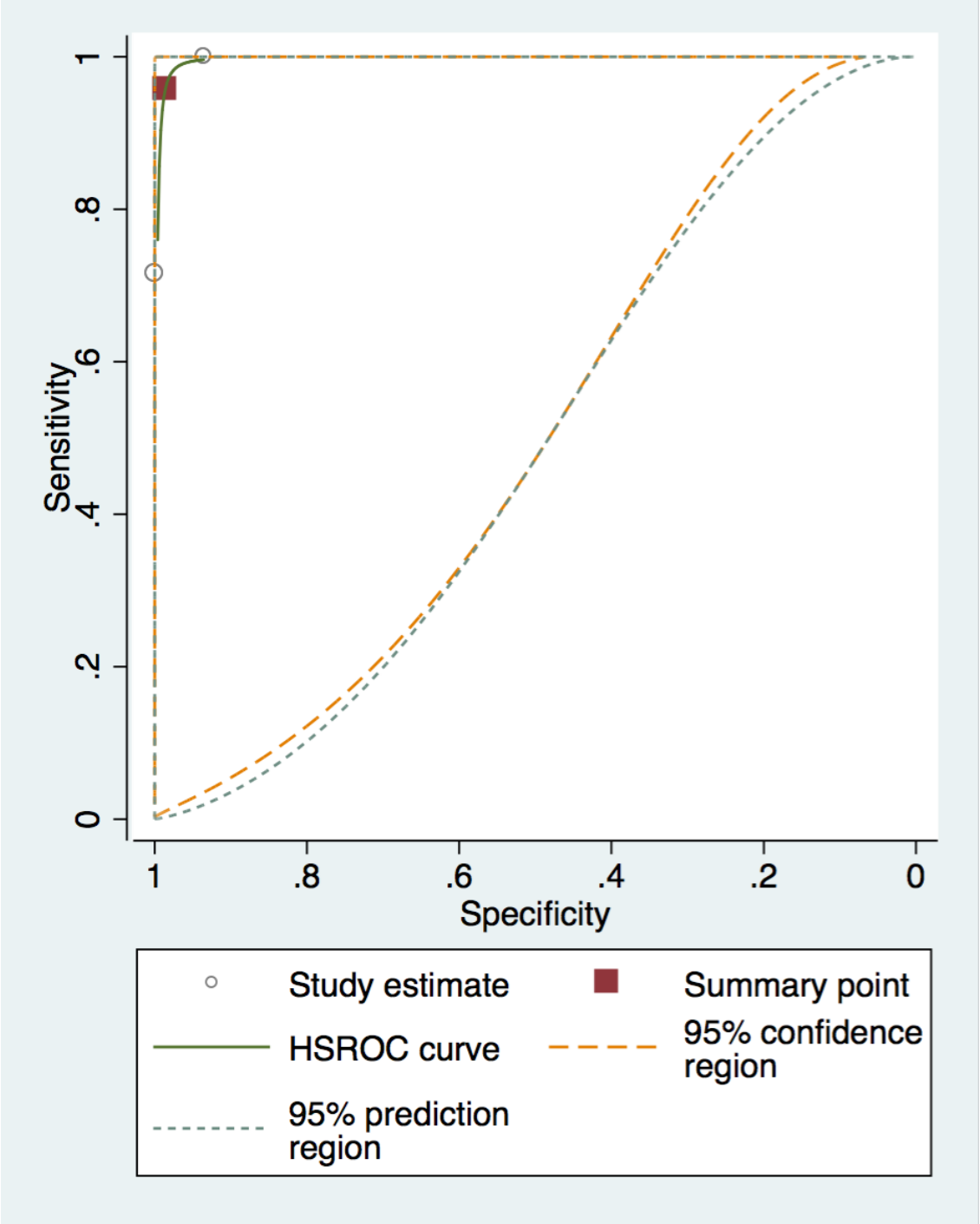


Figure 4. Pooled estimates of sensitivity and specificity of the Frontal Lobe Epilepsies and Parasomnias (FLEP) scale including the 95% confidence and prediction regions.



Abbreviations: HSROC = hierarchical summary receiver operator characteristic curve

The pooled estimates of sensitivity and specificity according to the bivariate model were 0.95 (95%CI 0.57 to 1.00) and 0.98 (95% CI 0.88 to 1.00) respectively (Figure 4). The corresponding positive likelihood ratio was 68 (95%CI 8 to 556) while the negative likelihood ratio was 0.04 (95%CI 0.002 to 0.63). There were too few studies (n=2) to formally analyse statistical heterogeneity[66].

The one study evaluating the cEEG rule combined a derivation and validation study that ultimately comprised 558 participants[71]. The derivation component of the study reported a sensitivity of 0.79 (95%CI 0.67 to 0.87) and a specificity of 0.73 (95%CI 0.67 to 0.78). The diagnostic accuracy was again not as robust in the validation component with a sensitivity of 0.59 (95%CI 0.48 to 0.70) and a specificity of 0.81 (95%CI 0.74 to 0.87; Figures 5 and 6) for detecting electrographic seizures.

Figure 5. Coupled forest plot of the sensitivity and specificity of the continuous EEG (cEEG) scale.

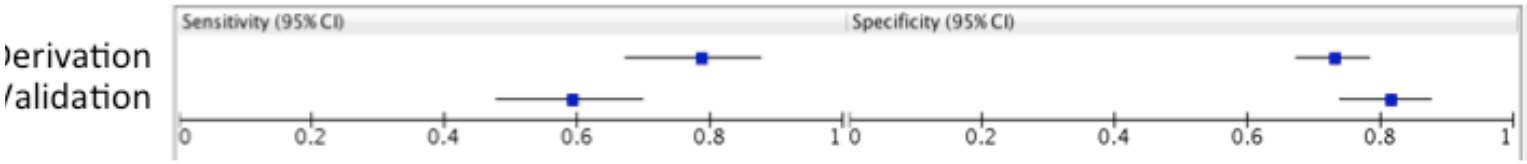
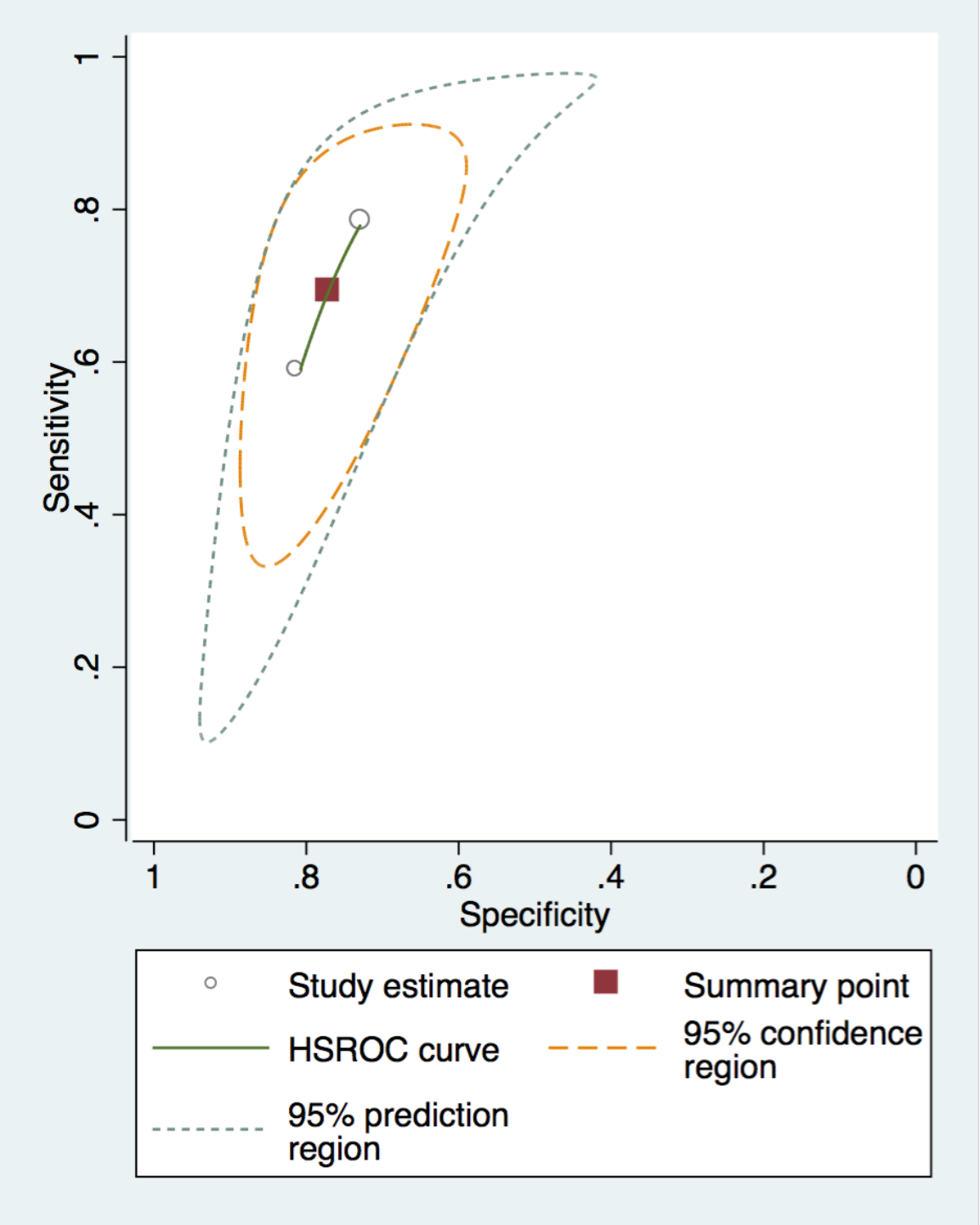


Figure 6. Pooled estimates of sensitivity and specificity of the continuous EEG (cEEG) scale including the 95% confidence and prediction regions.



Abbreviations: HSROC = hierarchical summary receiver operator characteristic curve

The pooled estimates of sensitivity and specificity according to the bivariate model were 0.69 (95%CI 0.58 to 0.78) and 0.77 (95%CI 0.71 to 0.81) respectively (Figure 6). The corresponding positive likelihood ratio was 3.0 (95%CI 2.5 to 3.5) while the negative likelihood ratio was 0.39 (95%CI 0.29 to 0.53). There were too few studies (n=2) to formally analyse statistical heterogeneity[66].

2.5.5 Publication bias

We were unable to evaluate publication bias due to the dearth of studies[73].

2.6 Discussion

This systematic review of the literature revealed five studies reporting on four scores that explicitly indicated a course of action thus meeting the criteria for a CDR. Three diagnostic CDR studies guided the use of cEEG, CT scanning, and using clinical parameters to diagnose nocturnal frontal lobe epilepsy whilst the lone treatment CDR guided the discontinuation of AEDs in children with epilepsy. Two studies were ultimately validated but demonstrated varying degrees of diagnostic accuracy.

The drop in diagnostic accuracy from CDR conception to validation is expected, which is why CDRs must undergo rigorous evaluation. Calibration (the agreement between predicted and observed outcomes) and discrimination (the ability to discern between those patients with and without an outcome of interest) tend to diminish in validation studies. This may be due to inadequacies in the

initial derivation of the rule, to over-fitting of the derivation model, to the unique characteristics of the external population in which the rule is validated, or to how new physicians interpret the rule[24]. Validation is a crucial prerequisite prior to CDR implementation. Physicians are correctly circumspect about applying CDRs in practice if they have not undergone rigorous validation and implementation testing. Hence, given the current state of the literature, it is not surprising that CDRs are lacking and underutilised in epilepsy.

In contrast, the epilepsy literature is rich in prognostic models. For instance, a model was created based on the MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) that stratifies the risk of seizure recurrence into high, medium, and low risk categories after a first seizure[74]. However, the model does not indicate a specific course of action (to treat or not) based on the patient's stratified risk group. Likewise, a nomogram now exists that indicates a patient's post-surgical probability of seizure-freedom but it does not indicate whether they should undergo the procedure based on a particular score threshold[75]. Additional studies using scoring systems to prognosticate neurodevelopmental and seizure outcomes in children exist but they do not indicate a specific course of action[76, 77].

Clinical decision rules have been used with considerable success in other medical disciplines. These tools have proliferated over the last 20 years and the number of scientific articles addressing the issue has more than doubled

between 1995 and 2005[24]. CDRs have mainly been derived for acute clinical conditions encountered in emergency medicine[25-27], internal medicine[28, 29], and surgery[30, 31]. For the most part, these rules have achieved a sensitivity of 100%; a measure that elevates confidence in ruling out a condition and thus promotes uptake[78, 79]. With the exception of stroke, few have been developed for neurology. However, scores such as the CHA_2DS_2-VASc[80] and HAS-BLED[81] have revolutionized the approach to prescribing antithrombotics for stroke prevention in non-valvular atrial fibrillation. It is anticipated that CDRs that address the correct clinical questions with high sensitivity and specificity could improve care in epilepsy in a similar fashion by streamlining decisions about the use of adjunct diagnostic tests and guiding the use of AEDs according to a patient's risk profile.

Unlike many conditions encountered in acute care medicine some clinical scenarios in epilepsy may not be conducive to CDR development. However, similar to stroke, epilepsy is the culmination of a plethora of underlying disease processes. Some of these are amenable to an algorithmic approach to diagnosis and treatment whilst others are not. However, despite the diversity of aetiologies, certain features remain common across the spectrum of the disease. For instance, those with drug resistant epilepsy should be considered for surgery and the development of a surgical nomogram has now been developed[75]. Crucially, there are many additional point-of-care decision nodes that can be improved with CDRs. Proper selection for inpatient and outpatient EEGs, and, in particular

continuous EEG in the critical care setting, are obvious choices. Additionally, correct choice of AED for specific populations of patients with epilepsy could promote safe, judicious, and efficacious prescription of the optimal AED. CDRs predicting the risk of AED-induced rash or drug-specific side effects, such as psychiatric reactions to levetiracetam, are both feasible and lacking.

We advocate a pragmatic approach to this issue that begins with a systematic review of the literature. Although our results were reasonably anticipated in advance of the study, this systematic review is the first to provide explicit evidence that epilepsy has fallen critically behind in an area of medicine that is designed to promote patient-centred, cost-effective care. The study therefore represents a critical foundation upon which these CDRs can be derived and validated. We propose that the next step should involve the development of a battery of CDRs designed to meet epilepsy-specific needs that will function as a proof of principle. The advent of ‘big data’ means that the potential now exists to rapidly derive and validate robust and reliable CDRs using large, linked administrative and EMR data collected during the course of routine care. These should target scenarios like AED prescription based on side-effect profiles, continuous EEG use, and status epilepticus therapy that are all amenable to the algorithmic approaches central to CDR derivation.

Our study has benefited from an extensive and thorough search strategy. We did not restrict the strategy by language, country, or year of publication. We used

conventional definitions of CDRs to ensure consistency of data abstraction and analysis. We were able to use the bivariate model to meta-analyse studies undergoing derivation and validation. This model accommodates the intrinsic trade-off between sensitivity and specificity permitting a pooled estimate of the overall diagnostic accuracy.

It is possible that CDRs were missed though this would be unlikely given the comprehensive search strategy. Often prognostic models provide implicit guidance for a course of action that requires individual physicians to interpret the patient's risk stratum. However, unless an explicit course of action was reported, we opted to exclude these articles from the review. Overall study quality of most articles was moderate at best (Table 2) thus limiting the validity and applicability of the results. Finally, few scores could be meta-analysed. This means that the overall estimates are likely underpowered, and therefore imprecise, and it precludes our ability to rigorously evaluate between study statistical heterogeneity. The overall pooled estimates of the two currently validated CDRs are limited by the paucity of studies thus leading to imprecision of the pooled estimates.

Although many medical CDRs have been derived, very few have been properly validated and implemented[24]. Hence, it is unsurprising to find so few for epilepsy. Validation and implementation studies are crucial since derived models often do not perform as well in independent populations. Properly validated and

implemented CDRs, accomplished through randomised cluster or controlled trial design, can offer enhanced, patient-centred, cost-effective care[23, 35, 36]. Thus, rules developed and validated for epilepsy with proper implementation will be expected to modify physician behaviour and result in improved patient outcomes with reductions in health-care costs.

There is a diverse array of therapeutic and diagnostic options for people with epilepsy. It is therefore becoming increasingly difficult to make efficient, cost-effective diagnostic and therapeutic decisions. CDRs have been empirically demonstrated to improve patient care and promote judicious use of limited resources in other settings[23] yet their usefulness for epilepsy has not been rigorously explored. The rules should target clinically accessible decision nodes, such as the use of diagnostic or therapeutic interventions that are amenable to the statistical and methodological constraints of the derivation process. These CDR studies should be a priority for future epilepsy research given their potential for promoting efficient provision of evidence-based, patient-centred health care.

Chapter 3: Prescription trends and psychiatric symptoms following first receipt of one of seven common antiepileptic drugs in general practice

3.1 Publication

This chapter has been published in *Epilepsy & Behavior*[2] and permission for use has been provided by all co-authors.

3.2 Abstract

We sought to examine the risk of psychiatric symptoms associated with a first prescription for specific antiepileptic drugs (AEDs) used in monotherapy in a general cohort of patients with epilepsy. We used The Health Improvement Network database (comprising years 2000-2012) to identify incident patients with epilepsy. The index date was that on which they met the case definition for epilepsy and analyses only included patients who remained on monotherapy or received no AED therapy following diagnosis to avoid confounding by polytherapy. Psychiatric symptoms were defined using mental health clinical or treatment (medical or therapeutic) code. We analysed the AED of interest as a time varying covariate in multivariate Cox proportional hazards regression models controlling for confounding factors. We identified 9595 patients with incident epilepsy of whom 7400 (77%) received a first-recorded AED prescription. Prescriptions for newer generation AEDs (lamotrigine and levetiracetam) steadily increased (constituting over 30% of all AED prescriptions by 2012) whilst valproate use significantly declined in females (~40% in 2002 to just over 20% by 2012). A total of 2190 patients were first exposed to

carbamazepine (29.3%) and 222 to lamotrigine (3%) both of which were associated with a lower hazard of any coded psychiatric symptom or disorder in multivariate analyses (hazard ratio [HR] 0.84, 95% confidence interval [95% CI] 0.73-0.97; p=0.02 and HR 0.83, 95%CI 0.70-0.99; p=0.03 respectively for carbamazepine and lamotrigine). Carbamazepine was also associated with a lower hazard for depression (HR 0.81; 95%CI 0.69-0.96; p=0.013) and anxiety (HR 0.77; 95%CI 0.63-0.95; p=0.013) in secondary analyses. This study provides evidence that carbamazepine and lamotrigine are associated with lower hazards for psychiatric symptoms following a diagnosis of epilepsy. These estimates can be used in clinical settings and the precision should improve with more contemporary data that include larger proportions of newer generation AEDs.

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3.3 Introduction

Psychiatric disorders are common in people with epilepsy. Approximately 23% of patients with epilepsy have active depression[82]. Furthermore, the odds of reporting anxiety and suicidal thoughts are 2.4 (95% confidence interval [95%CI] 1.5-3.8) and 2.2 (95%CI 1.4-3.3) fold higher, respectively, in people with epilepsy compared to the general population[8]. Not surprisingly, psychiatric comorbidities are also a major determinant of quality of life in those with epilepsy[83].

In addition to comorbidities, AEDs themselves can unmask subclinical psychiatric disorders or elicit *de novo* affective symptoms[84]. In particular, there is evidence

that, in select populations with epilepsy, levetiracetam, clobazam, barbiturates, and phenytoin are associated with a variety of psychiatric adverse effects that include affective disorders, psychosis, and irritability/aggression[85].

Having determined that no CDRs exist for guiding AED prescription according to the risk of a psychiatric adverse effect in our systematic review, the next goal was to determine if the development of a such a rule was feasible using electronic medical records (EMR) data. The Health Improvement Network (THIN) EMR database was chosen to develop such because of its large size, reliable coding, and potential for high external validity. Thus, in conjunction with Aim 2, the first objective was to determine whether there is indeed a relationship between AED prescription status and the risk of a psychiatric adverse event.

Prior studies using large, administrative and electronic medical records data have typically focused on AEDs as a class, rather than on individual medications, or examined their association with a limited range of conditions focusing primarily on the association between overall AED use and suicidal behaviour[86-88]. There is a relative paucity of evidence quantifying the unique contribution of each individual AED to the overall risk of psychiatric symptoms. Therefore, an additional aim of this chapter was to address the hazard of overall psychiatric symptoms (stratified by subtypes) attributed to individual AEDs following a first-ever prescription.

3.4 Methods

3.4.1 The Health Improvement Network

The THIN database is an EMR data platform of anonymized primary care patients. The patients are derived from GP clinics that constitute approximately 5% of the UK population. These patients are broadly representative of the general population[89]. All medical events are coded using Read codes[90] and include specialist evaluations and emergent medical care records that are routinely sent to the patient's GP. Prescription data are recorded by the GP, coded by the UK Prescription Pricing Authority, and classified by the British National Formulary[91, 92]. Missing data are imputed using a two-fold fully conditional specification algorithm[93]. We used THIN version 1205 and restricted the timeframe to January 1, 2000 to May 31, 2012, since 2000 was the year in which levetiracetam, the newest of the seven studied AEDs, was approved.

3.4.2 Study population

To increase the chance of identifying an incident cohort of epilepsy patients, we used a modified version of a published case definition designed specifically for THIN[94] using a conventional five-year washout period. The published definition requires a single Read code for an epilepsy syndrome or two Read codes for symptoms of epilepsy (i.e. codes for non-febrile seizures on two or more occasions) and two AED codes within 4 months and is 92% accurate for detecting cases of paediatric epilepsy[94]. Our modified definition only differs from

the published version by omitting the necessity for AED codes. This was decided *a priori* to isolate the additional hazard associated with a single AED in monotherapy compared to no treatment following an incident diagnosis of epilepsy. This case definition has recently been validated for identifying adults with epilepsy (sensitivity = 86% [95%CI 80%-91%]; specificity = 97% [95%CI 92%-99%]) in the Secure Anonymised Information Linkage (SAIL) Databank, a similarly constructed Welsh electronic medical records database[95].

To mitigate the risk of immortal time bias we required all patients to be active in the database after the Acceptable Mortality Reporting date (the date when mortality reporting was considered complete) for each individual practice[96]. We increased the chance of excluding prevalent cases of epilepsy by using a five-year washout period from enrolment to first epilepsy code. We then compared those with and without a psychiatric code at any point over the five or more years of follow-up prior to meeting the EMR epilepsy phenotype. A history of psychiatric symptom or treatment was defined using medical and therapeutic Read and Multilex codes (medication codes that are assigned by First Databank and are linked directly to the British National Formulary). This definition of a psychiatric outcome, as well as subsets of psychiatric events, was reached through a consensus-driven process between two authors (Dr. Colin Josephson and Dr. Scott Patten; Appendix 3). Finally, we excluded any patient receiving an AED over at least 5 years prior to the index date and those receiving two or more AEDs at any point during follow-up to isolate the unique effects of each specific

medication used in monotherapy. All patients aged 18 years or greater at epilepsy diagnosis, who met these conditions, were included in the analysis.

3.4.3 Statistical analysis

The index date (time zero) was that on which the patient met our case definition for epilepsy. A code for first AED prescription was treated as the exposure. We required that first prescriptions occurred after the year 2000 (the year levetiracetam, the newest of the seven evaluated AEDs, was approved by the European Medicines Agency) and followed patients for two-years after the first AED prescription. The primary exposure was the first AED prescription. We divided follow-up into four 6-month periods. Exposure to each AED was recorded as a dichotomous ("yes"/"no") time-varying covariate during each 6-month epoch, based on the presence or absence of a prescription record during that time period. We then determined whether a person had a psychiatric code during each epoch. The patient was considered to have incurred the outcome of interest (any code for a psychiatric sign, symptom, or disorder as listed in Appendix 3) during the epoch in which they were coded for the adverse effect. Otherwise, patients were censored at the end of the 24-month analysis period, loss to follow-up, or death if no outcome occurred.

Descriptive statistics were used to compare populations of interest. Time-varying Cox proportional hazards regression analysis was used to estimate the hazard of a psychiatric adverse event following a putative first-ever prescription for an AED

in monotherapy. Goodness of fit was determined using the concordance statistic (C statistic). All models controlled for age at index date, sex, a history of a psychiatric code a history of a psychiatric code (defined as the presence of any psychiatric code listed in Appendix 3 from inception in the general practice until the day prior to the index date) since inception into the THIN database, baseline Charlson comorbidity index[97], and the Townsend index of social deprivation[98]. All these potential confounders have been independently associated with presumed incident depression in epilepsy patients identified in THIN[99]. We considered a p-value of ≤0.05 to be statistically significant.

3.4.4 Secondary analyses

We anticipated that prescription patterns for certain AEDs would change over time and that this may be sex-dependent[100, 101]. Hence, we evaluated unique AED prescriptions as a percentage of total AED prescriptions each year from January 1, 2000 to May 31, 2012. We compared proportions from the beginning and end of the study period stratified by sex and between sexes in the year 2012. We subsequently evaluated the risk of subsets of psychiatric symptoms and disorders. We categorised psychiatric codes into depression, anxiety, psychosis/mania, and suicidal ideation/completed suicide. A prescription for an antidepressant was counted as both a depression and anxiety event, since we were unable to determine the reason for prescription, and depression and anxiety are often intermixed. A prescription for an antipsychotic medication was classified as a psychosis/mania outcome.

3.4.5 Software

All analyses were conducted using Hive 0.13.1, R version 3.1.2[102], and Python 2.7[103].

3.4.6 Ethics

THIN has been used for scientific research since approval from the NHS South-East Multi-Centre Research Ethics Committee in 2003. Ethics approval for this study was obtained both through the University of Calgary's Conjoint Health Research Ethics Board (REB15-0203) and the CSD Medical Research's Scientific Review Committee in December 2015 (SRC Reference number 15THIN087).

3.5 Results

3.5.1 Demographics

We identified 9595 out of 11,194,182 patients (85.7 cases per 100,000 persons), over a maximal time of registration in THIN of 12 years, who met our case definition for presumed incident epilepsy. Of these, 7400 (77%) were prescribed an AED at the point of meeting the case definition of incident epilepsy. Those prescribed an AED were older (median 48 years [interquartile range, 'IQR' 32-68] *versus* 40 years [IQR 29-57]; p<0.001), less likely to be female (48% *versus* 51%; p=0.022), and more likely to have a history of a psychiatric code prior to the

index date (43% versus 39%; p<0.001). Although the Charlson comorbidity and Townsend indices were statistically significantly different between the two groups, they were clinically comparable (Table 3).

Table 3. Demographic characteristics of all epilepsy patients (n=9595) stratified by receipt of an AED in monotherapy.

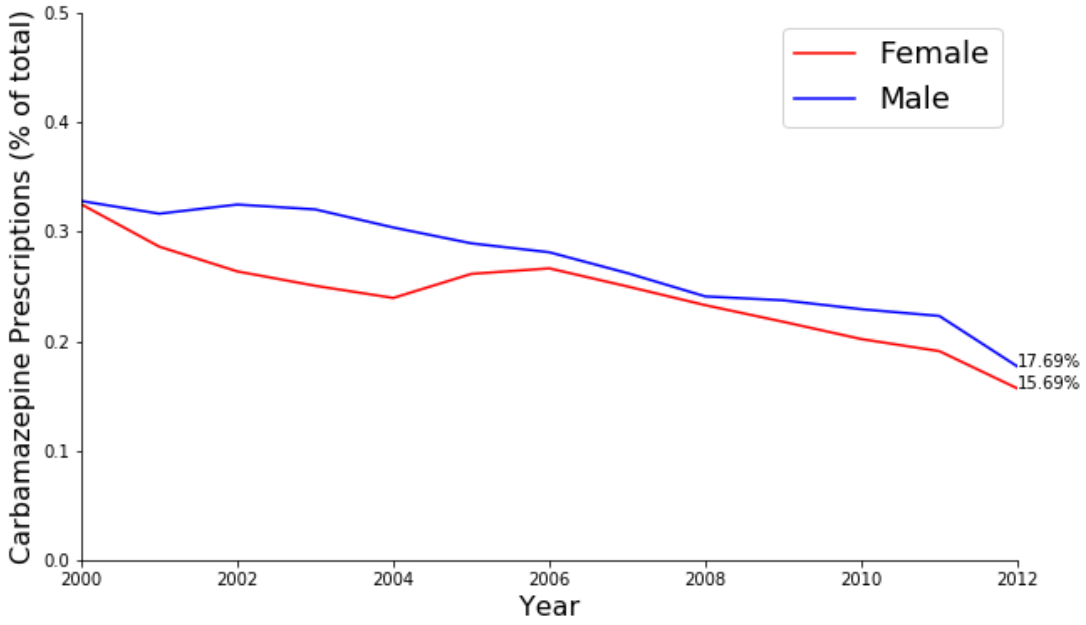
Characteristic	AED	No AED	p-value
n (%)	7400 (77%)	2195 (23%)	n/a
Age in years (median; IQR)	48 (32-68)	40 (29-57)	<0.001
Female sex	3552 (48%)	1119 (51%)	0.022
Charlson comorbidity index (median; IQR)	0 (0-1)	0 (0-1)	<0.001
Townsend Index (median, IQR)	3 (2-4)	3 (2-4)	<0.001
History of a psychiatric code	3182 (43%)	856 (39%)	0.001
First AED prescribed			
Carbamazepine	2162 (29.2%)	n/a	n/a
Clobazam	25 (0.3%)	n/a	n/a
Lamotrigine	1211 (16.4%)	n/a	n/a
Levetiracetam	202 (3%)	n/a	n/a
Phenytoin	917 (12.2%)	n/a	n/a
Topiramate	31 (0.4%)	n/a	n/a
Valproic acid	2852 (38.5%)	n/a	n/a

Abbreviations: AED = antiepileptic drug; IQR = interquartile range

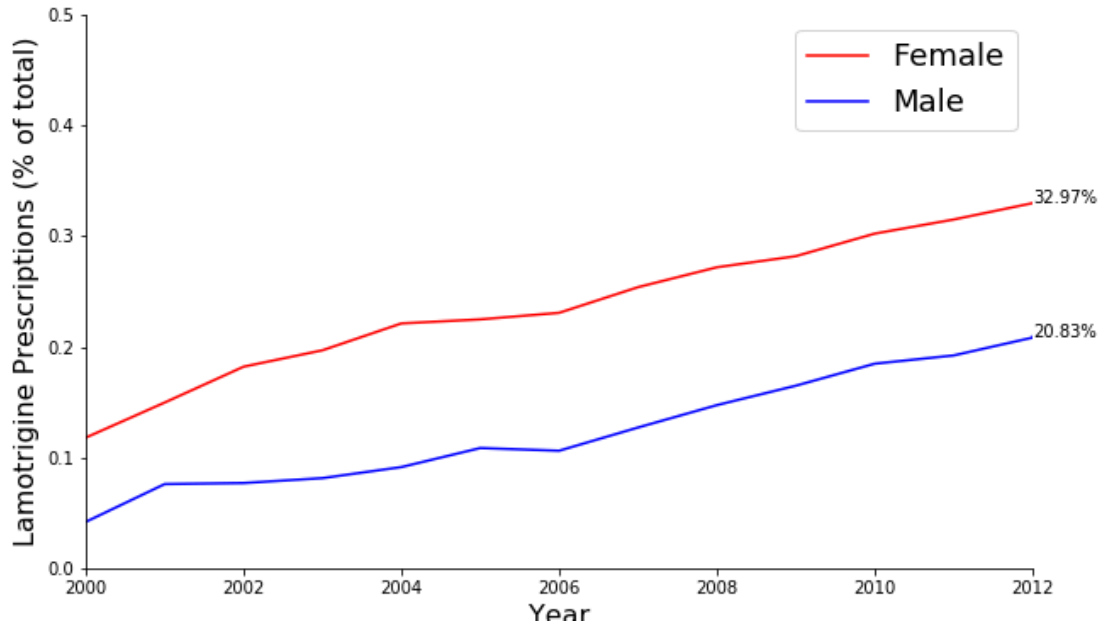
There were statistically significant differences in prescription patterns of AEDs between 2000 and 2012. Carbamazepine constituted over 30% of total presumed first-ever AED prescriptions in 2000 but declined to under 20% by 2012 (Figure 7). By contrast, lamotrigine and levetiracetam were significantly more likely to be prescribed in 2012 compared to 2000 (Figure 7). Finally, valproic acid prescriptions remained relatively stable in males but dropped significantly in females over time ($p<0.001$; Figure 7). Topiramate, clobazam, and phenytoin constituted a low percentage of total AEDs prescribed in 2012 (Figure 8).

Figure 7. United Kingdom general practice prescription trends (unique prescriptions as a total of all antiepileptic drug prescriptions) by year from 2000-2012 stratified by sex (orange = male; blue = female) for (A) carbamazepine, (B) lamotrigine, (C) levetiracetam, and (D) valproic acid.

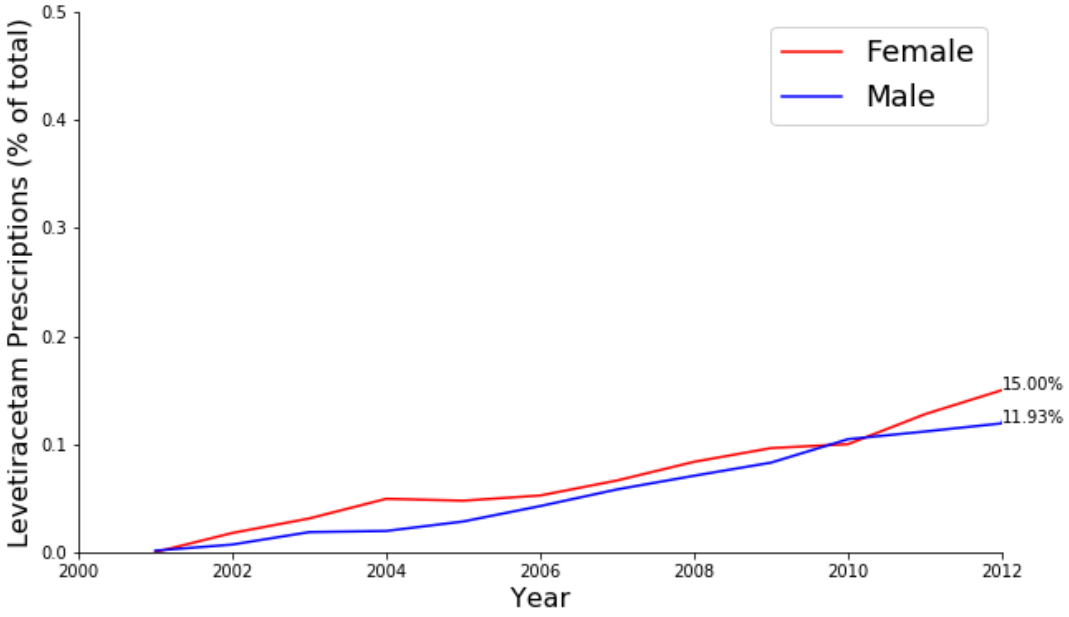
(A)



(B)


Female
Male
32.97%
20.83%
Lamotrigine Prescriptions (% of total)
0.0
0.1
0.2
0.3
0.4
0.5
2000
2002
2004
2006
2008
2010
2012
Year

(C)


Female
Male
Levetiracetam Prescriptions (% of total)
0.5
0.4
0.3
0.2
0.1
0.0
2000
2002
2004
2006
2008
2010
2012
Year
15.00%
11.93%

(D)

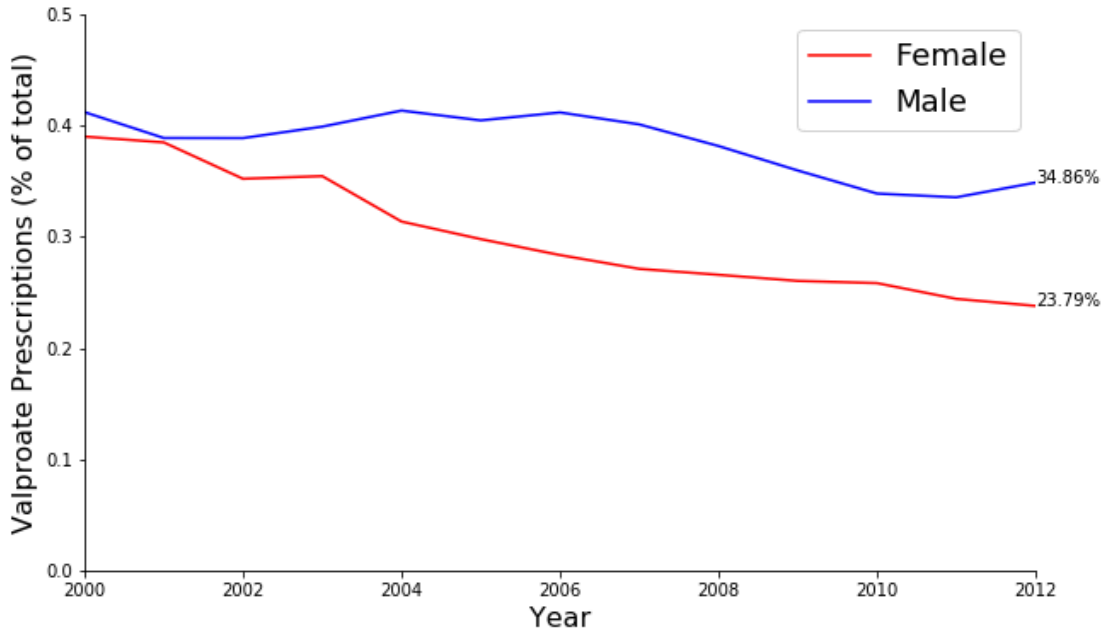
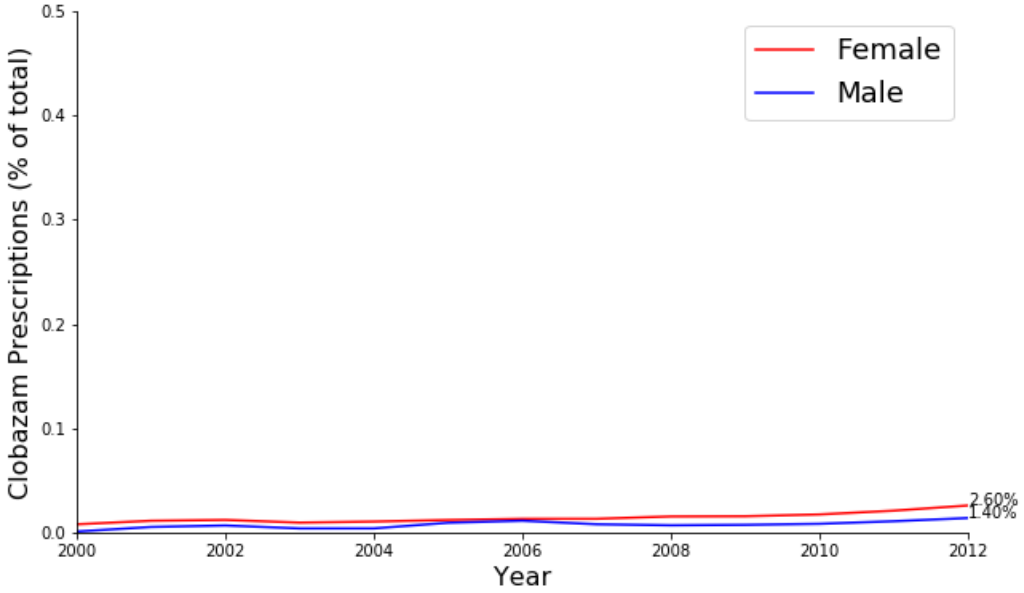
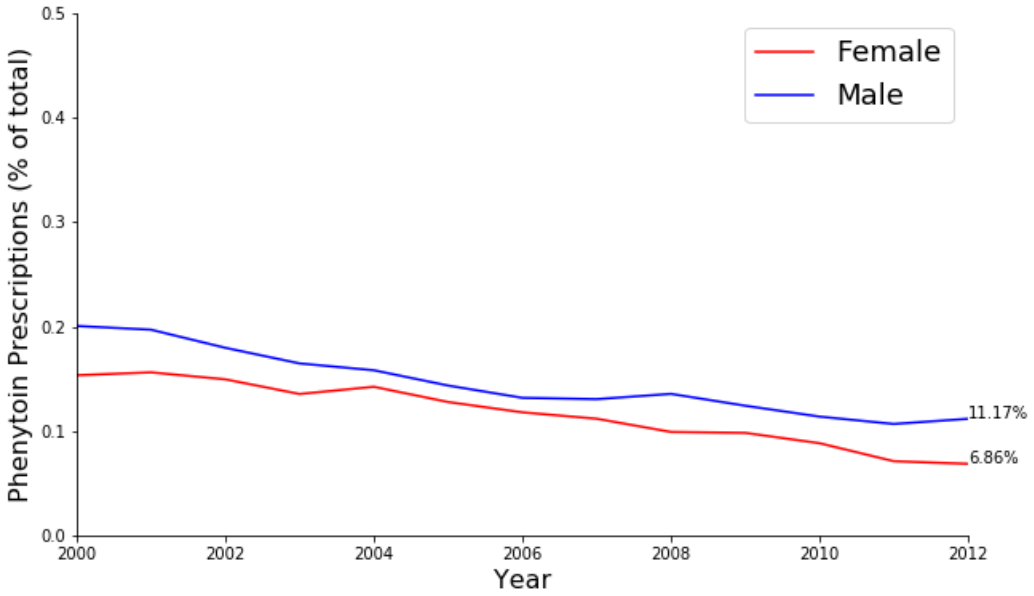

Female
Male
34.86%
23.79%
Valproate Prescriptions (% of total)
Year
0.0
0.1
0.2
0.3
0.4
0.5
2000
2002
2004
2006
2008
2010
2012

Figure 8. United Kingdom general practice prescription trends (unique prescriptions as a total of all antiepileptic drug prescriptions) by year from 2000-2012 stratified by sex (orange = male; blue = female) for (A) clobazam, (B) phenytoin, and (C) topiramate.

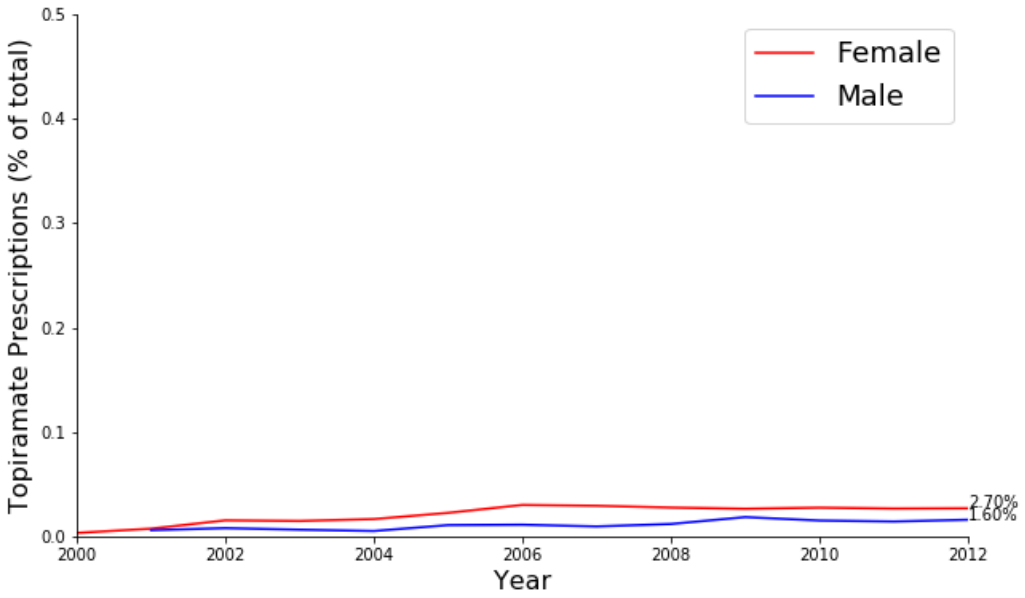
(A)



(B)


Female
Male
Phenytoin Prescriptions (% of total)
0.5
0.4
0.3
0.2
0.1
0.0
2000
2002
2004
2006
2008
2010
2012
Year
11.17%
6.86%

(C)


Female
Male
Topiramate Prescriptions (% of total)
0.5
0.4
0.3
0.2
0.1
0.0
2000
2002
2004
2006
2008
2010
2012
Year
2.70%
1.60%

The incidence of a composite psychiatric symptom or disorder over the first two-years following the index date was 19.1 per 1000 person-years in those exposed to a presumed first-ever AED in monotherapy compared to 19.2 per 1000 person-years in those unexposed to an AED. Although most analyses were robust, it should be noted topiramate (n=31) and clobazam (n=25) were prescribed in low numbers, likely due to their limited role as first choice monotherapy in newly diagnosed patients with epilepsy (Table 4).

Table 4. Numbers (%) developing a psychiatric sign, symptom, or disorder over two-years of follow-up from index date in epilepsy patients (n=9595) receiving no therapy or an antiepileptic drug (AED) in monotherapy.

Exposure	n	Psychiatric outcome
Levetiracetam	202	30 (15%)
Topiramate	31	8 (26%)
Valproate	2852	548 (19%)
Carbamazepine	2162	352 (16%)
Lamotrigine	1211	216 (18%)
Clobazam	25	7 (28%)
Phenytoin	917	187 (20%)
No AED	2195	413 (19%)

3.5.2 Hazard of a putative first-ever code for any psychiatric symptom or disorder

The risk of reporting any presumed new psychiatric symptom or disorder over two years of follow-up was reduced following a first prescription of carbamazepine (hazard ratio [HR] 0.84; 95%CI 0.73-0.97; p=0.02) and lamotrigine (HR 0.83; 95%CI 0.70-0.99; p=0.037). No other AED was associated with either a statistically significant decreased or increased hazard at an alpha level of significance of 0.05. In addition to AED prescription, female sex, a higher Charlson comorbidity index score, history of a psychiatric code, and a higher Townsend index score were all independently associated with an increased risk of reporting any new psychiatric symptom or disorder within two years after the first AED prescription (Table 5a and b; Figure 9). Advancing age was associated with decreased risk of psychiatric symptoms or disorders in all models. The C statistic for models ranged from 0.63 to 0.65.

Table 5. Hazard ratio for any psychiatric code over two-years follow-up in patients with probable incident epilepsy receiving a code for carbamazepine (a) or lamotrigine (b) compared to those not receiving an AED at any point during 2-years follow-up. Both AEDs were treated as time-varying covariates during discrete 6-month epochs over the 2-years.

(A)

	Hazard ratio	95%CI	P value
Age	0.99	0.98-0.99	<0.001
Female sex	1.24	1.07-1.44	0.002
Charlson Comorbidity Index	1.07	1.01-1.14	0.009
Townsend Index	1.05	1.00-1.10	0.042
History of a psychiatric code	2.56	2.21-2.98	<0.001
Carbamazepine	0.84	0.73-0.97	0.020

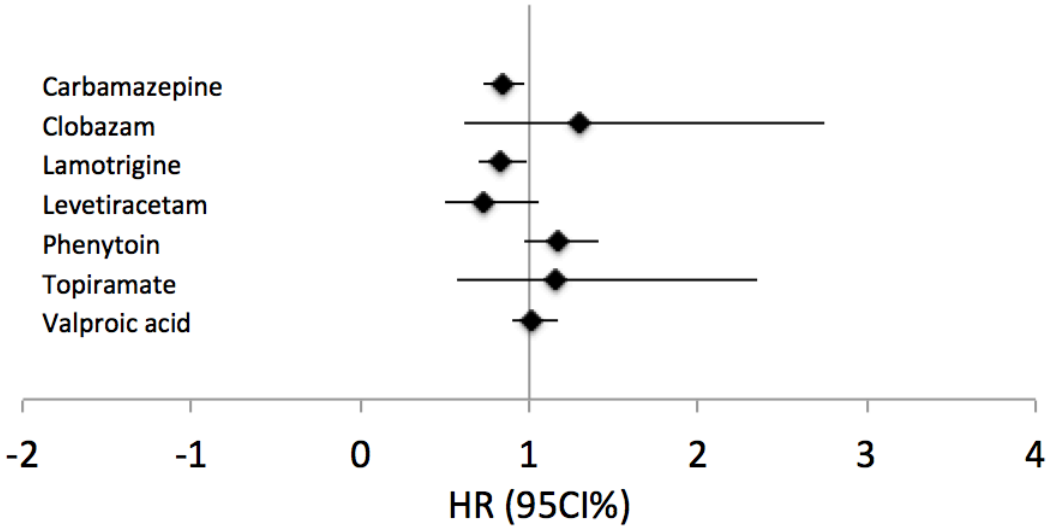
Abbreviations: 95%CI = 95% Confidence interval

(B)

	Hazard ratio	95%CI	P value
Age	0.98	0.98-0.99	<0.001
Female sex	1.23	1.04-1.45	0.012
Charlson Comorbidity Index	1.08	1.02-1.16	0.009
Townsend Index	1.09	1.03-1.15	0.001
History of a psychiatric code	2.62	2.22-3.09	<0.001
Lamotrigine	0.83	0.70-0.99	0.037

Abbreviations: 95%CI = 95% Confidence interval

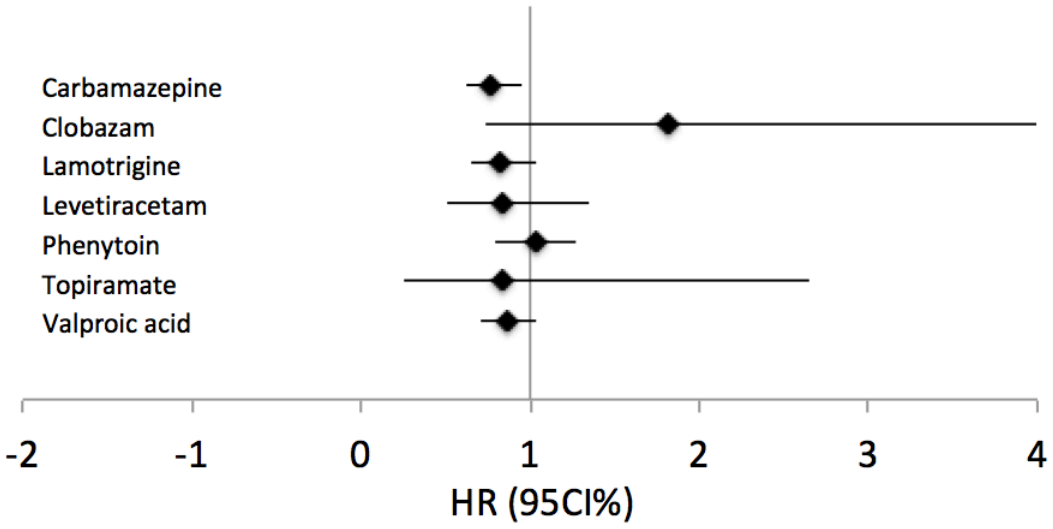
Figure 9. Hazard ratios with 95% confidence intervals (HR; 95%CI) for a composite outcome of any psychiatric symptom, disorder, or treatment code following a first prescription for one of seven antiepileptic drugs prescribed in monotherapy following a presumed incident diagnosis of epilepsy.



3.5.3 Hazard of a putative first-ever code for a depression symptom or disorder

Carbamazepine was associated with a lower hazard of a presumed first-ever code for a depressive symptom or disorder (HR 0.81; 95%CI 0.69-0.96; p=0.013). Similar to the above analyses, female sex (HR 1.35; 95%CI 1.15-1.59; p<0.001), higher Charlson comorbidity index score (HR 1.11; 95%CI 1.05-1.19; p<0.001), and a history of a psychiatric diagnosis or treatment code (HR 2.35; 95%CI 1.99-2.77; p<0.001) were also independently associated with an increased risk of depression. The C statistic for the model was 0.65 (standard error [se] = 0.01). No other AED was associated with an elevated risk (Figure 10).

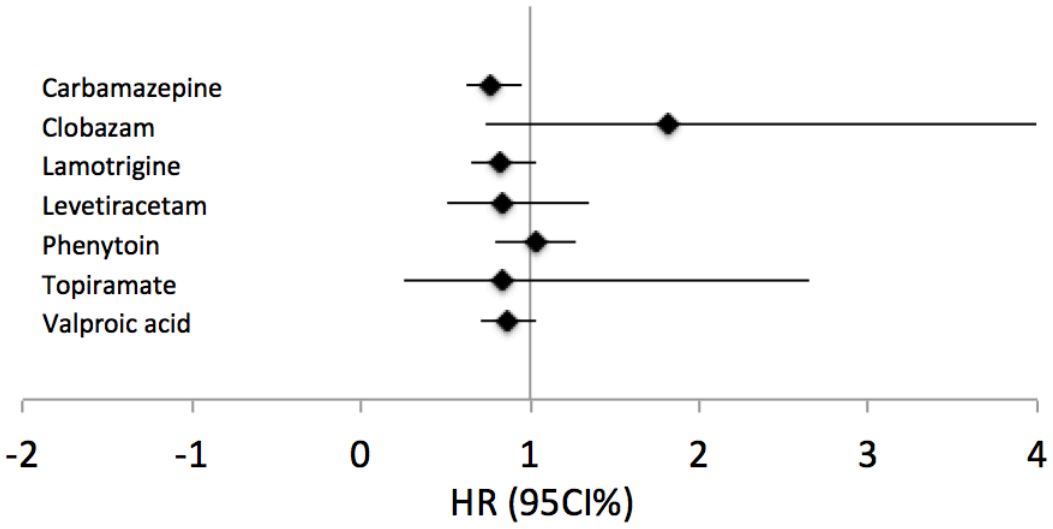
Figure 10. Hazard ratios with 95% confidence intervals (HR; 95%CI) for a depression symptom, disorder, or treatment code following a first prescription for one of seven antiepileptic drugs prescribed in monotherapy following a presumed incident diagnosis of epilepsy.



3.5.4 Hazard of a putative first-ever code for an anxiety symptom or disorder

Similarly, carbamazepine was associated with a reduced hazard of a putative first-ever code for anxiety (HR 0.77; 95%CI 0.63-0.95; p=0.013). Additionally, female sex (HR 1.23; 95%CI 1.01-1.51; p=0.034) and a history of a psychiatric diagnosis or treatment code (HR 1.40; 95%CI 1.14-1.71; p=0.001) were also independently associated with an increased risk of anxiety. The C statistic for the model was 0.59 (se = 0.01). No other AED was associated with an elevated hazard (Figure 11).

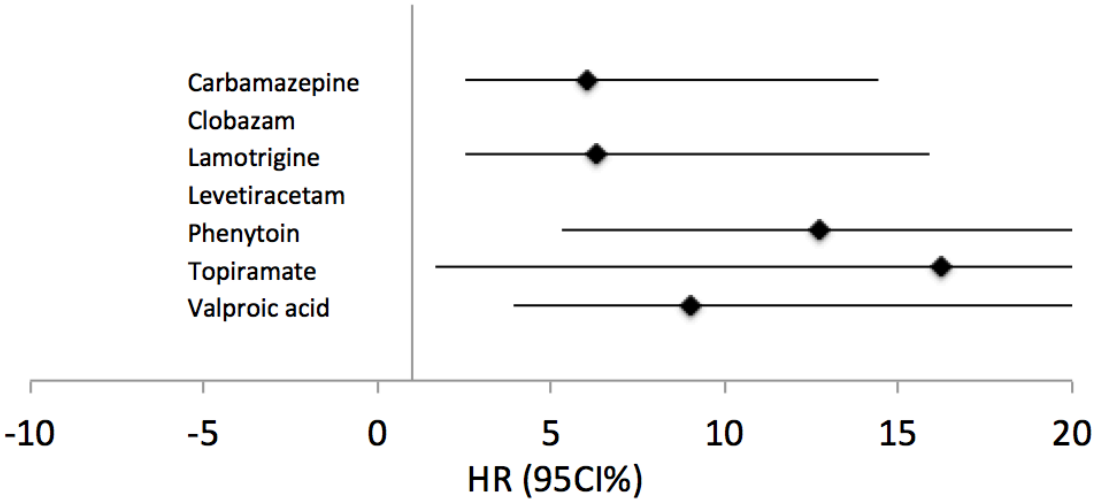
Figure 11. Hazard ratios with 95% confidence intervals (HR; 95%CI) for an anxiety symptom, disorder, or treatment code following a first prescription for one of seven antiepileptic drugs prescribed in monotherapy following a presumed incident diagnosis of epilepsy.



3.5.5 Hazard of a putative first-ever code for a psychosis/mania symptom or disorder

A combination of low sample sizes and few events limited the analyses of psychosis and mania. Estimates were not possible for clobazam and levetiracetam. Carbamazepine (HR 6.04; 95%CI 2.53-14.42; p<0.001), lamotrigine (HR 6.31; 95%CI 2.50-15.89; p<0.001), phenytoin (HR 12.7; 95%CI 5.33-30.48; p<0.001), topiramate (HR 16.22; 95%CI 1.68-156.68; p=0.016), and valproic acid (HR 9.04; 95%CI 3.90-20.91; p<0.001) were all associated with elevated risk of psychosis and mania when controlling for age, sex, Charlson comorbidity index score, Townsend index, and a history of a psychiatric code (Figure 12).

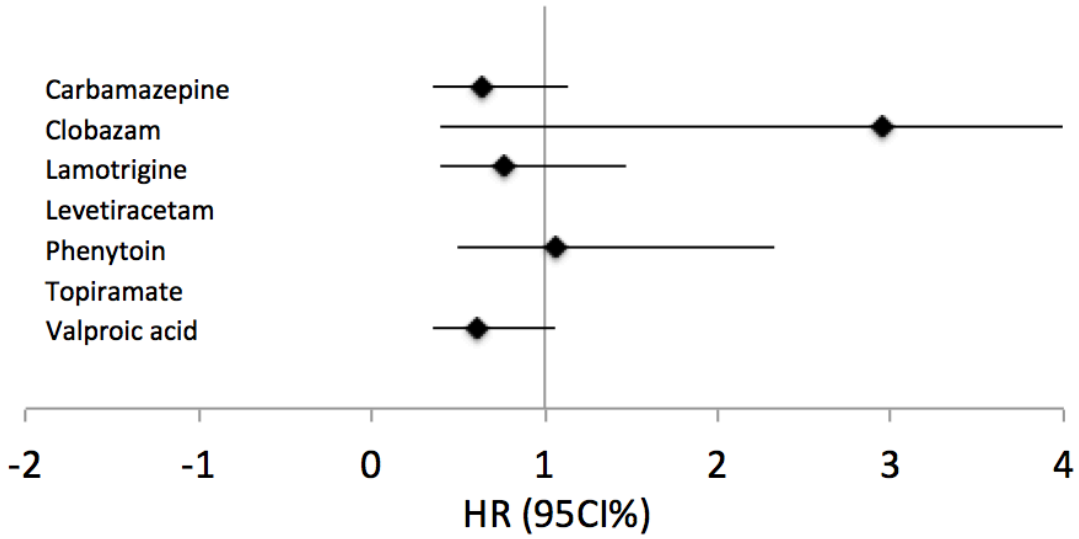
Figure 12. Hazard ratios with 95% confidence intervals (HR; 95%CI) for a psychosis/mania symptom, disorder, or treatment code following a first prescription for one of seven antiepileptic drugs prescribed in monotherapy following a presumed incident diagnosis of epilepsy. Insufficient data were available to evaluate the hazard from clobazam and levetiracetam.



3.5.6 Hazard of a putative first-ever code for suicidal ideation or completed suicide

No AED was associated with an increased or decreased risk of suicidal ideation/completed suicide (Figure 13). Increasing age and a history of a psychiatric diagnosis or treatment code were consistently associated with reduced and elevated risks of suicide respectively across all models (Figure 13).

Figure 13. Hazard ratios with 95% confidence intervals (HR; 95%CI) for a suicidal ideation/completed suicide disorder code following a first prescription for one of seven antiepileptic drugs prescribed in monotherapy following a presumed incident diagnosis of epilepsy. Estimates were not possible for levetiracetam or topiramate due to insufficient numbers.



3.6 Discussion

This study demonstrates a statistically significant decrease in the hazard of a composite outcome of any psychiatric adverse effect following a first-ever prescription for carbamazepine and lamotrigine, when used in monotherapy and when controlling for age at index date, sex, Charlson comorbidity index, Townsend index, and a history of a psychiatric diagnosis. Carbamazepine was additionally associated with a lower hazard of depression and anxiety. Despite the large overall sample size, numbers and outcomes for specific AEDs were limited in some cases precluding a robust analysis of psychosis and mania. Interestingly, carbamazepine, lamotrigine, phenytoin, topiramate, and valproic acid were all independently associated with increased risks of this psychiatric outcome, though the estimates were imprecise. No AED was associated with an increased or decreased risk of suicide.

This study benefits from using a large prospective EMR database from general practice. We used a validated case definition of epilepsy with a high sensitivity (86%) and specificity (97%) when applied to a UK EMR database similar in design to THIN[95]. The case definition performed well since the incidence of epilepsy (~85.7 cases per 100,000 persons) is comparable to that reported in a recent meta-analysis[104]. The THIN database also confers substantial statistical power that is evidently necessary for these analyses given the wide 95% confidence intervals encountered for specific AEDs and secondary outcomes. The comprehensive, population-based nature of the database also permitted a

descriptive analysis of AED prescription patterns over time. Newer generation AEDs, such as lamotrigine and levetiracetam, comprised a steadily larger percentage of total AED prescriptions per annum over the 12-year study period whilst use of older AEDs, such as phenytoin and carbamazepine, gradually declined. There also appeared to be sex differences in that, in the year 2000, valproic acid represented approximately 40% of all AED prescriptions irrespective of sex while, in the year 2012, there was a statistically significantly difference between males (where the proportion remained stable) and females where the proportion dropped by over 15% (Figure 7d). In conjunction with this, with this, lamotrigine prescriptions progressively rose, especially in females, likely as a result increasingly recognised concerns over teratogenicity and long-term *in utero* complications of valproic acid[100, 101].

Another strength is the strict methodology we used to optimise the accuracy of our results. Specifically, we used a 5-year washout period to maximize the chances of identifying incident epilepsy cases and psychiatric outcomes (since pre-index follow-up was greater than 5 years for all patients). We controlled for the coding of any psychiatric diagnostic, therapeutic or psychotropic medication code prior to the index date. We used broad definitions to identify the outcomes of interest (definitions requiring a single code for a disorder, therapeutic modality or a psychotropic medication) to increase the sensitivity of identifying psychiatric symptoms and disorders that are known to be routinely under-coded in large population-based records such as administrative data[105] and likely electronic

medical records. We also stratified follow-up into 6-month epochs to ensure close chronological approximation between individual AED exposure and coding for a psychiatric disorder. Finally, we treated each prescription as a time varying covariate to minimise the risk of immortal time bias.

Despite these strengths, there are limitations to the analyses. Unexpected results were encountered for psychosis and mania. This may be due to an inability to account for epilepsy severity. Psychosis and mania are more common in those with epilepsy when compared to the general population[106]. Furthermore, such disorders have a higher prevalence in medication-resistant epilepsy[107]. Since those with more severe epilepsy are more likely to receive an AED, selection bias may have skewed the results such that those receiving an AED in monotherapy at incident diagnosis would be more prone to severe epilepsy compared to those for whom no prescription was documented. The lack of granular data may have also resulted in relative imprecision. Though the C statistics for all models ranged from 0.63-0.65, we were unable to extract reliable data on seizure frequency and a past history of any drug-related adverse events. Efforts to include these features, as well as defined daily dose of AEDs, and other concomitant medications, would be anticipated to improve prediction.

Misclassification bias may have been inadvertently introduced via an imbalance in epilepsy severity since ictal and postictal symptoms, especially those related to temporal lobe seizures, may be mistaken for interictal or medication-related

psychosis[107]. Hence, those prescribed an AED may be more likely to be misclassified as having psychosis. Misclassification bias may also be present since we cannot entirely exclude the possibility that a patient had a psychiatric disorder that was not coded in THIN prior to first AED exposure[105]. Under these circumstances, we would have failed to exclude a pre-existing psychiatric disorder and, given the high prevalence of psychiatric conditions in patients with epilepsy[8], we may simply be capturing the natural history of their disease rather than identifying a drug-related adverse effect. Finally, protopathic bias[108] could distort the true relationship if initiation of the drug occurred in response to premonitory symptoms of an as yet undiagnosed condition such as psychosis that is only later recognised, diagnosed, and coded[86]. In this circumstance, there is a risk of 'reverse causation' in which one draws the spurious conclusion that the medication caused the disease and not *vice versa*. This concept has already been invoked to explain the specious association between AED use and suicide-related behaviour[86]. Ultimately, though, these estimates should be interpreted with caution due to a lack of precision as denoted by the wide confidence intervals. Medication non-adherence may also play a role but could not be evaluated in the THIN database. Finally, we used a p-value of ≤0.05 to define significance. Therefore, Type I error is possible though the analyses were well structured with predefined primary and secondary outcomes, were typically highly significant ($p<0.001$), and were consistent with clinical intuition and literature reviews.

Our study did not reveal any statistically significant associations between presumed incident AED use in monotherapy and elevated risks of psychiatric symptoms or disorders. One possible explanation may be non-adherence to AEDs. We cannot examine adherence, ensure the prescriptions were filled, or determine the defined daily dose for each patient. However, we partially mitigated this issue by dividing follow-up into 6-month epochs (rather than reporting associations over a 1- or 2-year span) to increase confidence in the timing between exposure and outcome. Furthermore, the mean medication possession ratio (MPR) for AEDs has been reported at over 80% in large electronic medical records and, of this group, approximately 65% demonstrate good adherence to AEDs (MPR ≥80%) in large electronic records datasets[109]. This proportion may be even higher for newer AEDs[109]. The absence of an association between AEDs and psychiatric symptoms could also be a manifestation of misclassification bias when recording psychiatric events during follow-up. Unlike concrete, typically acute, non-paroxysmal and self-limited adverse events, reactions with more discrete and persistent physical manifestations are more likely to be consistently and accurately coded. Likewise, enduring somatic symptoms, especially those with physical manifestations, are more likely to be reliably recorded than mental health symptoms that lack visibly identifiable features. Physicians may be less vigilant with respect to recording more intangible symptoms, and patients may be reluctant to report them due to fears of stigma. Insufficient statistical power can at least partially explain these results since many newer AEDs were not used as a first-prescription in

monotherapy until later in our study period (Figure 7 and 8). Code selection may have also inadvertently led to misclassification. Though we developed the case definitions through a consensus building process, the result may be a list that emphasised specificity to reduce false positives. For example, relatively non-specific terms for irritability, anger, and hostility were not used. In this scenario, sensitivity could have been compromised leading to an underestimate of the association between certain AEDs, such as levetiracetam, and behavioural outcomes. Finally, even despite 12 years of follow-up, few were prescribed topiramate or clobazam as their initial AED following incident diagnosis and levetiracetam only exceeded 10% of all prescriptions by 2010 (Figure 7). Based on the observed prescription trends, low statistical power will be mitigated in future iterations of THIN with more contemporary follow-up.

Ultimately, this study provides estimates with precise confidence intervals for particular AEDs and specific outcomes that are likely generalisable to high-income countries. The major finding is that carbamazepine and lamotrigine are both associated with lower hazards of a composite of any psychiatric sign, symptom, or disorder, as compared to no treatment, within two-years of an index diagnosis of epilepsy. Ultimately, these estimates can be used to counsel general patients with newly diagnosed epilepsy as to the risk of any psychiatric symptom or diagnosis over the two-years following prescription. Estimates for subcategories of psychiatric events varied in precision according to their prevalence (depression and anxiety were relatively comparable to the primary

outcome whilst psychosis/mania and suicidal ideation/completed suicide were underpowered). Therefore, investigations such as these should be viewed as an iterative process that is periodically revisited as additional data are acquired and vetted. This is particularly poignant for AED-related adverse effects since they constitute a major determinant of quality-of-life in patients with epilepsy[110, 111]. Use of similar methodology employing sensitive and specific definitions of exposure and outcome, sufficient washout periods, and stratified follow-up are warranted to unleash the potential of large EMR data for the purposes of advances in pharmacoepidemiology.

Chapter 4: Prediction tool for psychiatric adverse effects following levetiracetam prescription

4.1 Abstract

Importance: Levetiracetam is a commonly used antiepileptic drugs yet psychiatric adverse effects are common and may lead to treatment discontinuation.

Objective: To derive prediction models to estimate the risk of psychiatric adverse effects from levetiracetam.

Design: Observational cohort study

Setting: A population-based primary care cohort.

Participants: All patients meeting an incident case definition for epilepsy after the Acceptable Mortality Recording in The Health Improvement Network database, inclusive years 2000-2012, who received a first-ever prescription for levetiracetam. Index date was that on which patients received their first prescription code for levetiracetam and follow-up lasted two-years.

Exposures: A presumed first-ever prescription for levetiracetam.

Main outcomes and measures: We defined the outcome of interest as the presence of Read codes for any psychiatric symptom or disorder as reached through consensus. We used univariable and multiple logistic regression to derive two prediction models; one for all patients and one for a subset lacking a history of a psychiatric code.

Results: We identified 7400 patients with incident epilepsy of whom 1173 (16%) received a first-ever prescription for levetiracetam. A total of 14% (165/1173)

were coded with a psychiatric symptom or disorder within two-years of index prescription. Odds of reporting a psychiatric symptom were significantly elevated for women and those with a pre-exposure history of depression, anxiety, recreational drug use, and higher social deprivation. The overall prediction model performed well after stratified k=5 fold cross-validation (area under the curve [AUC] 0.68; 95% confidence interval 0.58-0.79). There was an incremental gradient in risk, with probabilities increasing from 8% for zero risk factors, 11-17% for one, 17-31% for two, 30-42% for three, and 49% when all risk factors are present. For those free of a psychiatric code prior to the index date, a second prediction model performed comparably well following k=5 fold cross-validation (AUC 0.72; 95%CI 0.54-0.90).

Conclusions and relevance: We derived two simple models that predict the risk of a psychiatric adverse effect from levetiracetam. These algorithms can be used to guide prescription in clinical practice.

4.2 Introduction

Levetiracetam is a commonly used antiepileptic drug (AED) in clinical practice. Its uptake has steadily increased since receiving approval in multiple jurisdictions in the early 2000s[112]. This is likely due to physician comfort considering the ease of use, efficacy, and lack of pharmacologic interactions associated with levetiracetam[113]. This medication can be rapidly titrated in urgent situations further establishing it as a first-line agent both amongst neurologists and primary care physicians working in emergency settings.

Another benefit is patient tolerance. Levetiracetam is generally well tolerated with low risks of idiosyncratic or life-threatening events[114] or major congenital malformations[115, 116]. However, one well-recognised complication is psychiatric adverse reactions; a potentially disruptive phenomenon that occurs in up to 16% of patients and frequently necessitates discontinuation[117]. Different symptoms have been reported including depression, anxiety, psychosis, aggression and mania[58, 118]. Despite this, there is a paucity of evidence on risk factors for the development of psychiatric adverse events in those using levetiracetam and no study has provided a predictive model. Two larger investigations have suggested that a history of a psychiatric disorder, generalised epilepsy of presumed genetic origin, faster titration rates, a history of febrile seizures and a history of status epilepticus all result in elevated risks[58, 118].

The purpose of this study was to explore whether large electronic medical record (EMR) data could be used to develop a predictive model that can guide levetiracetam use based on the risk of a psychiatric adverse event. Electronic medical records benefit from robust statistical power and longitudinal follow-up. The hypothesis was that a user-friendly, clinically applicable model guiding levetiracetam prescription can be derived from large clinical data sources using routinely collected during practice in a data-driven, clinically informed approach.

4.3 Methods

4.3.1 The Health Improvement Network

The Health Improvement Network (THIN) database is an EMR data platform based in the United Kingdom (UK) that consists of anonymized general practice (GP) patient records. All non-emergency specialist care in the UK requires GP registration. General practitioners are responsible for management and coordination of all health issues including charting consultations with emergency and specialist physicians to ensure continuity of care. The THIN database contains GP records for approximately 5% of the national population[89]. All medical events are coded using Read codes[90] whilst prescription data are classified according to the British National Formulary[91, 92]. A two-fold conditional specification algorithm is used to impute missing data[93]. This study was performed using THIN version 1205 in which analyses were restricted to January 1, 2000 to May 31, 2012 to account for levetiracetam approval by the European Medicines Agency in 2000.

4.3.2 Study population

This study used a retrospective open cohort design. To identify patients of interest, a five-year wash-out was applied to the date prior to which each patient met the published case definition designed for THIN that required a either a single Read code for an epilepsy syndrome or two Read codes for symptoms of epilepsy plus two AED codes within 4 months[94]. This case definition has 92%

accuracy for detecting cases of paediatric epilepsy in THIN and has a high sensitivity and specificity (86% and 97% respectively) in a similarly designed Welsh database, the Secure Anonymised Information Linkage (SAIL) Databank[94, 95]. Patient inclusion only occurred after their practice met the Acceptable Mortality Reporting date (the date when mortality reporting was considered complete)[96] in order to mitigate immortal time bias. All patients aged 18 years or greater at epilepsy diagnosis, who met these conditions, were included in the analysis.

4.3.3 Exposure and outcome

Any prescription code for levetiracetam represented the exposure. The outcome was defined as any Read code or Multilex therapeutic code for a psychiatric sign, symptom, or disorder, as defined through a consensus-driven process between two authors (CBJ and SP; Appendix 3).

4.3.4 Selection of clinical variables

Potentially pertinent predictor clinical variables were identified through a two-stage process. First, a search strategy was developed (Appendix 4) to interrogate Medline and Embase for predictors of psychiatric signs and symptoms related to levetiracetam use in patients with epilepsy. Senior authors (NJ and SW) provided expert opinion on potential risk factors to supplement the search.

Following this, a modified Delphi process was employed for final variable selection. All candidate features identified through the literature search and expert opinion were included in this consensus building stage. The twelve-member panel comprised seven adult epileptologists, three psychiatrists, and two neuropsychologists from the University of Calgary with a median total of 10.5 (interquartile range [IQR] 4-25) years of practice experience. Each participant completed a questionnaire in which they rated all potential variables on a 5-point Likert scale (where '1' meant the criterion was not very important at all and '5' meant the criterion was very important). Panellists were also asked to indicate if they had no judgement on the item and were given space for additional handwritten comments. Finally, space was provided at the end of the questionnaire to permit panellists to indicate additional criteria that they considered important. Each panellist was assigned a random code and the questionnaire was emailed to each participant, all of whom were allotted 14 days to complete the first round of ranking. A follow-up email was sent to those who had not responded by day ten.

The median and interquartile range were used to rate overall appropriateness for inclusion in the final model. Items with median ratings of 1-2 were excluded due to irrelevance; items scoring 3 were considered to be of uncertain relevance and were re-evaluated in a second round, and items scoring 4-5 were used to build the final predictive model. Medians falling in the intermediate ranges (i.e. 2.5 and

3.5) were placed in the higher relevance category (e.g. 2.5 would be considered to be of uncertain relevance)[119]. Disagreement was defined as when at least four panellists rated the item as irrelevant (1-2) and at least four panellists rate the same item as relevant (4-5) [119].

The second questionnaire was similar in design to the first form. However, panellists were provided additional information regarding the frequency distribution of how each item was scored in the first iteration along with a reminder of how they individually ranked the item. Particular focus was reserved for those items that were considered to be of uncertain relevance or those in which there was disagreement. Disagreement can occur due to differences in clinical opinion ('real' disagreement) or to misunderstanding ('artifactual' disagreement)[119]. Therefore, questions related to items in which there was disagreement were re-worded where appropriate to assuage concerns regarding confounding by artifactual disagreement[119]. Also included were extra items identified by panellists during the first round. All items with a median score of 4 to 5 in the first or second round were included in prediction modelling. To facilitate variable inclusion, we used a consensus-building process between two authors (CBJ and SS), to identify Read and Multilex codes to define each clinical feature of interest.

4.3.5 Statistical analysis

The index date (time zero) was that on which the patient met our case definition for presumed incident epilepsy. The follow-up period was for two-years after the first levetiracetam prescription. Descriptive parametric and non-parametric statistics were used to compare populations of interest. Data were fully available for all variables but levetiracetam daily dose (65% complete). The pattern of missing values did not differ according to each co-variable, therefore providing no evidence they were missing not at random, and thus Rubin's multiple imputation was used to replace null values[120]. All variables achieving a significance of ≤0.05 in univariable analyses were further evaluated in multivariable logistic regression. The final model consisted of all significant variables at a p ≤0.05 following multivariable regression. Brier score was used to assess model performance, model discrimination was evaluated using mean area under the receiver operating characteristic curve (AUC), calibration was explored using the Hosmer-Lemeshow goodness of fit test, and generalizability was determined through stratified k=5 fold cross-validation to account for outcome imbalance between groups[121]. The predicted probability was calculated using 1/(1+exp[-risk score]) where the risk score is equal to the output of the multivariable logistic regression model. Sensitivity and specificity were graphed according to the probability cut-off to select a threshold that optimises balance between the two metrics. All analyses were completed using Hive 0.13.1, Stata version 13.0[65], and Python 3.2[103].

4.3.6 Ethics

THIN has been used for scientific research since approval from the NHS South-East Multi-Centre Research Ethics Committee in 2003. Ethics approval for this study was obtained both through the University of Calgary's Conjoint Health Research Ethics Board (REB15-0203) and the CSD Medical Research's Scientific Review Committee in December 2015 (SRC Reference number 15THIN087).

4.4 Results

4.4.1 Variable selection

Our search of Medline (from 1946) and Embase (from 1974) yielded 136 articles of which 103 remained after de-duplication. A history of febrile seizures[58], status epilepticus[43], duration of epilepsy[122], 'psychiatric comorbidities' and 'behavioural issues'[58, 122-127], and cognitive impairment[128] were associated with increased risks and odds of developing psychiatric adverse effects from levetiracetam. Conversely, co-administration of lamotrigine was associated with a protective effect[58]. An additional 29 variables were recommended for inclusion following consultation with senior authors. Based on these two sources of data, the first round of the Delphi consisted of a questionnaire containing 36 items (Appendix 5). Consensus for inclusion was ultimately achieved for 14 of 36 variables of which 12 (86%) were considered relevant and 2 were considered irrelevant (Table 6).

Table 6. Items reaching consensus for inclusion (shaded) and exclusion in Round 1 of the modified Delphi method.

Variable	Relevance score	IQR
History of mania	5	5-5
History of psychosis	5	5-5
History of depression	5	5-5
History of anxiety	5	4-5
History of another Axis I disorder	4	4-5
Levetiracetam dose	4	3.5-5
Prescription of a psychotropic drug	4	3.5-5
History of conversion disorder	4	2-4
Current age	4	2-5
Number of concurrent AEDs	3.5	3-4
Socioeconomic status*	3.5	2.5-4
Sex	3.5	2-4.5
History of status epilepticus	1	1-2
History of febrile seizures	1	1-1

*Measured using the Townsend Index of Deprivation
Abbreviations: AED = antiepileptic drug; IQR = interquartile range

Uncertainty still remained for the residual 22 variables. In addition, 13 extra items were identified through the first round and, therefore, the questionnaire for the second round consisted of 35 items (Table 7). Of these 35 variables, 11 (31%) met consensus for inclusion (Table 7).

Table 7. Items reaching consensus for inclusion (shaded) and exclusion in Round 2 of the modified Delphi method.

Variable	Relevance score	IQR
History of anger/behavioural outbursts	5	4.5-5
History of suicidal ideation/suicide attempts	5	4.5-5
Family history of psychiatric disorder	4.5	4-5
History of a personality disorder	4	4-4.5
History of recreational drug use	4	4-4
History of multiple drug side-effects	4	3-4.5
History of alcohol misuse	4	3-4
Dementia or mild cognitive impairment	4	3-4
History of developmental delay	3.5	3-4
History of traumatic brain injury	3.5	3-4
Higher Charlson comorbidity index	3.5	3-4
Source of income	3	3-3
History of a neurological deficit	3	2.5-4
Number of Emergency Department visits	3	2.5-3.5
Lower level of education	3	2.5-3.5
History of medication resistant epilepsy	3	2-4
History of post-traumatic epilepsy	3	2-4
Concurrent use of perampanel	3	2-4
Concurrent use of topiramate	3	2-3
Longer epilepsy duration	3	2-3
Marital status	2	2-3
Concurrent use of clobazam	2	2-2
Ethnicity	2	1-2
Urban versus rural setting	2	1-2
Concurrent use of carbamazepine	1	1-3
Concurrent use of lamotrigine	1	1-3
Concurrent use of valproic acid	1	1-3
History of a neurosurgical procedure	1	1-2
Concurrent use of phenobarbital	1	1-2
Concurrent use of phenytoin	1	1-2
Prolonged postictal state	1	1-2
History of any alcohol use	1	1-1
Concurrent use of lacosamide	1	1-1
Concurrent use of oxcarbazepine	1	1-1
Concurrent use of ethosuximide	1	1-1

Abbreviations: AED = antiepileptic drug; IQR = interquartile range

Ultimately, two variables, a ‘history of an Axis I disorder’ and a ‘history of multiple drug side-effects’ were subsequently excluded due to redundancy (Axis I disorder) and challenges in phenotyping the variable in EMR data. As such, 21 variables (12 from the first round and 9 from the second) were evaluated for inclusion in the prediction model (Table 8).

Table 8. Demographic characteristics of all incident epilepsy patients receiving levetiracetam (n=1173) during follow-up in The Health Improvement Network general practice database stratified by receipt of a post-prescription code for psychiatric symptom, disorder, or treatment.

Characteristic	No outcome	Psychiatric outcome	p-value
n (%)	1008 (86%)	165 (14%)	n/a
Age in years	39 (35-57)	42 (25-54)	0.88
Female sex	493 (49%)	97 (59%)	0.019
Charlson comorbidity index	0 (0-1)	0 (0-1)	0.53
Townsend Index	3 (2-4)	3 (2-4)	0.002
Medical and social history			
Cognitive impairment	36 (4%)	2 (1%)	0.113
Traumatic brain injury	109 (11%)	20 (12%)	0.619
Depression	192 (19%)	70 (42%)	<0.001
Anxiety	118 (12%)	42 (25%)	<0.001
Aggression	51 (5%)	13 (8%)	0.139
Mania/psychosis	30 (3%)	7 (4%)	0.388
Conversion disorder	9 (1%)	3 (2%)	0.274
Developmental disorder	86 (9%)	14 (9%)	0.984
Personality disorder	12 (1%)	10 (6%)	<0.001
Suicidal ideation	26 (3%)	12 (7%)	0.002
Alcohol misuse	70 (7%)	18 (11%)	0.073
Recreational drug use	65 (6%)	30 (18%)	<0.001
Medication history			
Levetiracetam daily dose (mg)	1500 (1000-2000)	1500 (1000-2000)	0.19
Number of AEDs	109 (11%)	20 (12%)	0.619
Psychotropic drugs	175 (18%)	43 (26%)	0.008

*Continuous and ordinal values reported as median and interquartile range
**Cognitive impairment includes mild cognitive impairment and dementia
***AEDs = antiepileptic drugs

4.4.2 Prediction modelling

Out of 11,194,182 patients registered in THIN, 9595 presumed incident cases (85.7 cases per 100,000 persons) were identified over a maximum of 12 years follow-up. Approximately 12% (n=1173) of these patients received an incident prescription for levetiracetam during this period. Of these patients, 165 (14%) experienced an outcome of any psychiatric symptom or therapeutic code over two-years of follow-up (Table 8). Those experiencing an outcome of interest were statistically more likely to be female (59% *versus* 49%; p=0.019), be of lower socioeconomic status according to the Townsend deprivation index[98] (median 3 [mean = 3.28], IQR 2-4 *versus* median 3 [mean = 2.93], IQR 2-4; p=0.002), have a history of psychiatric conditions including depression (42% *versus* 19%; p<0.001), anxiety (25% versus 12%), a personality disorder (6% *versus* 1%; p<0.001), and suicidal ideation/suicide attempts (7% *versus* 3%; p=0.002), have taken a psychotropic medication (26% *versus* 17%; p=0.008), and have a history of recreational drug use (18% *versus* 6%; p<0.001).

When evaluating all aforementioned significant variables in multivariable logistic regression, the odds of reporting a psychiatric symptom or treatment code within 2 years of levetiracetam use were elevated for those with a pre-exposure history of depression (odds ratio [OR] 2.20, 95% confidence interval [95%CI] 1.49-3.24; p<0.001) or anxiety (OR 1.74, 95%CI 1.11-2.72; p=0.015), recreational drug use (OR 2.02, 95%CI 1.20-3.37; p=0.008), and increasing social deprivation (OR 1.15, 95%CI 1.01-1.31; p=0.028). There was a trend toward significance for

female sex (OR 1.41, 95%CI 0.99-2.01; p=0.052). All other variables failed to reach a significance level of 0.05.

The Townsend deprivation index is tailored specifically for epidemiological research. Therefore, while it is valuable to know social deprivation increases the odds of reporting a psychiatric symptom or disorder following levetiracetam prescription, a decision was made to exclude this variable from the final model since it would be impossible to assign a value to anyone located outside the UK. Hence, the final model was selected:

Risk score = -2.34 + 0.27*(female sex) + 0.82*(history of depression) + 0.74*(history of recreational drug use) + 0.47*(history of anxiety)

There was no evidence of multicollinearity in the final model with variance inflation factors ranging from 1.15 (history of recreational drug use) to 1.42 (history of depression). The model performed well overall with a Brier score of 0.11. The model had moderate discriminative capacity after stratified k=5 fold cross validation (AUC = 0.68; 95%CI 0.58-0.79; Figure 14). The sensitivity and specificity varied by the probability cutoff threshold with model achieving high specificity (83%) at a probability cutoff of 0.1 (Figure 15).

Figure 14. Displayed below is the receiver operating characteristic curve and attendant area under the curve for the rate of true positives (sensitivity) by the rate of false positives (1-specificity).

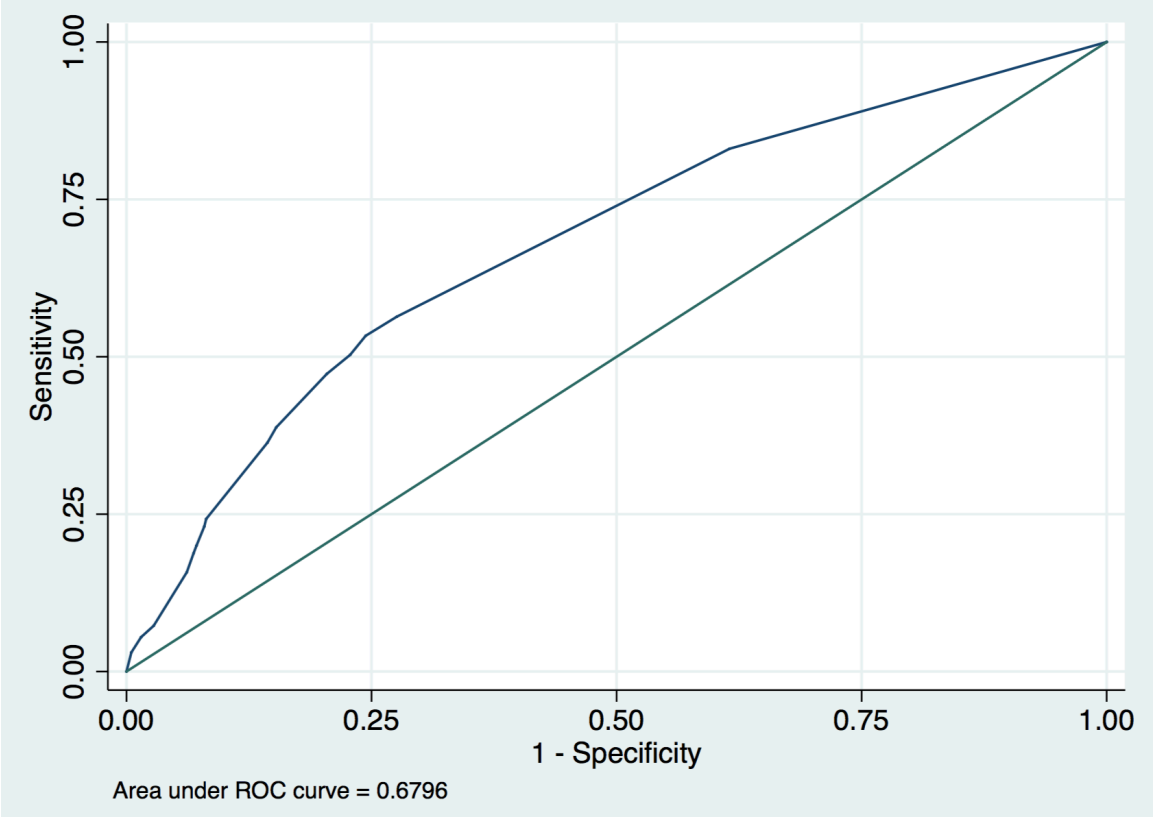
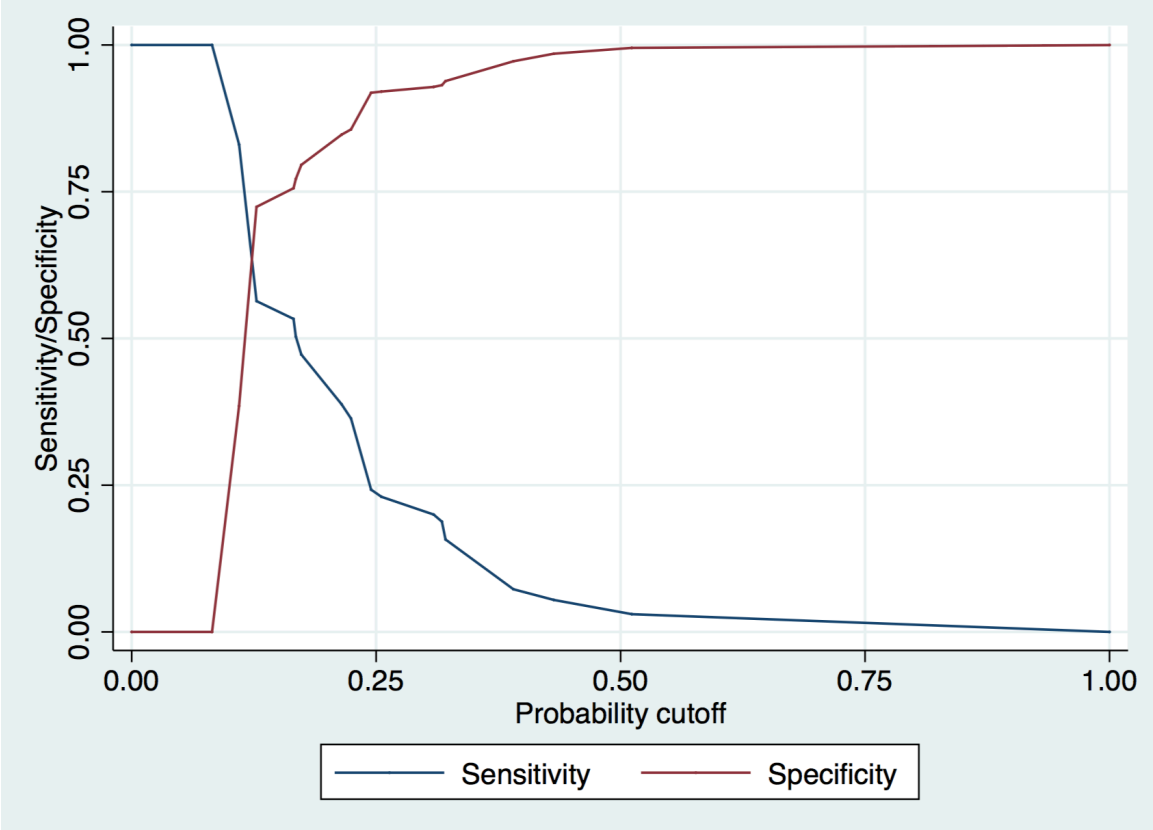


Figure 15. The sensitivity and specificity trade-off for predicting a psychiatric adverse event following prescription of levetiracetam according to variations in the risk model probability threshold.

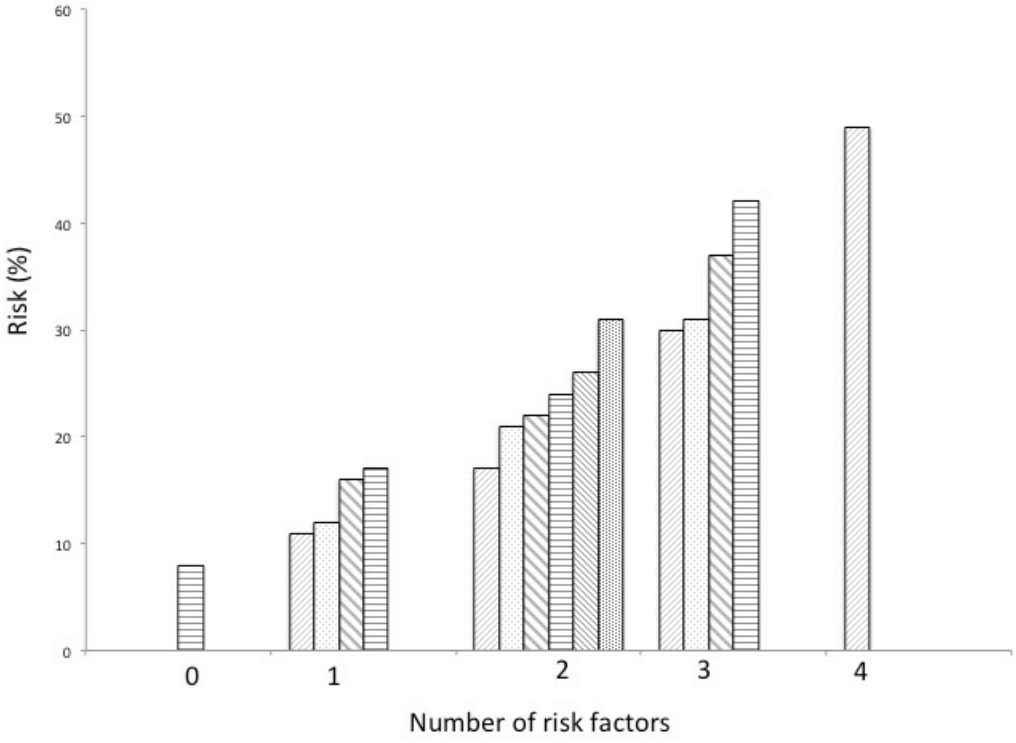


There was no evidence of poor calibration (Hosmer-Lemeshow goodness of fit test p=0.29; 10 groups). A gradient in risk was revealed wherein those with increasing numbers of risk factors were at incrementally greater probabilities of a psychiatric outcome (Table 9). For instance, the baseline risk for those with no risk factors was 8%, the risk for those with 1 risk factor ranged from 11-17%, the risk for those with two risk factors ranged from 17-31%, the risk for those with three risk factors ranged from 31-43%, and the risk for those with all four risk factors was 51% (Figure 16; Table 9).

Table 9. Estimated probabilities of a psychiatric sign, symptom, or need for treatment within two years of starting levetiracetam stratified by risk factors.

Risk factors	Probability of outcome
Four	51%
Three	
Anxiety, depression, recreational drugs	43%
Depression, female recreational drugs	39%
Anxiety, depression, female	32%
Anxiety, female, recreational drugs	31%
Two	
Depression and recreational drugs	31%
Anxiety and depression	26%
Anxiety and recreational drugs	24%
Depression and female	22%
Female and recreational drugs	21%
Anxiety and female	17%
One	
Depression	17%
Recreational drugs	17%
Anxiety	13%
Female	11%
None	8%

Figure 16. The probability gradient of reporting a psychiatric sign, symptom, or disorder within two-year of an index prescription for levetiracetam according to the number of risk factors (female sex, history of depression, history of anxiety, and recreational drug use) present. For those with two or three risk factors, the probability tended to be higher for individuals with a history of depression or recreational drug use.



For each stratum, the presence of depression and recreational drug use, singularly or in combination, were consistently associated with higher risks.

4.5 Discussion

Using a large EMR collected and managed during routine clinical care, a prediction model for the risk of a psychiatric sign or symptom following a first-ever prescription for levetiracetam in patients with presumed incident epilepsy was derived. The model is well calibrated with moderate discrimination. In particular, it has a high specificity for predicting those with a psychiatric outcome, meaning few false positives were identified using our model. Therefore, this model, if validated in prospective cohorts, could be useful at point of care for a broad spectrum of epilepsy patients seen in general practice and epilepsy clinics alike.

Perhaps the most useful application from this model is the scaled gradation of risk. It is interesting to note that there is an incremental rise in risk according to the number of constituent risk factors. These data can help counsel patients in clinic by providing general estimates of risk that the patient can balance against perceived benefit. Furthermore, the fundamental underlying associations that are used to construct the model are consistent with the published literature. For instance, psychiatric adverse events from levetiracetam do not appear to be dose-dependent whilst those with a history of psychiatric disorder are at elevated risk[58]. Our study also highlights the independent effect that concurrent recreational drug use and social deprivation exert on this association. Though

measures of social deprivation are challenging to incorporate into accessible, user-friendly models, its putative role remains of particular interest since physicians can still intuitively apply this knowledge when determining whether a patient may experience harm from levetiracetam.

This study benefited from a clinically informed approach. The modified Delphi panel was comprised of experts in the field with varied but extensive interests in epilepsy, AEDs, and neuropsychiatry. Model construction benefited from the large statistical power conferred by the THIN database (over 1000 patients with presumed incident epilepsy who received a prescription for levetiracetam were identified). The definitions of exposure and outcome also appeared to perform well when compared to currently published frequency estimates; for instance, the incidence proportion of epilepsy in our study (85.7 cases per 100,000 persons) is comparable to that reported in the literature[104]. Likewise, the demographics and social habits mirrored what is expected based on prior studies[129, 130]. The exposures also appeared to be reliably coded whereby the proportions meeting the case definitions for depression (22%)[82], anxiety (14%)[131], and psychosis (3%)[132] were consistent with that reported in the literature for patients with epilepsy. Finally, it is reassuring that the psychiatric adverse event rate following a prescription or levetiracetam in our study (~14%) conforms to that reported in the literature[117]. Ultimately, a robust model was derived using an iterative-based consensus approach to variable selection and definition, in collaboration with

content experts, to identify discrete tiers of risk based on the reported risk factor profile.

Despite these strengths, there are potential limitations to this work. Due to the constraints of routinely collected EMR data, it was impossible to extract informative indices of seizure type, seizure frequency, seizure severity, and epilepsy type. In addition, though the analyses controlled for levetiracetam dose and use of concomitant AEDs, it is not feasible to extract measures of medication adherence. Inclusion of these variables could further improve model discrimination including enhanced measures of sensitivity. Although the discriminative capacity of the model (AUC 0.68; 95%CI 0.58-0.79) was fair at best, it remains comparable to that published for a nomogram predicting outcome after epilepsy surgery (AUC 0.60)[133]. The possibility of underreporting of psychiatric events in primary care data repositories cannot be excluded[134, 135]. This likely constitutes non-differential misclassification bias wherein the overall effect estimates are diluted by the equal reluctance of both exposed and unexposed individuals to report psychiatric symptoms due to a myriad of factors including fear of stigma. This would be anticipated to produce conservative estimates of association. Finally, the model has only completed the derivation stage. Future validation in independent external populations is warranted before it can be universally applied to clinical settings.

This study has successfully derived a prediction tool for the development of psychiatric adverse effects following a first prescription for levetiracetam in a general population of patients with epilepsy. Gradients of risk clearly discriminate specific populations of patients based on known and newly identified factors. In particular, those with depression and a history of recreational drug use, either alone or in combination, appear particularly susceptible to this outcome. The estimates of generalizability to external populations, using a stratified k=5 fold cross-validation, are highly encouraging though future efforts are still required to validate this model in independent populations. Additional efforts into enhanced discrimination should involve inclusion of markers of seizure and epilepsy type, aetiology, and severity, and, where possible, multimodal data such as neuroimaging, electroencephalographic, and genetic data. Ultimately, this is an important first step toward generating empirical, efficient, and yet practical, prediction models with direct application clinical settings.

Chapter 5: Conclusion

5.1 Summary of findings

This dissertation used a methodical approach to start the development of a clinical decision rule for the use of the AED levetiracetam based on its risk of psychiatric adverse events. To address Aim 1, a systematic review and meta-analysis was performed to describe the current state of the literature with respect to clinical decision rules in epilepsy. Four fully derived clinical decision rules were identified. Since then, two additional rules have been derived and validated, one for seizure freedom after resective epilepsy surgery[133], and one for continuing seizure freedom following AED withdrawal[136]. Therefore, to date, six CDRs of which four have undergone some form of validation have been identified. No epilepsy-specific clinical care rule has been examined in an implementation study.

To address Aim 2, the THIN EMR data repository was used to first examine the association between levetiracetam use and psychiatric signs, symptoms and disorders. It was then used to develop a prediction model and associated clinical decision rule guiding the prescription of levetiracetam based on the risk of psychiatric adverse events. Though a statistically significant association between levetiracetam prescription and receipt of a code for a psychiatric sign, symptom, or disorder, was not found, the analyses were underpowered. This is likely due to the fact that for the purposes of isolating the effect of a single AED on the risk of psychiatric adverse effects, it was required that each medication be prescribed in

monotherapy. Levetiracetam, though approved by the European Medicines Agency in 2000, was initially reserved as add-on therapy and only later in the decade were physicians starting to use it more regularly in monotherapy. Updated versions of THIN should compensate for this limitation. Ultimately, however, there appeared to be a reduction in the hazard of any psychiatric sign, symptom, or disorder following a first prescription for carbamazepine (hazard ratio [HR] 0.84, 95% confidence interval [95% CI] 0.73-0.97; p=0.02) and lamotrigine (HR 0.83, 95%CI 0.70-0.99; p=0.03). These findings are consistent with what would be anticipated based on smaller studies[137] and clinical experience.

Finally, a CDR was successfully developed for levetiracetam using a large EMR system, a type of data repository that has yet to be fully exploited for clinical decision rule development. Here, the CDR incorporated sex, a pre-prescription history of a code for depression, a pre-prescription history of anxiety, and recreational drug use. This model had no evidence of poor calibration, had moderate discriminative capacity following stratified k=5 fold cross validation, had good overall performance, and demonstrated a clear incremental gradient in risk according to the number of risk factors possessed by the patient. A threshold of 0.1 was chosen to define the rule due to its high specificity (83%).

5.2 Discussion of findings

The entirety of this dissertation highlights a significant knowledge gap that warrants further attention. Clinical decision rules have proliferated and flourished in other fields of medicine. Rules now exist guiding management of specific conditions in emergency medicine[27, 138-140], internal medicine[141, 142], and surgery[143]. Beyond this, stroke neurology has embraced clinical decision rules to improve outcomes and encourage rational allocation of finite health care resources[144-148]. It should be noted, though, that many of the rules, even those validated in other fields, have yet to undergo rigorous implementation analyses[149, 150]. This may be amongst the reason why CDRs have not yet proliferated in epilepsy. As outlined in Chapter 2, the fundamental reasons why CDR development has languished behind in epilepsy remain opaque. It may be that, without strong evidence of a beneficial change to practice, especially in the absence of implementation studies that prove clear improvements in quality of care and resource efficiency, the enthusiasm for pledging significant time and resources will remain muted. Furthermore, many of the conditions for which such rules have been developed, such as ischaemic stroke, pulmonary embolism, and fractures, are more acute and necessitate an immediate treatment decision. Hence, having a user-friendly, intuitive rule with immediate feedback on patient-specific risk and benefit is desirable and can save precious time by facilitating the decision-making process in pressured situations.

Conversely, it may be that too many treatment modalities are available for epilepsy and therefore a challenge is how to make a non-binary decision. For many of the aforementioned conditions, the decision is often a dichotomous 'yes' or 'no' question about whether to treat. This is comparatively simpler when it comes to anticoagulation (e.g. the CHA_2DS_2-VASc score[144, 151]), thrombolytic therapy, or ordering x-rays for a possible fracture since the treatment choices are limited (warfarin or a new oral anticoagulant for anticoagulation, tissue-type plasminogen activator for thrombolysis, a plain film x-ray for a fracture). In epilepsy, the decision is typically more complex whereby, if the answer to the first question, whether to treat or not, is affirmative then one needs to select from over 15-20 AEDs as the first agent. This decision is not easy since relative efficacy is comparable for each drug after accounting for epilepsy type (generalized *versus* focal)[152]. Rather than efficacy, each decision is context dependent and frequently predicated on seizure type, patient demographics, patient comorbidities, and socioeconomic status. Hence, it is perhaps not surprising that the only decision rules developed to date have been diagnostic or, when therapeutic, confined to a simple question of medication withdrawal or surgical management (where the decision is again binary).

Despite this, medication-specific CDRs could well be meritorious and feasible, especially when focusing on discrete outcomes like a particular adverse event. However, it is unlikely that these CDRs will receive much support or be endorsed with enthusiasm without undergoing pragmatic development from derivation to

implementation. Additionally, such a rule should be as broadly applicable as possible. Narrow rules restricted to uncommon outcomes would require significant work and result in limited application. Most successful rules focus on a common population or a frequent or critical outcome in order to enhance relevance. There is a plethora of circumstances to which this applies in epilepsy. The purpose of this thesis, therefore, was to choose a broad population and common outcome for which to devise a rule.

Epilepsy is a common, but not highly prevalent condition, affecting about 0.6 to 0.7% of the population at any one time[104]. Prospectively recruiting sufficient patients to derive a rule would thus be resource-intensive and time-consuming. Existing large EMR databases have yet to be comprehensively exploited to this effect. Hence, efforts were spent at determining whether these datasets could represent untapped resources for the purposes of deriving CDRs. The Health Improvement Network database contains over 11 million general practice patients of which there should be over 7,000 incident and 70,000 prevalent cases of all-cause epilepsy. Therefore, a large population of patients is readily available with high external validity[89] and broad applicability to all-cause epilepsy. Furthermore, AED adverse effects are common, affecting up to 88% when systematically screened, and function as the immediate cause of medication discontinuation in up to 25% of patients with epilepsy[84, 111]. For levetiracetam, a commonly used AED with a unique mechanism of action, up to 10% will complain

of a psychiatric adverse event, and thus the problem is not infrequent but is serious in nature[58].

Having established these prerequisites, it is imperative to next evaluate availability and reporting characteristics for specific variables of interest. Routine demographic and clinical data are collected and coded on all patients as a part of their primary care evaluations. Furthermore, GPs in the UK act as the primary gateway to specialist care and will readily record all interactions[153] and communication in the patient's chart. As such, many of the features of interest should be available in this database. To confirm this, in advance of the study, two physicians, one with an expertise in epilepsy and the other in psychiatry, participated in a consensus-building process to identify and collate diagnostic and therapeutic codes for the outcome of interest, namely any psychiatric sign, symptom, or disorder. Having established that phenotying the outcome (a psychiatric sign, symptom, or disorder) through Read and Multilex codes was practical, it was determined that it was feasible to proceed with the planned research. Hence, the conclusion was that large EMR databases, such as THIN, could enhance efficiency and research output all while reducing cost.

Studies addressing the second aim of the thesis benefited from the large statistical power conferred by THIN. Variations of EMR case definitions for epilepsy that were validated in paediatric[94] and adult populations[95] were available and could be readily employed. Data were evaluated in advance of the study to

identify the seven most common AEDs prescribed in the United Kingdom. Selection bias was avoided through inclusion of all patients meeting the case definition for epilepsy in general practice. Likewise, the study design helped mitigate immortal time bias by requiring that no patient could be included until after the date their GP office met the Acceptable Mortality Reporting (AMR) criteria. This is primarily a quality control measure since the AMR date indicates when the mortality reporting for the GP practice was consistent with that reported in the national census. This is critical because, before this date, the risk exists that a deceased patient may never have been coded as dying, thus making it appear as if that individual is still alive and thus functionally 'immortal'. By extension, the concern is that other features, such as psychiatric signs, symptoms, and disorders may be inconsistently coded prior to this date meaning patients may spuriously appear resistant to the outcome of interest. The analyses were also limited only to those incident patients exposed to AED monotherapy. This was an unavoidable methodological decision since multiple regression would be cumbersome, requiring an equation with over 5000 interaction terms to differentiate between the relative effect of a specific AED alone compared to that incurred from no treatment and that specific AED compared to particular combinations of polytherapy with other medications if not implemented.

Using this rigorous methodology, it was concluded that carbamazepine and lamotrigine, when used in monotherapy, are associated with a reduced hazard of any coded psychiatric sign, symptom, or disorder over two-years following

incident prescription when compared to those left untreated. Interestingly, an association between levetiracetam use and an increased relative hazard of a coded psychiatric symptom or disorder was not revealed. This is despite the fact that 18/202 (9.0%) patients with incident epilepsy first prescribed levetiracetam were coded with a psychiatric sign, symptom, or disorder within two-years of exposure; a proportion that is consistent with what has been reported in the literature[58]. A number of explanations exist for this finding. It may be that psychiatric issues in those with untreated epilepsy go underreported or underappreciated in routine practice meaning our empirical impression is skewed by differential misclassification bias. Alternatively, this study may suffer from non-differential misclassification bias whereby the overall estimate of association is diluted due to an equal propensity for underreporting or under-ascertainment of psychiatric issues in both the exposed and unexposed groups potentially due to the stigma of reporting mental health issues. Additionally, it is virtually impossible to account for medication adherence in EMR data since levetiracetam serum levels are expensive, challenging to obtain, infrequently requested[154]. As such, under these circumstances, the lack of association may be secondary to unavoidable limitations in the methodology that result in a biased, but conservative, estimate.

Having established that it is possible to evaluate associations between a specific AED prescription and psychiatric events, the final goal was to begin to generate a CDR specific to levetiracetam. To this end, a similar methodology was used to

that employed for the second aim. First, though, it was integral to identify potential clinical predictors. A literature search and expert opinion were initially used to create a list of candidate predictors. Following this, a two-step modified Delphi method, involving a panel of 12 experts, was used to filter the list down to only those strongly felt to influence the relationship between levetiracetam and psychiatric signs, symptoms, and disorders. After completion of this process, 21 variables were used to build a prediction model. After univariable comparisons, five variables were considered for inclusion in the final model. Though there was a significant and independent association between lower socioeconomic status and increased odds of a post-prescription psychiatric sign, symptom, or disorder, inclusion of this variable in a prediction model can be troublesome. It is challenging to quantify this characteristic in a quick and simplistic manner in a busy clinical setting. Furthermore, the Townsend index of social deprivation is primarily a research tool and translation to a clinical setting would likely be impractical. For this reason, though the association is informative, a decision was made to exclude it from a formal predictive model to promote generalizability.

The final model therefore consisted of four variables (sex, depression status, anxiety status, and recreational drug use). A risk score was developed using multiple logistic regression and, after formal evaluation, was found to have good calibration, discriminative properties, and overall performance. Furthermore, using a threshold of 0.1, the risk score had a specificity of 83% (thus exceeding the threshold of 80% sought in advance of the study) suggesting a high

propensity for accurately identifying those who will experience a psychiatric outcome. It is critical to note, though, that this specificity was achieved at the expense of sensitivity and therefore the potential of inadvertently misclassifying less extreme cases as false negatives exists. Finally, the model is able to stratify patients into four groups of risk. Those with no risk factors had the lowest probability at ~8%. Those with one risk factor had a probability that ranged from ~10-20%, those with two ranged from ~20-30%, those with three ranged from ~30-40%, and those with all four had a probability of ~50%. In particular, a history of depression and recreational drug use seemed to drive risk within each discrete stratum.

Future attempts to augment performance, and optimize sensitivity, should be pursued. This may involve considering more sophisticated data or algorithms. The addition of multimodal data could theoretically enhance predictive accuracy. To this end, the model can be field tested in more discrete settings, such as in prospective observational cohorts like the Calgary Comprehensive Epilepsy Program database. Here, after initial evaluation, the model can be adjusted to include more granular metrics like epilepsy type, seizure type, seizure frequency, patient-reported outcomes, electroencephalographic, and neuroimaging data to further tease apart clinically discrete groups of risk. Measures of performance can then be compared. Although only in its nascent stage, combining clinical with complex forms diagnostic data has been attempted and appears to hold promise[155].

Alternatively, construction of more complex algorithms from the existing data may optimize application of this model. For instance, our current model uses a rule incorporating a threshold 0.1 that is primarily based on the tradeoff between sensitivity and specificity. Here, scoring under 0.1 would indicate it is safe to prescribe levetiracetam based on the risk of psychiatric adverse effects. However, use of a threshold of 0.1 may be too simplistic and, under these circumstances, additional analyses designed to test points-based algorithms, recursive partitioning models, or nomogram are desirable. This could help refine estimates and facilitate ease of use in busy clinical scenarios. Machine learning may also be a breakthrough methodology with the power to advance predictive modeling and subsequent CDR development. These techniques have benefits that include flexibility and the lack of reliance on the assumption of stochastic data models[156]. Classification-based supervised machine learning essentially automates the prediction problem. Similar to a human trying to sort pictures of apples and oranges, the machine is initially given a set of classes (apples or oranges) and then learns from the data to determine what features (for instance, shape and colour) equate to a class of an apple or orange. Here, one informs the computer of the correct class (a psychiatric adverse effect) and then it would iteratively learn to correctly classify each patient based on their features (clinical data).

Despite unquestionable success in other disciplines, medicine frequently falls afoul of the *n* (population size) versus *p* (number of predictors) problem[45, 157]. Here, the number of subjects is frequently substantially fewer than the number of predictors. Under these circumstances, the excess number of predictors may impede the ability to produce accurate probability estimates[45]. Another issue to be considered is complexity. It may be that many machine learning algorithms are best deployed in EMR settings since it is often impractical to apply many of them at the bedside without the assistance of high-performance computing.

Once the final rule is consolidated, taking the above into consideration, the critical next step is internal validation ('reproducibility') to ensure the model does not overfit the data. The final model can be subjected to bootstrapping or cross-validation, which are preferred to the split-sample validation approach[158]. The model should ideally be equally applied to an independent population for external validation ('transportability'). This will involve either identifying a large general practice source outside of England/Wales or attempting to see if the model can be adapted to other datasets such as prospectively accrued populations[159].

Finally, once these steps have been completed to satisfaction, attempts at implementation are essential to promote broad uptake. If the rule has little to no impact on patient care then the resource-intensive efforts to implement it will not only be futile but potentially detrimental. Randomised controlled trials in which the intervention is the clinical decision rule (compared to routine practice as the

control) are best performed using a cluster or controlled trial design. This step will establish generalizability, and provide convincing evidence that the rule does indeed change practice for the better. Here, one typically focuses on outcomes and processes of care (patient safety and satisfaction) and health economics. Health provider comfort should also be evaluated since mistrust or antipathy can delay or prevent adoption of what is actually a highly valuable CDR[23]. Conventional means of encouraging health provider comfort include disseminating novel findings through publications and conference presentations though this passive approach is usually unsuccessful in promoting successful knowledge translation[160]. More active techniques, using administrative and educational strategies, embedded in EMR systems, may well be the ideal means of successfully promoting uptake of impactful CDRs.

Ultimately, when considering the CDR for levetiracetam, studies will initially have to evaluate the rates of predicted to actual psychiatric outcomes. After demonstrating a decrease in psychiatric adverse effects in sites using the rule, additional metrics including improved patient satisfaction (using, for instance, a visual analogue scale[161]), quality of life (using the quality of life in epilepsy scale[162]), and resource savings will be required to establish the rule. For instance, reductions in emergency visits, epilepsy outpatient visits, prescriptions for psychotropic drugs, and psychiatry consultations would be desirable outcomes in implementation studies. Strategies in which this can be achieved in

trials include abstracts, presentations, continuing medical education, smartphone and web-based applications, and provider-to-provider endorsement.

5.3 Limitations

Despite the systematic approach, there are limitations to these analyses that must be acknowledged. Though codes for epilepsy have been validated through chart review[94, 95], the codes for psychiatric signs, symptoms, and disorders have not been validated. Validated codes for these outcomes do not yet exist in the literature and, due to logistical constraints, it was not possible externally validate these EMR phenotypes during the course of this dissertation. However, it is encouraging to note that the proportions with a history of a psychiatric code in our cohort (3182/7400 [43%] taking an AED and 856/2195 [39%] in those not prescribed an AED) are similar to that reported in prior studies of patients with epilepsy (30-50%)[163, 164]. External validation through a chart or hospital record review, though, would instill further confidence in the validity of our choice of codes.

In addition, the decision was made to use a relatively simple logistic regression model with parameter regularization. Calibration, discrimination, and overall model performance were encouraging. Likewise, the model appears to be moderately generalizable with an AUC of 0.68 (95%CI 0.58-0.79) following stratified k=5 fold cross validation. Despite this, experimentation with different models, such as advanced machine learning algorithms, may have yielded

higher degrees of discrimination. Unlike logistic regression, random forest classifiers, support vector machines, and nearest neighbour based classifiers may theoretically offer more flexibility and consistency and exist as potential alternatives[156]. Thus, performance may be enhanced but, importantly, this is at the expense of interpretability, a critical point that often undermines uptake of useful but unintuitive rules during implementation and application stages[165].

With respect to feature selection, it may seem self-evident that a history of anxiety or depression predicts future risk of psychiatric sign, symptom, or disorder following a prescription for levetiracetam. However, it was critical to include these features in model construction for a number of reasons since they met consensus for high relevance in the modified Delphi process. This is one of the benefits of a combined consensus and data-driven approach. Here, it makes intuitive sense that levetiracetam may unleash what was previously a subclinical, subsyndromic, or masked mental health disorder. Irrespective of whether the psychiatric issues arose *de novo* or was exacerbated by levetiracetam, the ultimate result is patient discomfort and a likely necessity to discontinue the medication. A predictive rule aims to determine the probability of a future event rather than explain it through inferential statistics. It was clear that all expert members felt that these features would convey a high predictive value and therefore recommended their inclusion. The consensus rating of these features indeed appears to be supported by the published literature since two prior

studies have suggested that a history of a psychiatric disorder predicts future risk of levetiracetam-related psychiatric adverse effects[58, 118].

Finally, a limitation common to predictive modeling in general is that one is limited by the variety and richness of the data source. Unfortunately, these repositories do not consistently, and often inaccurately, record indices such as epilepsy type, seizure type, and seizure frequency[166], which all could conceivably confer significant predictive value. Inclusion of these more granular features would be expected to enhance model performance. On this background, it must be emphasized that this was designed as a prototype study to see if CDRs can be generated using 'big data'. Sources of data of this size are not commonly accessible for epilepsy. Hence, the decision was made to use an EMR registry since these repositories frequently contain millions of patients; a number that far exceeds cohort sizes in traditional clinical studies. With increasing access to 'big data', potentially linked to genomic, imaging, and EEG data, it is anticipated that researchers will have exposure to more granular information, as well as higher dimensional inputs such as electroencephalography, neuroimaging, and genetic, that should theoretically portend to unprecedented performance.

5.4 Future directions

The results of this dissertation clearly inform future studies that are warranted to build on the present results. Efforts should next be made to validate performance in an external population of patients. This is feasible and can be pursued using

alternative repositories of EMR data, such as existing prospective registries such as the Calgary Comprehensive Epilepsy Program database[129], or through prospective recruitment of candidate patients. Following this, the onus is to produce implementation studies demonstrating that the rule improves and optimizes clinical care. These can be achieved through cluster randomized controlled trials where specific sites are trained and asked to routinely employ the rule whilst control sites simply engage in standard, routine practice[167]. Outcomes of interest would include rates of psychiatric adverse effects, physician visits, the need for and cost of psychotropic medications or AED transitions, and comparative rates of emergency departments for severe psychiatric reactions.

In tandem with these studies, efforts should be made to refine the rule. As larger, more highly dimensional sources of data become increasingly available these should be exploited to determine whether calibration and discrimination could be improved. This would involve including more granular indices of epilepsy and seizures, as well as genetic and epigenetic measures and raw signal data from electroencephalography and neuroimaging that convey valuable metrics of brain structure and function. Enhanced models would then be exposed to similar validation and implementation procedures as described above. Once successful, this method of CDR derivation, validation, and implementation, using large repositories of clinical data, can be exploited to develop further CDRs for epilepsy that guide diagnostic testing, medication use, and surgical selection.

5.5 Conclusion

Ultimately, this dissertation has set the foundations for important future studies. Clinical decision rules have already revolutionised other disciplines, such as emergency medicine and stroke neurology, resulting in improved outcomes, patient satisfaction, and optimised resource allocation. The advent of ‘big data’, advanced analytics, and engaged patients now means the epilepsy is ready to enter the modern era of digitised medicine and generate robust CDRs with broad clinical application.

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Appendices

Appendix 1. Medline and Embase search strategy

1. (models, biological/ or models, statistical/ or Monte Carlo method/ or probability/ or regression analysis/ or multivariate analysis/ or predict$.mp.) and (Decision Trees/ or predictive value of tests/ or ((decision$ or predict$ or prognos$) adj5 (rule$ or model$ or algorithm$ or aid or scor$ or index)).ti,ab.)
2. exp epilepsy/
3. 1 and 2
4. Limit 3 to humans

Appendix 2. Modified quality assessment tool for studies deriving and validating clinical decision rules (adapted from two prior studies[22, 33]).

STUDY CHARACTERISTICS	
What is the study aim?	
OPTIONS: DIAGNOSTIC, THERAPEUTIC, OTHER	
Were inclusion and exclusion criteria explicitly stated?	
OPTIONS: YES or NO	
What is the study design?	
OPTIONS: DERIVATION, VALIDATION, IMPLEMENTATION *If this is a validation, impact, or implementation study, to which original score* *does it refer (include reference):*	
How were patients identified?	
OPTIONS: RETROSPECTIVE, PROSPECTIVE, BOTH, DATABASE, OTHER	
Details of the database if one was used:	
What was the study setting?	
OPTIONS: POPULATION-BASED, TERTIARY CARE, EMERGENCY, PRIMARY CARE, OTHER, UNCLEAR	
STATISTICAL METHODS	
Model	
OPTIONS: MULTIPLE LOGISTIC REGRESSION, NOMOGRAM, CART, NEURAL NETWORK, OTHER	
Details of the statistical method	
STUDY QUALITY	
Was the clinical question clearly stated?	QUADAS2 CRITERION*
The question should include a definition of the tool, the intended use of the tool, *the population for which it is intended, and any comparator/reference standard* OPTIONS: YES, NO, UNCLEAR	
Is the clinical question important?	
The outcome should be clearly defined and clinically important OPTIONS: YES, NO, UNCLEAR	
Was the study site described?	
Primary care, secondary care, tertiary care, quaternary care, ER, GP, *etc. as well as any sources of referral ('referral filter')*	

OPTIONS: YES, NO, UNCLEAR	
Were patients selected in an unbiased fashion?	QUADAS2 CRITERION
Patients should be representative of the true spectrum of disease, there should be *a consecutive or random selection of patients, a case-control design must be* *avoided, and inappropriate exclusion criteria must be avoided* OPTIONS: YES, NO, UNCLEAR	
Were prognostic factors defined *a priori*?	
Ideally: *(1) All variables are defined in advance of the study* *(2) EVERY variable evaluated should be explicitly reported in the paper* *(i.e. a full list of both significant and non-significant variables is available)* *(3) A clear definition for each variable should be proved to enhance interrater reliability* OPTIONS: YES, NO, UNCLEAR	
Were prognostic factors assessed in a blinded fashion?	QUADAS2 CRITERION
Ideally the presence or absence of a prognostic variable should be determined without knowledge of patient outcome OPTIONS: YES, NO, UNCLEAR	
Was the outcome explicitly defined?	QUADAS2 CRITERION
Ideally outcome should be: *(1) Decided in advance of the study (2) Clearly defined to enhance inter-rater reliability* *(3) Identified using the same, reliable reference standard in ALL patients* *(4) Reflect the true purpose of the CPR (e.g. not a surrogate marker)* OPTIONS: YES, NO, UNCLEAR	
Was there blind assessment of outcome?	QUADAS2 CRITERION
Presence or absence of an outcome should be determined without knowledge of the prognostic variables OPTIONS: YES, NO, UNCLEAR	
Were the statistical techniques appropriate and described in sufficient detail?	QUADAS2 CRITERION
Statistical techniques must be: *(1) Defined. Typical examples include logistic regression, discriminant analysis, neural networks, decision tress, nomograms* *(2) Appropriate (e.g. must obey the rule of at least 10 outcomes per variable)* *(3) Any thresholds should be defined in advance* OPTIONS: YES, NO, UNCLEAR	

Were all patients accounted for at the end of the study?	QUADAS2 CRITERION
Any patient lost to follow-up must be accounted for to ensure external validity OPTIONS: YES, NO, UNCLEAR	
Did all patients undergo testing at the same stage of their care process?	QUADAS2 CRITERION
The precision of the CPR may be influenced by the stage of the disease OPTIONS: YES, NO, UNCLEAR	
Were important patient characteristics defined?	
Those characteristics known to or, at the very least, are likely to affect the rule OPTIONS: YES, NO, UNCLEAR	
Were the results of the rule described?	
A quantifiable outcome including 95%CI should be reported (sensitivity, specificity, *LR, PPV, NPV, OR, RR, proportions with an outcome etc.)* OPTIONS: YES, NO, UNCLEAR	
Was reproducibility of predictive variables evaluated?	
Did the authors report inter-rater reliability of those assessing each prognostic variable? OPTIONS: YES, NO, UNCLEAR	
Was reproducibility of the rule evaluated?	
Did the authors report inter-rater reliability for correctly applying the rule (i.e. achieving the same outcome)? OPTIONS: YES, NO, UNCLEAR	
Is the rule clinically sensible?	
The likelihood the rule will be used will increase if the rule is clinically sensible, easy to use, and suggests a course of action OPTIONS: YES, NO, UNCLEAR	
Is the rule easy to use?	
The likelihood the rule will be used will increase if the rule is clinically sensible, easy to use, and suggests a course of action OPTIONS: YES, NO, UNCLEAR	
Is a course of action described?	
The likelihood the rule will be used will increase if the rule is clinically sensible, easy to use, and suggests a course of action (rather than simply the probability of a disease state) OPTIONS: YES, NO, UNCLEAR	
Is the probability of disease described?	
Are the pre- and post-test probabilities of disease described? OPTIONS: YES, NO, UNCLEAR	
Was the rule prospectively validated?	
This should ideally be performed in a group of patients distinct from the original study population and by different clinicians	

OPTIONS: YES, NO, UNCLEAR, N/A (IF A DERIVATION STUDY)	
Were the effects of clinical use prospectively evaluated?	
It must be proven that the rule will be used in clinical practice and that it will improve patient care OPTIONS: YES, NO, UNCLEAR, N/A (IF A DERIVATION STUDY)	
BASIC RESULTS	
Number of patients screened	
n	
Number of patients eligible	
n (% of screened)	
Number of patients enrolled	
n (% of eligible)	
Were there study withdrawals?	
OPTIONS: YES, NO, UNCLEAR	
Were study withdrawals explained?	
OPTIONS: YES, NO, UNCLEAR *If yes, please provide details:*	
Gender	
Female (n and %)	
Age	
Mean/median +/- STD/IQR/Range	
Ethnicity	
Specify (%)	
Outcome	
Overall n (%) with outcome of interest	
CDR VARIABLES	
Interobserver agreement for correctly identifying the presence of each variable	
Variables and kappa	
Intraobserver agreement for correctly identifying the presence of each variable	
Variables and kappa	

Univariable analysis	
Variables and their associated OR or levels of significance	
Multivariable analysis	
Variables and their associated OR or levels of significance	
CDR OUTCOME	
Interobserver agreement for identifying the outcome of interest	
Variables and kappa	
Intraobserver agreement for identifying the outcome of interest	
Variables and kappa	
Results of the rule	
Outcome measures (e.g. sensitivity, specificity, LR, PPV, NPV, proportions, etc.)	
USE OF THE RULE	
Interobserver agreement for obtaining the same result for each patient	
Variables and kappa	
Intraobserver agreement for obtaining the same result for each patient	
Variables and kappa	
Accuracy in using the rule	
% of cases in which the rule was correctly applied as judged by the investigators	
Was ease of use assessed?	
OPTIONS: YES, NO, UNCLEAR If yes, please provide details:	
Were smart phone applications, computer programs, or other technology developed?	
OPTIONS: YES, NO, UNCLEAR If yes, please provide details:	
Forward citations	
Number	

ADDITIONAL NOTES ON PAPER	

*QUADAS2 = Quality Assessment of Diagnostic Accuracy Studies 2 scale

Appendix 3. Read and multilex codes used to identify a pre-exposure history of a psychiatric disorder.

DEPRESSION

E112.	Single major depressive episode / Agitated depression / Endogenous depression first episode / Endogenous depression first episode / Endogenous depression
E1120	Single major depressive episode, unspecified
E1121	Single major depressive episode, mild
E1122	Single major depressive episode, moderate
E1125	Single major depressive episode, partial or unspecified remission
E1126	Single major depressive episode, in full remission
E112z	Single major depressive episode NOS
E113.	Recurrent major depressive episode / Endogenous depression - recurrent
E1130	Recurrent major depressive episodes, unspecified
E1131	Recurrent major depressive episodes, mild
E1132	Recurrent major depressive episodes, moderate
E1135	Recurrent major depressive episodes, partial/unspecified remission
E1136	Recurrent major depressive episodes, in full remission
E1137	Recurrent depression
E113z	Recurrent major depressive episode NOS
Eu320	[X]Mild depressive episode
Eu321	[X]Moderate depressive episode
Eu324	[X]Mild depression
Eu325	[X]Major depression, mild
Eu326	[X]Major depression, moderately severe
Eu32y	[X]Other depressive episodes / [X]Atypical depression / [X]Single episode of masked depression NOS
Eu32z	[X]Depressive episode, unspecified / [X]Depression NOS / [X]Depressive disorder NOS / [X]Prolonged single episode of reactive depression / [X] Reactive depression NOS
Eu330	[X]Recurrent depressive disorder current episode mild
Eu331	[X]Recurrent depressive disorder current episode moderate
Eu334	[X]Recurrent depressive disorder currently in remission
Eu33y	[X]Other recurrent depressive disorders
Eu33z	[X]Recurrent depressive disorder unspecified / [X]Monopolar depression NOS
Eu3y1	[X]Other recurrent mood affective disorders / [X]Recurrent brief depressive episodes
Eu920	[X]Depressive conduct disorder
1465.	H/O: depression
Eu32.	[X]Depressive episode / [X]Single episode of depressive reaction / [X]Single episode of psychogenic depression / [X]Single episode of reactive depression

Eu322	[X]Severe depressive episode without psychotic symptoms / [X]Single episode agitated depressn without psychotic symptoms / [X]Single episode major depression without psychotic symptoms / [X]Single episode vital depression without psychotic symptoms
Eu323	[X]Severe depressive episode with psychotic symptoms / [X]Single episode of major depression and psychotic symptoms / [X]Single episode of psychogenic depressive psychosis / [X]Single episode of psychotic depression / [X]Single episode of reactive depressive psychosis
Eu327	[X]Major depression, severe without psychotic symptoms
Eu33.	[X]Recurrent depressive disorder / [X]Recurrent episodes of depressive reaction / [X]Recurrent episodes of psychogenic depression / [X]Recurrent episodes of reactive depression / [X]Seasonal depressive disorder / [X]SAD - Seasonal affective disorder
Eu328	[X]Major depression, severe with psychotic symptoms
Eu332	[X]Recurr depress disorder cur epi severe without psychotic symptoms / [X]Endogenous depression without psychotic symptoms / [X]Major depression recurrent without psychotic symptoms / [X]Manic-depress psychosis depressed no psychotic symptoms / [X]Vital depression recurrent without psychotic symptoms
Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp / [X]Endogenous depression with psychotic symptoms / [X]Manic-depress psychosis depressed type+psychotic symptoms / [X]Recurr severe episodes/major depression+psychotic symptom / [X]Recurr severe episodes/psychogenic depressive psychosis / [X]Recurrent severe episodes of psychotic depression / [X]Recurrent severe episodes/reactive depressive psychosis
62T1.	Puerperal depression
E11y2	Atypical depressive disorder
E11z2	Masked depression
E135.	Agitated depression
E204.	Neurotic depression reactive type / Postnatal depression
E2112	Depressive personality disorder
E2B..	Depressive disorder NEC
E2B1.	Chronic depression
E1134	Recurrent major depressive episodes, severe with psychosis
E1133	Recurrent major depressive episodes, severe with no psychosis
E1124	Single major depressive episode, severe with psychosis
Eu341	[X]Dysthymia / [X]Depressive neurosis / [X]Depressive personality disorder / [X]Neurotic depression / [X]Persistent anxiety depression
1BT..	Depressed mood / Low mood / Sad mood
1S40.	Dysphoric mood
Eu530	[X]Mild mental/behav disorder assoc with the puerperium NEC / [X]Postnatal depression NOS / [X]Postpartum depression NOS

E1123 Single major depressive episode, severe without psychosis

ANXIETY

Eu41z	[X]Anxiety disorder unspecified / [X]Anxiety NOS
Eu41y	[X]Other specified anxiety disorders / [X]Anxiety hysteria
Eu413	[X]Other mixed anxiety disorders
Eu412	[X]Mixed anxiety and depressive disorder / [X]Mild anxiety depression
Eu411	[X]Generalized anxiety disorder / [X]Anxiety neurosis / [X]Anxiety reaction/[X]Anxiety state
Eu410	[X]Panic disorder [episodic paroxysmal anxiety] / [X]Panic attack / [X]Panic state
Eu41.	[X]Other anxiety disorders
Eu40z	[X]Phobic anxiety disorder unspecified / [X]Phobia NOS / [X]Phobic state NOS
Eu40y	[X]Other phobic anxiety disorders
Eu40.	[X]Phobic anxiety disorders
Eu054	[X]Organic anxiety disorder
E202.	Phobic disorders / Social phobic disorders / Phobic anxiety
E200z	Anxiety state NOS
E2005	Recurrent anxiety
E2004	Chronic anxiety
E2003	Anxiety with depression
E2002	Generalised anxiety disorder
E2000	Anxiety state unspecified
E200.	Anxiety states
1466.	H/O: anxiety state
146G.	H/O: agoraphobia

PSYCHOSIS AND MANIA

E114.	Bipolar affective disorder currently manic / Manic-depressive - now manic
E115.	Bipolar affective disorder currently depressed/Manic-depressive - now depressed
E1150	Bipolar affective disorder currently depressed unspecified
E1151	Bipolar affective disorder currently depressed mild
E1152	Bipolar affective disorder currently depressed moderate
E1155	Bipolar affect disorder now depressed part/unspec remission
E1156	Bipolar affective disorder now depressed in full remission
E115z	Bipolar affective disorder currently depressed NOS
E1164	Mixed bipolar affective disorder severe with psychosis
E1163	Mixed bipolar affective disorder severe without psychosis
E1154	Bipolar affect disord now depressed severe with psychosis

E1153	Bipolar affect disord now depressed severe no psychosis
E1144	Bipolar affect disord currently manic severe with psychosis
E1143	Bipolar affect disord currently manic severe no psychosis
E1104	Single manic episode severe with psychosis
E1113	Recurrent manic episodes severe without mention psychosis
E1114	Recurrent manic episodes severe with psychosis
E1103	Single manic episode severe without mention of psychosis
E110.	Manic disorder single episode / Hypomanic psychoses
E11..	Affective psychoses / Bipolar psychoses / Depressive psychoses / Manic psychoses
E1...	Non-organic psychoses
E0z..	Organic psychoses NOS
E0y..	Other specified organic psychoses
E04z.	Chronic organic psychosis NOS
E04y.	Other specified chronic organic psychoses
E03z.	Transient organic psychoses NOS
E04..	Other chronic organic psychoses
E03yz	Other transient organic psychoses NOS
E03y3	Unspecified puerperal psychosis
E03y.	Other transient organic psychoses
E03..	Transient organic psychoses
E00z.	Senile or presenile psychoses NOS
E00y.	Other senile and presenile organic psychoses / Presbyophrenic psychosis
E0...	Organic psychotic conditions
286..	Poor insight into neurotic condition / Poor insight into psychotic condition
285..	Neurotic condition insight present / Psychotic condition insight present
Eu052	[X]Organic delusional [schizophrenia-like] disorder / [X]Paranoid organic state / [X]Schizophrenia-like psychosis in epilepsy
Eu05y	[X]Oth sp mental disord brain damag/dysfunction/physcal disd / [X]Epileptic psychosis NOS
Eu20y	[X]Other schizophrenia / [X]Cenesthopathic schizophrenia / [X]Schizophreniform disord NOS / [X]Schizophrenifrm psychos NOS
Eu21.	[X]Schizotypal disorder / [X]Latent schizophrenic reaction / [X]Borderline schizophrenia / [X]Latent schizophrenia / [X]Prepsychotic schizophrenia / [X]Prodromal schizophrenia / [X]Pseudoneurotic schizophrenia / [X]Pseudopsychopathic schizophrenia / [X]Schizotypal personality disorder
Eu220	[X]Delusional disorder / [X]Paranoid psychosis / [X]Paranoid state / [X]Paraphrenia - late / [X]Sensitiver Beziehungswahn / [X]Paranoia
Eu23.	[X]Acute and transient psychotic disorders
Eu230	[X]Acute polymorphic psychot disord without symp of schizoph / [X]Bouffee delirante / [X]Cycloid psychosis

Eu231	[X]Acute polymorphic psychot disord with symp of schizophren / [X]Bouffee delirante with symptoms of schizophrenia / [X]Cycloid psychosis with symptoms of schizophrenia
Eu232	[X]Acute schizophrenia-like psychotic disorder / [X]Brief schizophreniform disorder / [X]Brief schizophrenifrm psych / [X]Oneirophrenia / [X]Schizophrenic reaction
Eu233	[X]Other acute predominantly delusional psychotic disorders / [X]Psychogenic paranoid psychosis
Eu23y	[X]Other acute and transient psychotic disorders
Eu23z	[X]Acute and transient psychotic disorder unspecified/[X]Brief reactive psychosis NOS / [X]Reactive psychosis
Eu250	[X]Schizoaffective disorder manic type / [X]Schizoaffective psychosis manic type / [X]Schizophreniform psychosis manic type
Eu251	[X]Schizoaffective disorder depressive type / [X]Schizoaffective psychosis depressive type / [X]Schizophreniform psychosis depressive type
Eu252	[X]Schizoaffective disorder mixed type / [X]Cyclic schizophrenia / [X]Mixed schizophrenic and affective psychosis
Eu25z	[X]Schizoaffective disorder unspecified / [X]Schizoaffective psychosis NOS
Eu2y.	[X]Other nonorganic psychotic disorders / [X]Chronic hallucinatory psychosis
Eu2z.	[X]Unspecified nonorganic psychosis / [X]Psychosis NOS
Eu301	[X]Mania without psychotic symptoms
Eu302	[X]Mania with psychotic symptoms / [X]Mania with mood-congruent psychotic symptoms / [X]Mania with mood-incongruent psychotic symptoms / [X]Manic stupor
Eu31.	[X]Bipolar affective disorder / [X]Manic-depressive illness /[X]Manic-depressive psychosis / [X]Manic-depressive reaction
Eu312	[X]Bipolar affect disorder cur epis manic with psychotic symp
Eu311	[X]Bipolar affect disorder cur epis manic wout psychotic symp
Eu314	[X]Bipol aff disord curr epis sev depress, no psychotic symp
Eu3z.	[X]Unspecified mood affective disorder / [X]Affective psychosis NOS
Eu44.	[X]Dissociative [conversion] disorders / [X]Conversion hysteria / [X]Conversion reaction / [X]Hysteria / [X]Hysterical psychosis
E13..	Other nonorganic psychoses / Reactive psychoses
E12z.	Paranoid psychosis NOS
E121.	Chronic paranoid psychosis / Sander's disease
E11zz	Other affective psychosis NOS
E11z.	Other and unspecified affective psychoses
E11z0	Unspecified affective psychoses NOS
E11yz	Other and unspecified manic-depressive psychoses NOS
E11y3	Other mixed manic-depressive psychoses
E11y0	Unspecified manic-depressive psychoses

E11y.	Other and unspecified manic-depressive psychoses
E1174	Unspecified bipolar affective disorder severe with psychosis
E1173	Unspecified bipolar affective disorder severe no psychosis
E130.	Reactive depressive psychosis / Psychotic reactive depression
E131.	Acute hysterical psychosis
E134.	Psychogenic paranoid psychosis
E13y.	Other reactive psychoses
E13y0	Psychogenic stupor
E13y1	Brief reactive psychosis
E13yz	Other reactive psychoses NOS
E13z.	Nonorganic psychosis NOS / Psychotic episode NOS
E14..	Psychoses with origin in childhood
E141.	Disintegrative psychosis / Heller's syndrome
E1410	Active disintegrative psychoses
E1411	Residual disintegrative psychoses
E141z	Disintegrative psychosis NOS
E14y.	Other childhood psychoses
E14y0	Atypical childhood psychoses
E14y1	Borderline psychosis of childhood
E14yz	Other childhood psychoses NOS
E14z.	Child psychosis NOS / Childhood schizophrenia NOS
E1y..	Other specified non-organic psychoses
E1z..	Non-organic psychosis NOS
E21z.	Personality disorder NOS / Psychopathic personality
Eu313	[X]Bipolar affect disorder cur epis mild or moderate depression
Eu204	[X]Post-schizophrenic depression
1Ba1.	Disorder of form of thought
1BH..	Delusions / Delusion
1BH0.	Delusion of persecution
1BH1.	Grandiose delusions
1BH2.	Ideas of reference
1BH3.	Paranoid ideation
1464.	H/O: schizophrenia
146D.	H/O: manic depressive disorder
146H.	H/O: psychosis
1S42.	Manic mood

BEHAVIOURAL ISSUES

E2C01	Anger reaction
R00z8	[D]Irritability and anger
Eu...	[X]Mental and behavioural disorders
Eu92.	[X]Mixed disorders of conduct and emotions / [X]Emotional behavioural problems

Eu91z	[X]Conduct disorder unspecified / [X]Childhood behavioural disorder NOS / [X]Childhood conduct disorder NOS
Eu9..	[X]Behavioural/emotional disorders onset childhood/adolescence
ZV403	[V]Other behavioural problems
ZV40y	[V]Other specified mental or behavioural problem
ZV40z	[V]Unspecified mental or behavioural problem
ZVu6K	[X]Personal history/other mental and behavioural disorders
E2C0.	Aggressive unsocial conduct disorder
E213.	Explosive personality disorder / Aggressive personality / Quarrelsome personality
Eu603	[X]Emotionally unstable personality disorder / [X]Aggressive personality disorder / [X]Borderline personality disorder / [X]Explosive personality disorder
28L..	O/E - impulsive behaviour
E2C..	Disturbance of conduct NEC / Behaviour disorder
Eu6..	[X]Disorders of adult personality and behaviour
Eu6y.	[X]Other disorders of adult personality and behaviour
Eu6yy	[X]Other specified disorders of adult personality/behaviour
Eu6z.	[X]Unspecified disorder of adult personality and behaviour
ZV40.	[V]Mental and behavioural problems / [V]Behavioural problems / [V]Mental problems / [V]Psychological problems
1469.	H/O: behaviour problem
1P02.	Disinhibited behaviour
1P52.	Verbally abusive behaviour
1P51.	Physically abusive behaviour
1P50.	Violent acts towards others
1P5..	Aggressive behaviour
1Ba0.	Obsessional thoughts

SUICIDAL IDEATION/COMPLETED SUICIDE

U2057	[X]Int self poison/exposure to narcotic drug on farm
U2054	[X]Intent self pois narcotic drug in street/highway
U205y	[X]Int self poison narcotic drug other spec place
U205z	[X]Intent self poison narcotic drug unspecif place
U206.	[X]Intent self poison/exposure to hallucinogen
U2060	[X]Int self poison/exposure to hallucinogen at home
U2061	[X]Intent self poison hallucinogen at res institut
U2062	[X]Int self poison hallucinogen in school/pub admin area
U2063	[X]Int self poison hallucinogen in sport/athletic area
U2064	[X]Intent self pois hallucinogen in street/highway
U2065	[X]Intent self pois hallucinogen in trade/service area
U2066	[X]Int self pois hallucinogen in indust/construct area
U2067	[X]Int self poison/exposure to hallucinogen on farm
U206y	[X]Int self poison hallucinogen other spec place
U206z	[X]Intent self poison hallucinogen in unspecif place

U207. [X]Intent self poison/exposure to oth autonomic drug
U2070 [X]Int self poison/exposure to oth autonomic drug at home
U2071 [X]Intent self poison oth autonomic drug at res institut
U2072 [X]Int self poison oth autonom drug school/pub admin area
U2073 [X]Int self poison oth autonom drug in sport/athletic area
U2075 [X]Intent self pois oth autonomic drug trade/service area
U2074 [X]Intent self pois oth autonomic drug in street/highway
U2076 [X]Int self pois oth autonomic drug indust/construct area
U207y [X]Int self poison oth autonomic drug other spec place
U2077 [X]Int self poison/exposure to oth autonomic drug on farm
U207z [X]Intent self poison oth autonomic drug unspecif place
U208. [X]Int self poison/exposure to other/unspec drug/medicament
U2080 [X]Int self poison/exposure to oth/unsp drug/medicam home
U2081 [X]Intent self poison oth/unsp drug/medicam res institut
U2082 [X]Int self poison oth/uns drug/med school/pub admin area
U2083 [X]Int self poison oth/uns drug/med in sport/athletic area
U2084 [X]Intent self pois oth/unsp drug/medic in street/highway
U2085 [X]Intent self pois oth/unsp drug/medic trade/service area
U2086 [X]Int self pois oth/unsp drug/medic indust/construct area
U2087 [X]Int self poison/exposure to oth/unsp drug/medic on farm
U208y [X]Int self poison oth/unsp drug/medic other spec place
U208z [X]Intent self poison oth/unsp drug/medic unspecif place
U209. [X]Intent self poison/exposure to alcohol
U2090 [X]Int self poison/exposure to alcohol at home
U2091 [X]Intent self poison alcohol at res institut
U2092 [X]Int self poison alcohol school/pub admin area
U2093 [X]Int self poison alcohol in sport/athletic area
U2094 [X]Intent self pois alcohol in street/highway
U2095 [X]Intent self pois alcohol trade/service area
U2096 [X]Int self pois alcohol indust/construct area
U2097 [X]Int self poison/exposure to alcohol on farm
U209y [X]Int self poison alcohol other spec place
U209z [X]Intent self poison alcohol unspecif place
U20A. [X]Intentional self poison organ solvent halogen hydrocarb/[X]Self poisoning from glue solvent
U20A1 [X]Int self poison org solvent halogen hydrocarb, res instit
U20A0 [X]Intent self pois organ solvent halogen hydrocarb inhome
U20A2 [X]Int self poison org solvent halogen hydrocarb in school
U20A3 [X]Int self poison org solvent halogen hydrocarb in sport area
U20A4 [X]Int self poison org solvent halogen hydrocarb in highway
U20A5 [X]Int self poison org solvent halogen hydrocarb in trade area
U20A6 [X]Int self pois org solvent halogen hydrocarb in indust area
U20A7 [X]Int self poison org solvent halogen hydrocarb on farm
U20Ay [X]Int self pois org solv halogen hydrocarb in oth spec place
U20Az [X]Int self pois org solv halogen hydrocarb in unspec place

U20B.	[X]Intent self poison/exposure to other gas/vapour / [X]Self carbon monoxide poisoning
U20B0	[X]Int self poison/exposure to other gas/vapour at home
U20B1	[X]Intent self poison other gas/vapour at res institut
U20B2	[X]Int self poison other gas/vapour school/pub admin area
U20B3	[X]Int self poison other gas/vapour in sport/athletic area
U20B5	[X]Intent self pois other gas/vapour trade/service area
U20B6	[X]Int self pois other gas/vapour indust/construct area
U20B4	[X]Intent self pois other gas/vapour in street/highway
U20B7	[X]Int self poison/exposure to other gas/vapour on farm
U20By	[X]Int self poison other gas/vapour other spec place
U20Bz	[X]Intent self poison other gas/vapour unspecif place
U20C.	[X]Intent self poison/exposure to pesticide / [X]Self poisoning with weedkiller / [X]Self poisoning with paraquat
U20C0	[X]Int self poison/exposure to pesticide at home
U20C1	[X]Intent self poison pesticide at res institut
U20C2	[X]Int self poison pesticide school/pub admin area
U20C3	[X]Int self poison pesticide in sport/athletic area
U20C4	[X]Intent self pois pesticide in street/highway
U20C5	[X]Intent self pois pesticide trade/service area
U20C6	[X]Int self pois pesticide indust/construct area
U20C7	[X]Int self poison/exposure to pesticide on farm
U20Cy	[X]Int self poison pesticide other spec place
U20Cz	[X]Intent self poison pesticide unspecif place
U20y.	[X]Intent self poison/exposure to unspecif chemical
U20y0	[X]Int self poison/exposure to unspecif chemical at home
U20y1	[X]Intent self poison unspecif chemical at res institut
U20y2	[X]Int self poison unspecif chemical school/pub admin area
U20y3	[X]Int self poison unspecif chemical in sport/athletic area
U20y4	[X]Intent self pois unspecif chemical in street/highway
U20y5	[X]Intent self pois unspecif chemical trade/service area
U20y6	[X]Int self pois unspecif chemical indust/construct area
U20y7	[X]Int self poison/exposure to unspecif chemical on farm
U20yy	[X]Int self poison unspecif chemical other spec place
U20yz	[X]Intent self poison unspecif chemical unspecif place
U21..	[X]Intent self harm by hanging strangulation / suffocation
U211.	[X]Intent self harm by hangng strangult/suffoct resid instit
U210.	[X]Intent self harm by hanging strangulat/suffocat occ home
U213.	[X]Intent self harm by hang strangl/suffc sport/athlet area
U214.	[X]Intent self harm by hangng strangult/suffoct street/h'way
U216.	[X]Intent self harm by hang strangl/suffc indust/constr area
U215.	[X]Intent self harm by hang strangl/suffc trade/service area
U217.	[X]Intent self harm by hanging strangulat/suffocat occ farm
U21y.	[X]Intent self harm by hangng strangul/suffoct oth spec plce
U21z.	[X]Intent self harm by hangng strangul/suffoct unspecif plce
U22..	[X]Intentional self harm by drowning and submersion

U220. [X]Intent self harm by drowning/submersion occurrn at home
U221. [X]Intent self harm by drowning/submersn occ resid instit'n
U222. [X]Intent self harm drown/submers occ sch/ins/pub adm area
U223. [X]Intent self harm by drown/submersn occ sport/athlet area
U225. [X]Intent self harm by drown/submersn occ trade/servce area
U226. [X]Intent self harm by drown/submers occ indust/constr area
U224. [X]Intent self harm by drowning/submersn occ street/highway
U227. [X]Intent self harm by drowning/submersion occurrn on farm
U22y. [X]Intent self harm by drown/submersn occ oth specif place
U22z. [X]Intent self harm by drown/submersn occ unspecified place
U23.. [X]Intentional self harm by handgun discharge
U230. [X]Intention self harm by handgun discharge occurrn at home
U231. [X]Intent self harm by handgun disch occ in resid instit'n
U232. [X]Intent self harm h'gun disch occ sch oth ins/pub adm area
U233. [X]Intent self harm by handgun disch occ sport/athlet area
U234. [X]Intent self harm by handgun disch occ on street/highway
U235. [X]Intent self harm by handgun disch occ trade/service area
U236. [X]Intent self harm by handgun disch occ indust/constr area
U237. [X]Intention self harm by handgun discharge occurrn on farm
U23y. [X]Intent self harm by handgun disch occ at oth specif plce
U24.. [X]Intent self harm by rifle shotgun/larger firearm disch
U23z. [X]Intent self harm by handgun disch occ at unspecif place
U240. [X]Intent self harm rifle sh'gun/largr firarm disch occ home
U241. [X]Int self harm rifl s'gun/lrg frarm disch occ resid instit
U243. [X]Int self harm rifl s'gun/lrg frarm disch sprt/athlet area
U244. [X]Int self harm rifl s'gun/lrg frarm disch occ street/h'way
U245. [X]Int self harm rifl s'gun/lrg frarm disch trad/servce area
U25.. [X]Intent self harm by other/unspecified firearm discharge
U24y. [X]Int self harm rifl s'gun/lrg frarm disch oth specif place
U24z. [X]Int self harm rifl s'gun/lrg frarm disch occ unspec place
U250. [X]Intent self harm oth/unspecif firearm disch occ at home
U251. [X]Intent self harm oth/unsp firearm disch occ resid instit
U252. [X]Inten self harm oth/uns firarm disch sch/ins/pub adm area
U253. [X]Inten self harm oth/uns firearm disch occ sprt/athl area
U254. [X]Intent self harm oth/unsp firearm disch occ street/h'way
U255. [X]Intent self harm oth/uns firearm disch trade/servce area
U256. [X]Inten self harm oth/uns firearm disch indust/constr area
U720. [X]Sequelae of intentional self-harm
U72.. [X]Sequel intentn self-harm assault+event of undeterm intent
U2zz. [X]Intent self harm by unspecif means occ at unspecif place
U2zy. [X]Intent self harm by unspecif means occ oth specif place
U2z6. [X]Intent self harm unspecif mean occurrn indust/constr area
U2z5. [X]Intent self harm unspecif means occurrn trade/servce area
U2z4. [X]Intent self harm by unspecif means occurrn street/highway
U2z7. [X]Intentional self harm by unspecif means occurrn on farm
U2y6. [X]Intent self harm oth specif means occ indust/constr area

U2z.. [X]Intentional self harm by unspecified means
U2z3. [X]Intent self harm unspecif means occurrn sport/athlet area
U2z2. [X]Intent self harm by unspec mean occ sch/ins/pub adm area
U2z1. [X]Intent self harm by unspecif means occurrn resid instit'n
U2z0. [X]Intentional self harm by unspecif means occurrn at home
U2y7. [X]Intentionl self harm by oth specif means occurrn on farm
U2yy. [X]Intent self harm oth specif means occ oth specif place
U2yz. [X]Intent self harm by oth specif means occ unspecif place
U2y5. [X]Intent self harm by oth specif means occ trad/servce area
U2y0. [X]Intentionl self harm by oth specif means occurrn at home
U2y1. [X]Intent self harm by oth specif means occ resid instit'n
U2y2. [X]Intent self harm oth specif mean occ sch/ins/pub adm area
U2y3. [X]Intent self harm by oth specif means occ sport/athl area
U2y4. [X]Intent self harm by oth specif means occ street/highway
U2y.. [X]Intentional self harm by other specified means
U2E.. [X]Self mutilation
U2Dz. [X]Intent self harm by crash motor vehic occ unspecif place
U2Dy. [X]Intent self harm by crash motor vehic occ oth specif plce
U2D7. [X]Intent self harm by crash of motor vehicl occurrn on farm
U2D6. [X]Intent self harm crash motor vehic occ indust/constr area
U2D5. [X]Intent self harm crash motor vehicl occ trade/servce area
U2D4. [X]Intent self harm by crash motor vehicl occ street/highway
U2D3. [X]Intent self harm by crash motor vehicl occ sprt/athl area
U2D2. [X]Int self harm crash motor vehicl occ sch/ins/pub adm area
U2D1. [X]Intent self harm by crash motor vehicl occ resid instit'n
U2D0. [X]Intent self harm by crash of motor vehicl occurring at home
U2D.. [X]Intentional self harm by crashing of motor vehicle
U2Cz. [X]Int self harm jump/lying bef mov obje occ unspecif place
U2Cy. [X]Int self harm jump/lying bef mov obje occ oth specif plce
U2C7. [X]Intent self harm by jump/lying befor moving obj occ farm
U2C6. [X]Int self harm jump/lying befr mov obj indust/constr area
U2C5. [X]Int self harm jump/lying bef mov obj occ trad/servce area
U2C4. [X]Int self harm jump/lying befr mov obje occ street/highway
U2C3. [X]Int self harm jump/lying bef mov obj occ sprt/athlet area
U2C2. [X]Int self harm jump/lying bef mov obj sch/ins/pub adm area
U2C1. [X]Int self harm jump/lying befr mov obje occ resid instit'n
U2C0. [X]Intent self harm by jump/lying befor moving obj occ home
U2C.. [X]Intent self harm by jumping / lying before moving object
U2Bz. [X]Int self harm by jump from high place occ unspecif place
U2B7. [X]Intent self harm by jumping from high place occ on farm
U2By. [X]Int self harm by jump from high place occ oth specif plce
U2B6. [X]Int self harm by jump from high place indust/constr area
U2B5. [X]Intent self harm by jump from high place trad/servce area
U2B4. [X]Intent self harm by jump from high place occ street/h'way
U2B3. [X]Intent self harm by jump from high place sport/athl area
U2B2. [X]Int self harm jump fr high place sch oth ins/pub adm area

U2B1. [X]Intent self harm by jump from high place occ resid instit
U2B0. [X]Intent self harm by jumping from high place occ at home
U2B.. [X]Intentional self harm by jumping from a high place
U2Az. [X]Intentional self harm by blunt object occ unspecif place
U2Ay. [X]Intention self harm by blunt object occ oth specif place
U2A7. [X]Intentional self harm by blunt object occurrence on farm
U2A6. [X]Intent self harm by blunt object occ indust/constr area
U2A5. [X]Intent self harm by blunt object occ trade/service area
U257. [X]Intent self harm oth/unspecif firearm disch occ on farm
U25y. [X]Intent self harm oth/unsp firearm disch oth specif place
U25z. [X]Intent self harm oth/unsp firearm disch occ unspecif plce
U26.. [X]Intentional self harm by explosive material
U260. [X]Intention self harm by explosive material occurrn home
U261. [X]Intention self harm by explosiv materl occ resid instit
U262. [X]Intent self harm by explosiv materl sch/ins/pub adm area
U263. [X]Intent self harm by explosv materl occ sport/athlet area
U264. [X]Intention self harm by explosiv materl occ street/highway
U265. [X]Intent self harm by explosv materl occ trade/servce area
U266. [X]Intent self harm by explosv materl occ indust/constr area
U267. [X]Intention self harm by explosive material occurrn farm
U26y. [X]Intent self harm by explosiv materl occ oth specif place
U26z. [X]Intent self harm by explosiv materl occ unspecif place
U27.. [X]Intentional self harm by smoke fire and flames
U270. [X]Intention self harm by smoke fire/flames occurrn at home
U271. [X]Intent self harm by smoke fire/flame occ resid instit'n
U272. [X]Intent self harm by smoke fire/flame sch/ins/pub adm area
U273. [X]Intent self harm by smok fire/flam occ sport/athlet area
U274. [X]Intent self harm by smoke fire/flame occ street/highway
U275. [X]Intent self harm by smok fire/flam occ trade/servce area
U276. [X]Intent self harm by smok fire/flam occ indust/constr area
U277. [X]Intention self harm by smoke fire/flames occurrn on farm
U27y. [X]Intent self harm by smoke fire/flame occ oth specif plce
U27z. [X]Intent self harm by smoke fire/flames occ unspecif place
U28.. [X]Intentional self harm by steam hot vapours / hot objects
U280. [X]Intent self harm by steam hot vapour/hot obj occ at home
U281. [X]Intent self harm by steam hot vapour/obj occ resid instit
U282. [X]Int self harm by steam hot vapor/obj sch/ins/pub adm area
U283. [X]Int self harm by steam hot vapour/obj occ sport/athl area
U284. [X]Intent self harm by steam hot vapour/obj occ street/h'way
U285. [X]Int self harm by steam hot vapour/obj trade/service area
U286. [X]Int self harm by steam hot vapour/obj indust/constr area
U29.. [X]Intentional self harm by sharp object
U28z. [X]Intent self harm by steam hot vapour/obj occ unspec place
U287. [X]Intent self harm by steam hot vapour/hot obj occ on farm
U28y. [X]Intent self harm by steam hot vapour/obj oth specif place
U290. [X]Intentional self harm by sharp object occurrence at home

U291.	[X]Intent self harm by sharp object occ resident instit'n
U292.	[X]Intent self harm sharp obj occ sch oth ins/pub adm area
U293.	[X]Intent self harm by sharp object occ sports/athlet area
U294.	[X]Intention self harm by sharp object occ street/highway
U295.	[X]Intent self harm by sharp object occ trade/service area
U296.	[X]Intent self harm by sharp object occ indust/constr area
U297.	[X]Intentional self harm by sharp object occurrence on farm
U29y.	[X]Intention self harm by sharp object occ oth specif place
U29z.	[X]Intentional self harm by sharp object occ unspecif place
U2A..	[X]Intentional self harm by blunt object
U2A0.	[X]Intentional self harm by blunt object occurrence at home
U2A1.	[X]Intent self harm by blunt object occ resident instit'n
U2A2.	[X]Intent self harm blunt obj occ sch oth ins/pub adm area
U2A3.	[X]Intent self harm by blunt object occ sports/athlet area
U2A4.	[X]Intention self harm by blunt object occ street/highway
ZV1B2	[V]Personal history of self-harm
ZX...	Self-harm / Self-damage
ZX1..	Self-injurious behaviour / Self-destructive behaviour / SIB - Self-injurious behaviour / Deliberate self-harm / Self-abusive behaviour
ZX13.	Cutting self / Cuts self
14K0.	H/O: repeated overdose
14K1.	Intentional overdose of prescription only medication
1BD1.	Suicidal ideation
1BD3.	Suicidal plans
1BD4.	Suicide risk
1BD5.	High suicide risk
1BD6.	Moderate suicide risk
1BD7.	Low suicide risk
1BD8.	At risk of DSH - deliberate self harm
1BDA.	Thoughts of deliberate self harm
1BDB.	Plans for deliberate self harm without intent
1BDC.	Intent of deliberate self harm with detailed plans
U2...	[X]Intentional self-harm / [X]Self inflicted injury / [X]Injury - self-inflicted / [X]Suicide / [X]Attempted suicide / [X]Para-suicide
U20..	[X]Intentional self poisoning/exposure to noxious substances / [X]Deliberate drug overdose / other poisoning
U200.	[X]Intent self poison/exposure to nonopioid analgesic / [X]Overdose - paracetamol / [X]Overdose - ibuprofen / [X]Overdose - aspirin
U2000	[X]Int self poison/exposure to nonopioid analgesic at home
U2001	[X]Intent self poison nonopioid analgesic at res institut
U2004	[X]Intent self pois nonopioid analgesic in street/highway
U2002	[X]Int self poison nonopioid analges school/pub admin area
U2005	[X]Intent self pois nonopioid analgesic trade/service area
U2003	[X]Int self poison nonopioid analges in sport/athletic area
U2006	[X]Int self pois nonopioid analgesic indust/construct area
U2007	[X]Int self poison/exposure to nonopioid analgesic on farm

U200y	[X]Int self poison nonopioid analgesic other spec place
U200z	[X]Intent self poison nonopioid analgesic unspecif place
U201.	[X]Intent self poison/exposure to antiepileptic
U2010	[X]Int self poison/exposure to antiepileptic at home
U2011	[X]Intent self poison antiepileptic at res institut
U2012	[X]Intent self pois nonopioid analges school/pub admin area
U2014	[X]Intent self pois antiepileptic in street/highway
U2013	[X]Int self poison antiepileptic in sport/athletic area
U2015	[X]Intent self pois antiepileptic trade/service area
U2016	[X]Int self poison antiepileptic indust/construct area
U2017	[X]Int self poison/exposure to antiepileptic on farm
U201y	[X]Intent self poison antiepileptic other spec place
U201z	[X]Intent self poison antiepileptic unspecif place
U202.	[X]Intent self poison/exposure to sedative hypnotic / [X]Overdose - sleeping tabs / [X]Overdose - diazepam / [X]Overdose - temazepam / [X]Overdose - flurazepam / [X]Overdose - nitrazepam / [X]Overdose - benzodiazepine / [X]Overdose - barbiturate / [X]Overdose - amobarbital
U2020	[X]Int self poison/exposure to sedative hypnotic at home
U2021	[X]Intent self poison sedative hypnotic at res institut
U2022	[X]Int self poison sedative hypnotic school/pub admin area
U2023	[X]Int self poison sedative hypnotic in sport/athletic area
U2024	[X]Intent self pois sedative hypnotic in street/highway
U2025	[X]Intent self pois sedative hypnotic trade/service area
U2026	[X]Int self pois sedative hypnotic indust/construct area
U2027	[X]Int self poison/exposure to sedative hypnotic on farm
U202y	[X]Int self poison sedative hypnotic other spec place
U202z	[X]Intent self poison sedative hypnotic unspecif place
U203.	[X]Intent self poison/exposure to antiparkinson drug
U2030	[X]Int self poison/exposure to antiparkinson drug at home
U2031	[X]Intent self poison antiparkinson drug at res institut
U2033	[X]Int self poison antparkinson drug in sport/athletic area
U2032	[X]Int self poison antparkinson drug school/pub admin area
U2034	[X]Intent self pois antiparkinson drug in street/highway
U2035	[X]Intent self pois antiparkinson drug trade/service area
U2036	[X]Int self pois antiparkinson drug indust/construct area
U2037	[X]Int self poison/exposure to antiparkinson drug on farm
U203y	[X]Int self poison antiparkinson drug other spec place
U203z	[X]Intent self poison antiparkinson drug unspecif place
U204.	[X]Intent self poison/exposure to psychotropic drug / [X]Overdose - antidepressant / [X]Overdose - amitriptyline / [X]Overdose - SSRI
U2040	[X]Int self poison/exposure to psychotropic drug at home
U2041	[X]Intent self poison psychotropic drug at res institut
U2042	[X]Int self poison psychotropic drug school/pub admin area
U2043	[X]Int self poison psychotropic drug in sport/athletic area
U2044	[X]Intent self pois psychotropic drug in street/highway

ZV111	[V]Personal history of affective disorder / [V]Personal history of manic-depressive psychosis / [V]Personal history of manic-depressive psychosis
U2045	[X]Intent self pois psychotropic drug trade/service area
U2046	[X]Int self pois psychotropic drug indust/construct area
U2047	[X]Int self poison/exposure to psychotropic drug on farm
U204y	[X]Int self poison psychotropic drug other spec place
U204z	[X]Intent self poison psychotropic drug unspecif place
U205.	[X]Intent self poison/exposure to narcotic drug / [X]Overdose - heroin
U2050	[X]Int self poison/exposure to narcotic drug at home
U2051	[X]Intent self poison narcotic drug at res institut
U2052	[X]Int self poison narcotic drug school/pub admin area
U2053	[X]Int self poison narcotic drug in sport/athletic area
U2055	[X]Intent self pois narcotic drug trade/service area
U2056	[X]Int self pois narcotic drug indust/construct area
8G6Z.	Anti-suicide psychotherapy NOS
146A.	H/O: attempted suicide
146B.	H/O: deliberate self harm

NONSPECIFIC PSYCHIATRIC CODES

146..	H/O: psychiatric disorder
146Z.	H/O: psychiatric disorder NOS

PSYCHOTROPIC MEDICATION TREATMENT CODES

67935979	Haloperidol 1.5mg/5ml oral suspension
81115998	Haloperidol 1mg/5ml oral suspension
79934979	Haloperidol 2mg/5ml oral solution
81081998	Haloperidol 1mg/5ml oral solution
79932979	Haloperidol 2mg/5ml oral suspension
79930979	Haloperidol 500micrograms/5ml oral solution
81467998	Haloperidol 10mg/5ml oral solution sugar free
87190998	Haloperidol 250micrograms/5ml oral suspension
91932990	Haloperidol 5mg/5ml oral solution sugar free
92815997	Haloperidol 2mg/5ml oral solution
93695998	Haloperidol 5mg/ml injection
96115990	Haloperidol 1.5mg tablets
95242990	Haloperidol 500microgram tablets
96242998	Haloperidol 5mg/5ml oral solution sugar free
96246998	Haloperidol 500microgram capsules
96245997	Haloperidol decanoate 100mg/1ml solution for injection ampoules
96247997	Haloperidol 10mg/ml oral solution
96248996	Haloperidol 5mg/5ml oral solution sugar free

96249997 Haloperidol 1.5mg tablets
96249996 Haloperidol 5mg tablets
96307992 Haloperidol decanoate 100mg/1ml solution for injection ampoules
96758992 Haloperidol 20mg/2ml injection
96889990 Haloperidol 5mg tablets
97135990 Haloperidol 500microgram tablets
83786998 Haloperidol 5mg/1ml solution for injection ampoules
97345998 Haloperidol 10mg/ml oral solution
97346997 Haloperidol 10mg tablets
97568992 Haloperidol 5mg/5ml oral solution sugar free
97944998 Haloperidol 5mg/1ml injection
97344998 Haloperidol decanoate 50mg/1ml solution for injection ampoules
97945997 Haloperidol 20mg tablets
97946996 Haloperidol 5mg tablets
98131989 Haloperidol 5mg/5ml oral solution sugar free
97946998 Haloperidol 500microgram capsules
98360988 Haloperidol 1.5mg tablets
98154990 Haloperidol 5mg tablets
98544990 Haloperidol 1.5mg tablets
98625989 Haloperidol 5mg/5ml oral solution sugar free
91921998 Haloperidol 1mg/ml sugar free Oral solution
81468998 Haloperidol 5mg/5ml oral solution sugar free
93695997 Haloperidol 20mg/2ml solution for injection ampoules
96244998 Haloperidol 500mcg tablets
96247996 Haloperidol 1mg/5ml oral solution
92815998 Haloperidol 1.5mg/5ml sugar free oral solution
96248997 Haloperidol 20mg tablets
96265992 Haloperidol 20mg tablets
96889988 Haloperidol 500microgram tablets
97344997 Haloperidol decanoate 100mg/1ml solution for injection ampoules
97346996 Haloperidol 10mg/5ml oral solution sugar free
97944997 Haloperidol 20mg/2ml injection
97945998 Haloperidol 10mg tablets
98080990 Haloperidol 1.5mg/5ml sugar free oral solution
98155990 Haloperidol 5mg/1ml solution for injection ampoules
83787998 Haloperidol 5mg/1ml solution for injection ampoules
98625988 Haloperidol 1mg/5ml oral solution
95086992 Haloperidol 1.5mg tablets
96245998 Haloperidol decanoate 50mg/1ml solution for injection ampoules
96248998 Haloperidol 10mg tablets
97135989 Haloperidol 1.5mg tablets
97346998 Haloperidol 5mg tablets
98544988 Haloperidol 5mg tablets

92815996 Haloperidol 10mg/5ml oral solution sugar free
96247998 Haloperidol 10mg/5ml oral solution sugar free
97345997 Haloperidol 10mg/2ml injection
96242997 Haloperidol 10mg/5ml oral liquid
98131990 Haloperidol 1.5mg tablets
97945996 Haloperidol 10mg/5ml oral solution sugar free
96249998 Haloperidol 500microgram tablets
98625990 Haloperidol 10mg/5ml oral solution sugar free
97946997 Haloperidol 1.5mg tablets
92542998 Lithium carbonate 400mg modified release tablets
93396997 Lithium with zinc sulphate 8% + 0.05% cream
93396998 Lithium succinate 8% / zinc sulfate 0.05% ointment
93397997 Lithium succinate 8% cream
93397998 Lithium succinate 8% ointment
96000996 Lithium citrate 509mg/5ml oral solution
96000998 Lithium citrate 564mg modified-release tablets
96002998 Lithium carbonate 450mg modified-release tablets
96004996 Lithium carbonate 300mg modified-release tablet
96004998 Lithium carbonate 200mg modified-release tablets
96865992 Lithium citrate 1.018g/5ml oral solution
97673992 Lithium chloride 400 mg sol
97705997 Lithium citrate 1.018g/5ml oral solution
98814998 Lithium carbonate 400mg modified-release tablets
97716998 Lithium citrate 1.018g/5ml oral solution
84977998 Lithium carbonate 200mg/5ml oral suspension
96000997 Lithium citrate 520mg/5ml oral solution sugar free
99858998 Lithium carbonate 250mg tablets
96003998 Lithium carbonate 400mg modified-release tablets
96335979 Lithium carbonate 400mg modified-release tablets
99217998 Lithium carbonate 200mg modified-release tablets
97674992 Lithium 250 mg cap
99465998 Lithium carbonate 450mg modified-release tablets
97979990 Lithium carbonate 400mg modified-release tablets
97534998 Lithium citrate 564mg modified release tablets
96004997 Lithium carbonate 250mg tablets
99217997 Lithium carbonate 400mg modified-release tablets
96001998 Lithium carbonate 300mg modified release tablets
97705998 Lithium citrate 509mg/5ml oral solution
93412998 Lithium carbonate 520mg/5ml sugar free liquid
52732979 Lithium citrate 509mg/5ml oral solution
85294998 Fluphenazine decanoate 100mg/1ml solution for injection ampoules
85295998 Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules
85299998 Fluphenazine decanoate 25mg/1ml solution for injection ampoules

85297998 Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules
85298998 Fluphenazine decanoate 50mg/2ml solution for injection ampoules
85300998 Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
85302998 Fluphenazine decanoate 25mg/1ml solution for injection ampoules
93032992 Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
85296998 Fluphenazine decanoate 100mg/1ml solution for injection ampoules
96342992 Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
96498998 Fluphenazine decanoate 50mg/2ml solution for injection ampoules
96500998 Fluphenazine enanthate 25mg/ml injection
96501997 Fluphenazine 2.5mg tablets
96742990 Fluphenazine decanoate 25mg/1ml solution for injection ampoules
98668990 Fluphenazine decanoate 100mg/1ml solution for injection ampoules
99408998 Fluphenazine enantate 25mg/1ml injection
99411997 Fluphenazine hydrochloride 2.5mg tablets
99414998 Fluphenazine decanoate 250mg/10ml oily injection
85303998 Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
96286990 Fluphenazine decanoate 25mg/1ml solution for injection ampoules
96501998 Fluphenazine 1mg tablets
99411996 Fluphenazine hydrochloride 5mg tablets
96498997 Fluphenazine decanoate 100mg/1ml solution for injection ampoules
85301998 Fluphenazine decanoate 50mg/2ml solution for injection ampoules
97466992 Fluphenazine hcl eli
99411998 Fluphenazine 1mg tablets
96501996 Fluphenazine 5mg tablets
98759998 Fluphenazine decanoate 100mg/1ml solution for injection ampoules
94164992 Perphenazine 8mg tablets
95575996 Perphenazine 4mg tablets
95575998 Perphenazine 5mg/ml injection
97786998 Perphenazine 2mg/5ml oral solution sugar free
98587998 Perphenazine 5mg/1ml injection
99651998 Perphenazine 2mg tablets
95575997 Perphenazine 2mg tablets
99651997 Perphenazine 4mg tablets
97877992 Perphenazine 8 mg tab
97786997 Perphenazine 4mg/5ml oral solution sugar free
94006997 Loxapine 25mg capsules
94006996 Loxapine 50mg capsules
94007997 Loxapine 25mg capsules
94007998 Loxapine 10mg capsules
94007996 Loxapine 50mg capsules
94006998 Loxapine 10mg capsules
54533979 Trifluoperazine 5mg tablets
59474979 Trifluoperazine 1mg/5ml oral solution sugar free

87435998 Trifluoperazine 5mg/5ml sugar free suspension
92623997 Trifluoperazine 1mg/5ml oral solution sugar free
92623996 Trifluoperazine 2mg modified-release capsules
54534979 Trifluoperazine 1mg tablets
92623998 Trifluoperazine 1mg tablets
95118996 Trifluoperazine 5mg/5ml oral solution sugar free
95118998 Trifluoperazine 15mg modified-release capsules
95143998 Tranylcypromine with trifluoperazine tablet
96586979 Trifluoperazine 1mg tablets
98052990 Trifluoperazine 5mg tablets
98206992 Trifluoperazine tab
99107997 Trifluoperazine 1mg/1ml injection
99108996 Trifluoperazine 10mg modified release capsules
95119997 Trifluoperazine 5mg tablets
99108998 Trifluoperazine 10mg/ml concentrate
99112998 Isopropamide iodide with trifluoperazine tablet
99280998 Tranylcypromine & trifluoperazine 10mg+1mg tablets
94626998 Trifluoperazine with tranylcypromine 1mg + 10mg tablet
95119996 Trifluoperazine 10mg modified-release capsules
98203992 Trifluoperazine 5mg/5ml oral solution sugar free
95607992 Trifluoperazine 1mg tablets
99107998 Trifluoperazine 15mg modified release capsules
99109996 Trifluoperazine 1mg/5ml oral solution sugar free
99109997 Trifluoperazine 5mg tablets
98400990 Trifluoperazine 1mg tablets
99109998 Trifluoperazine 1mg tablets
98052989 Trifluoperazine 1mg tablets
95118997 Trifluoperazine 1mg/ml injection
99108997 Trifluoperazine 2mg modified release capsules
95119998 Trifluoperazine 10mg/ml concentrate
82892998 Chlorpromazine 100mg tablets
64779979 Chlorpromazine 100mg/5ml oral suspension
93242998 Chlorpromazine hydrochloride 25mg/5ml syrup
93587998 Chlorpromazine 100mg suppositories
85702998 Chlorpromazine 50mg/2ml solution for injection ampoules
94107992 Chlorpromazine 50mg tablets
94761997 Chlorpromazine 50mg tablets
93593997 Chlorpromazine 100mg/5ml oral solution
94821992 Chlorpromazine 25mg tablets
95364990 Chlorpromazine 50mg tablets
95687990 Chlorpromazine 25mg/5ml oral solution
85704998 Chlorpromazine 25mg/1ml solution for injection ampoules
96102992 Chlorpromazine 50mg/2ml solution for injection ampoules

96673979 Chlorpromazine hydrochloride 25mg/5ml syrup
96689979 Chlorpromazine 50mg tablets
96689997 Chlorpromazine 50mg tablets
96690996 Chlorpromazine 25mg/5ml oral solution
96691997 Chlorpromazine 100mg tablets
96701979 Chlorpromazine hydrochloride 25mg tablets
96690998 Chlorpromazine 100mg/5ml oral solution
96919989 Chlorpromazine 100mg tablets
97021992 Chlorpromazine 50mg/2ml solution for injection ampoules
97134992 Chlorpromazine 200 mg tab
97131992 Chlorpromazine 25mg suppositories
97236989 Chlorpromazine 50mg tablets
97871998 Chlorpromazine hydrochloride 100mg suppositories
97880996 Chlorpromazine 50mg tablets
97880998 Chlorpromazine hydrochloride 10mg tablets
98062990 Chlorpromazine 25mg/5ml oral solution
97877998 Chlorpromazine hydrochloride 100mg/5ml sugar free suspension
98189990 Chlorpromazine 25mg tablets
98192989 Chlorpromazine 100mg tablets
99010990 Chlorpromazine 50mg tablets
93590998 Chlorpromazine 25mg/ml injection
94111992 Chlorpromazine 100mg tablets
95200992 Chlorpromazine hydrochloride 100mg/5ml sugar free suspension
59529979 Chlorpromazine 10mg capsules
96674979 Chlorpromazine 25mg/5ml oral solution
96689998 Chlorpromazine 25mg tablets
96691996 Chlorpromazine 25mg/5ml oral solution
97129992 Chlorpromazine hcl 10 mg inj
96702979 Chlorpromazine hydrochloride 10mg tablets
97236988 Chlorpromazine 100mg tablets
97874998 Chlorpromazine 50mg/2ml solution for injection ampoules
97880997 Chlorpromazine hydrochloride 25mg tablets
98192990 Chlorpromazine 50mg tablets
95365990 Chlorpromazine 25mg tablets
96689996 Chlorpromazine 100mg tablets
93593998 Chlorpromazine 100mg/5ml oral suspension
97132992 Chlorpromazine 50mg/2ml solution for injection ampoules
97879998 Chlorpromazine 100mg tablets
96691998 Chlorpromazine 10mg tablets
98192988 Chlorpromazine 25mg tablets
98186990 Chlorpromazine 50mg/2ml solution for injection ampoules
94761998 Chlorpromazine 25mg tablets
96690997 Chlorpromazine 50mg/5ml oral suspension

97236990 Chlorpromazine 25mg tablets
99007990 Chlorpromazine 25mg/5ml oral solution
96919990 Chlorpromazine 50mg tablets
96614992 Chlorpromazine 100mg/5ml oral suspension
98062989 Chlorpromazine 100mg/5ml oral solution
78405978 Aripiprazole 400mg powder and solvent for suspension for injection vials
78406978 Aripiprazole 400mg powder and solvent for suspension for injection vials
85832998 Aripiprazole 1mg/ml oral solution
85833998 Aripiprazole 15mg orodispersible tablets sugar free
85835998 Aripiprazole 1mg/ml oral solution
85837998 Aripiprazole 10mg orodispersible tablets sugar free
87090998 Aripiprazole 5mg tablets
87449998 Aripiprazole 15mg tablets
87450998 Aripiprazole 10mg tablets
85834998 Aripiprazole 10mg orodispersible tablets sugar free
85836998 Aripiprazole 15mg orodispersible tablets sugar free
87453998 Aripiprazole 10mg tablets
87448998 Aripiprazole 30mg tablets
87451998 Aripiprazole 30mg tablets
87089998 Aripiprazole 5mg tablets
89532979 Aripiprazole 5mg tablets
87452998 Aripiprazole 15mg tablets
83903998 Aripiprazole 9.75mg/1.3ml solution for injection vials
52748979 Risperidone 2mg tablets
55523979 Risperidone 25mg powder and solvent for suspension for injection vials
63094979 Risperidone 125micrograms/5ml oral solution
85038998 Risperidone 4mg orodispersible tablets sugar free
85039998 Risperidone 3mg orodispersible tablets sugar free
85040998 Risperidone 4mg orodispersible tablets sugar free
86983998 Risperidone 500microgram orodispersible tablets sugar free
88163998 Risperidone 37.5mg powder and solvent for suspension for injection vials
89908998 Risperidone 50mg powder and solvent for suspension for injection vials
90396998 Risperidone 2mg orodispersible tablets sugar free
91676998 Risperidone 25mg powder and solvent for suspension for injection vials
92107998 Risperidone 2mg orodispersible tablets sugar free
92908990 Risperidone 1mg/ml oral solution sugar free
92023998 Risperidone 500microgram tablets
92954990 Risperidone 3mg tablets
79816978 Risperidone 2mg tablets
93240998 Risperidone 4mg tablets
96554979 Risperidone 1mg tablets
98585996 Risperidone 3mg tablets
93240996 Risperidone 6mg tablets

98585998 Risperidone 1mg tablets
99637997 Risperidone 1mg/ml oral solution sugar free
99649996 Risperidone 3mg tablets
99649998 Risperidone 1mg tablets
86984998 Risperidone 500microgram orodispersible tablets sugar free
91968998 Risperidone 500microgram tablets
90395998 Risperidone 1mg orodispersible tablets sugar free
92491990 Risperidone 500microgram orodispersible tablets sugar free
92957990 Risperidone 500microgram tablets
95519998 Risperidone 50mg powder and solvent for suspension for injection vials
98585997 Risperidone 2mg tablets
99637998 Risperidone 4mg tablets
85042998 Risperidone 3mg orodispersible tablets sugar free
91374998 Risperidone 1mg orodispersible tablets sugar free
92953990 Risperidone 4mg tablets
99649997 Risperidone 2mg tablets
96914992 Risperidone 3mg tablets
92089998 Risperidone 37.5mg powder and solvent for suspension for injection vials
99637996 Risperidone 6mg tablets
93240997 Risperidone 1mg/ml oral solution sugar free
88164998 Risperidone 25mg powder and solvent for suspension for injection vials
52736979 Quetiapine 200mg tablets
59369979 Quetiapine 200mg modified-release tablets
58638979 Quetiapine 25mg tablets
58799979 Quetiapine 50mg modified-release tablets
59370979 Quetiapine 300mg modified-release tablets
55083979 Quetiapine 50mg modified-release tablets
59468979 Quetiapine 25mg tablets
63671979 Quetiapine 50mg/5ml oral suspension
66389979 Quetiapine 25mg/5ml oral solution
64621979 Quetiapine 50mg modified-release tablets
72638978 Quetiapine 400mg modified-release tablets
68593978 Quetiapine 400mg modified-release tablets
53079979 Quetiapine 150mg modified-release tablets
81923998 Quetiapine 150mg modified-release tablets
81236998 Quetiapine 12.5mg/5ml oral solution
82772998 Quetiapine 100mg/5ml oral suspension
83490998 Quetiapine 400mg modified-release tablets
83492998 Quetiapine 200mg modified-release tablets
83994998 Quetiapine 300mg modified-release tablets
83996998 Quetiapine 50mg modified-release tablets
87907998 Quetiapine 300mg tablets
88734996 Quetiapine 100mg tablets

88733997 Quetiapine 150mg tablets
88734998 Quetiapine 25mg+100mg+150mg tablets starter pack
88736998 Quetiapine 200mg tablets
88924979 Quetiapine 400mg modified-release tablets
63673979 Quetiapine 50mg/5ml oral solution
66395979 Quetiapine 125mg/5ml oral suspension
88737997 Quetiapine 25mg tablets
81473998 Quetiapine 25mg/5ml oral suspension
59467979 Quetiapine 25mg tablets
82773998 Quetiapine 100mg/5ml oral solution
72639978 Quetiapine 200mg modified-release tablets
83493998 Quetiapine 50mg modified-release tablets
83995998 Quetiapine 200mg modified-release tablets
88736997 Quetiapine 150mg tablets
88737998 Quetiapine starter pack
88733998 Quetiapine 200mg tablets
59469979 Quetiapine 25mg tablets
70478978 Quetiapine 50mg modified-release tablets
81924998 Quetiapine 150mg modified-release tablets
83993998 Quetiapine 400mg modified-release tablets
88938979 Quetiapine 300mg modified-release tablets
81113998 Quetiapine 12.5mg/5ml oral suspension
87908998 Quetiapine 300mg tablets
64622979 Quetiapine 50mg modified-release tablets
88734997 Quetiapine 25mg tablets
83491998 Quetiapine 300mg modified-release tablets
72640978 Quetiapine 300mg modified-release tablets
88737996 Quetiapine 100mg tablets
81419998 Paliperidone 100mg/1ml suspension for injection pre-filled syringes
54953979 Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes and paliperido for injectio
81422998 Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
81421998 Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes
81418998 Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
81423998 Paliperidone 100mg/1ml suspension for injection pre-filled syringes
81425998 Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes
84524998 Paliperidone 3mg modified-release tablets
81424998 Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
84526998 Paliperidone 6mg modified-release tablets
84523998 Paliperidone 6mg modified-release tablets
84525998 Paliperidone 9mg modified-release tablets
84527998 Paliperidone 3mg modified-release tablets
81420998 Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes

61131979 Olanzapine 15mg oral lyophilisates sugar free
61581979 Olanzapine 20mg oral lyophilisates sugar free
61145979 Olanzapine 20mg oral lyophilisates sugar free
61166979 Olanzapine 5mg oral lyophilisates sugar free
61165979 Olanzapine 10mg orodispersible tablets sugar free
61579979 Olanzapine 5mg oral lyophilisates sugar free
61583979 Olanzapine 15mg oral lyophilisates sugar free
64673979 Olanzapine 2.5mg/5ml oral suspension
61602979 Olanzapine 5mg oral lyophilisates sugar free
80972998 Olanzapine 15mg oral lyophilisates sugar free
80970998 Olanzapine 20mg oral lyophilisates sugar free
80974998 Olanzapine 15mg oral lyophilisates sugar free
80979998 Olanzapine 5mg oral lyophilisates sugar free
80981998 Olanzapine 5mg oral lyophilisates sugar free
80977998 Olanzapine 10mg orodispersible tablets sugar free
81041998 Olanzapine 5mg orodispersible tablets sugar free
82202998 Olanzapine embonate 210mg powder and solvent for suspension for injection vials
82199998 Olanzapine embonate 300mg powder and solvent for suspension for injection vials
85377998 Olanzapine 20mg oral lyophilisates sugar free
86325998 Olanzapine 20mg oral lyophilisates sugar free
87647998 Olanzapine 10mg powder for solution for injection vials
89567997 Olanzapine 7.5mg tablets
89569998 Olanzapine 5mg tablets
90659997 Olanzapine 5mg oral lyophilisates sugar free
90664998 Olanzapine 2.5mg tablets
89569996 Olanzapine 10mg tablets
91618997 Olanzapine 10mg oral lyophilisates sugar free
91828990 Olanzapine 20mg oral lyophilisates sugar free
91870990 Olanzapine 10mg tablets
97111998 Olanzapine 15mg tablets
97995998 Olanzapine 15mg oral lyophilisates sugar free
61610979 Olanzapine 15mg oral lyophilisates sugar free
80971998 Olanzapine 20mg oral lyophilisates sugar free
80976998 Olanzapine 10mg orodispersible tablets sugar free
82198998 Olanzapine embonate 405mg powder and solvent for suspension for injection vials
80980998 Olanzapine 5mg oral lyophilisates sugar free
85376998 Olanzapine 20mg oral lyophilisates sugar free
87646998 Olanzapine 10mg injection (powder for reconstitution)
89567998 Olanzapine 5mg tablets
90659996 Olanzapine 10mg orodispersible tablets sugar free
91364998 Olanzapine 15mg oral lyophilisates sugar free
91869990 Olanzapine 15mg tablets
97433998 Olanzapine 15mg tablets

80978998 Olanzapine 10mg orodispersible tablets sugar free
80969998 Olanzapine 20mg oral lyophilisates sugar free
82201998 Olanzapine embonate 300mg powder and solvent for suspension for injection vials
89567996 Olanzapine 10mg tablets
90659998 Olanzapine 2.5mg tablets
80973998 Olanzapine 15mg oral lyophilisates sugar free
96421979 Olanzapine 2.5mg tablets
86324998 Olanzapine 20mg oral lyophilisates sugar free
91618998 Olanzapine 5mg oral lyophilisates sugar free
81040998 Olanzapine 10mg orodispersible tablets sugar free
61585979 Olanzapine 10mg orodispersible tablets sugar free
89569997 Olanzapine 7.5mg tablets
82798998 Clozapine 50mg/ml oral suspension sugar free
82799998 Clozapine 50mg/ml oral suspension sugar free
82801998 Clozapine 200mg tablets
82800998 Clozapine 200mg tablets
82802998 Clozapine 50mg tablets
87019998 Clozapine 100mg tablets
87340998 Clozapine 100mg tablets
93595997 Clozapine 100mg tablets
87020998 Clozapine 25mg tablets
93595998 Clozapine 25mg tablets
93596997 Clozapine 100mg tablets
87341998 Clozapine 25mg tablets
93596998 Clozapine 25mg tablets
82803998 Clozapine 50mg tablets
80548979 Clomipramine 50mg/5ml oral solution
83878998 Clomipramine 50mg/5ml oral suspension
93360992 Clomipramine hydrochloride 10mg capsules
96638998 Clomipramine 75mg modified-release tablets
96639998 Clomipramine 25mg/5ml oral solution
96640997 Clomipramine 25mg capsules
93358992 Clomipramine 50mg capsules
96901988 Clomipramine 50mg capsules
96637998 Clomipramine hydrochloride 25mg/2ml injection
97167992 Clomipramine 25 mg tab
97548989 Clomipramine 25mg capsules
97773989 Clomipramine 25mg capsules
98144997 Clomipramine 25mg capsules
98340990 Clomipramine 10mg capsules
98340988 Clomipramine 50mg capsules
99297989 Clomipramine 25mg capsules
99794992 Clomipramine hydrochloride 25mg/2ml injection

97548988 Clomipramine 50mg capsules
96640998 Clomipramine 10mg capsules
98144998 Clomipramine 10mg capsules
99297988 Clomipramine 50mg capsules
96640996 Clomipramine 50mg capsules
98142998 Clomipramine 75mg modified-release tablets
97548990 Clomipramine 10mg capsules
96901989 Clomipramine 25mg capsules
98144996 Clomipramine 50mg capsules
99297990 Clomipramine 10mg capsules
98340989 Clomipramine 25mg capsules
98143998 Clomipramine hydrochloride 25mg/5ml syrup
94249992 Nortriptyline 10mg/5ml oral solution
95695997 Nortriptyline 25mg capsule
95695998 Nortriptyline 10mg capsule
95695996 Nortriptyline 10mg/5ml oral solution
95696997 Nortriptyline 25mg tablets
96248979 Nortriptyline 10mg tablets
98152997 Nortriptyline 25mg tablets
98154996 Nortriptyline hydrochloride 10mg/5ml liquid
98154998 Nortriptyline hydrochloride 10mg capsules
98152998 Nortriptyline 10mg tablets
98154997 Nortriptyline hydrochloride 25mg capsules
95696998 Nortriptyline 10mg tablets
94630997 Nortriptyline 30mg / fluphenazine 1.5mg tablets
94630998 Nortriptyline 10mg / fluphenazine 500microgram tablets
96499998 Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
97632998 Fluphenazine hydrochloride & nortriptyline 1.5mg+30mg tablets
97634998 Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
81084998 Amitriptyline 10mg/5ml oral solution
70290979 Amitriptyline 2.5mg/5ml oral solution
92808996 Amitriptyline 10mg/5ml oral solution
81085998 Amitriptyline 10mg/5ml oral solution
92808997 Amitriptyline 25mg/5ml oral solution sugar free
94704997 Amitriptyline 25mg / chlordiazepoxide 10mg capsules
94771990 Amitriptyline 25mg tablets
96924998 Amitriptyline 10mg/ml injection
94067992 Amitriptyline 75 mg tab
96925997 Amitriptyline 50mg modified-release capsules
96925998 Amitriptyline 25mg modified-release capsules
97223998 Amitriptyline 10mg tablets
98128998 Amitriptyline 10mg/5ml sugar free oral solution
98129998 Amitriptyline hydrochloride 100mg/10ml injection

98130997 Amitriptyline hydrochloride 25mg tablets
98150996 Amitriptyline hydrochloride 50mg tablets
98067989 Amitriptyline 50mg/5ml oral solution sugar free
98138997 Amitriptyline hydrochloride 50mg modified release capsules
99824992 Amitriptyline 100 mg tab
99861989 Amitriptyline 25mg tablets
99826992 Amitriptyline 200 mg tab
99863989 Amitriptyline 25mg tablets
99862990 Amitriptyline 25mg tablets
98150998 Amitriptyline hydrochloride 10mg tablets
99864988 Amitriptyline 50mg tablets
99864990 Amitriptyline 10mg tablets
99866988 Amitriptyline 50mg tablets
99866990 Amitriptyline 10mg tablets
99868988 Amitriptyline 50mg tablets
99869989 Amitriptyline 50mg tablets
99868990 Amitriptyline 10mg tablets
99870988 Amitriptyline 50mg tablets
99870990 Amitriptyline 10mg tablets
99871989 Amitriptyline 25mg tablets
92808998 Amitriptyline 50mg/5ml oral solution sugar free
96925996 Amitriptyline 75mg modified-release capsules
81024979 Amitriptyline 5mg/5ml oral suspension
98067990 Amitriptyline 25mg/5ml oral solution sugar free
98130996 Amitriptyline hydrochloride 50mg tablets
97223997 Amitriptyline 25mg tablets
98138998 Amitriptyline hydrochloride 25mg modified release capsules
98343998 Amitriptyline 25mg / chlordiazepoxide 10mg capsules
99825992 Amitriptyline 300 mg tab
99861990 Amitriptyline 10mg tablets
99865990 Amitriptyline 25mg tablets
99863990 Amitriptyline 10mg tablets
99869988 Amitriptyline 25mg tablets
99870989 Amitriptyline 25mg tablets
99871990 Amitriptyline 10mg tablets
94704998 Amitriptyline 12.5mg / chlordiazepoxide 5mg capsules
98129997 Amitriptyline hydrochloride 75mg modified release capsules
98150997 Amitriptyline hydrochloride 25mg tablets
99864989 Amitriptyline 25mg tablets
99871988 Amitriptyline 50mg tablets
98130998 Amitriptyline hydrochloride 10mg tablets
96891992 Amitriptyline 25mg/5ml oral solution sugar free
99868989 Amitriptyline 25mg tablets

97223996 Amitriptyline 50mg tablets
99863988 Amitriptyline 50mg tablets
99869990 Amitriptyline 10mg tablets
99866989 Amitriptyline 25mg tablets
99472998 Amitriptyline & chlordiazepoxide 12.5mg+5mg capsules
94076990 Amitriptyline 25mg tablets
99867989 Amitriptyline 25mg tablets
98067988 Amitriptyline 10mg/5ml oral solution
94703997 Amitriptyline 25mg / Perphenazine 2mg tablets
94703998 Amitriptyline 10mg / perphenazine 2mg tablets
95574997 Amitriptyline 25mg / Perphenazine 2mg tablets
95574998 Perphenazine 2mg with amitriptyline 10mg tablet
99017997 Amitriptyline hydrochloride & perphenazine 10mg+2mg tablets
99017998 Amitriptyline 25mg / Perphenazine 2mg tablets
96442998 Desipramine 25mg tablets
98146998 Desipramine hydrochloride 25mg tablets
62948979 Imipramine 25mg/5ml oral solution sugar free
85437998 Imipramine oral solution
93839990 Trimipramine 50mg capsules
82432998 Imipramine 25mg/5ml oral solution sugar free
93841990 Trimipramine 10mg tablets
93840990 Trimipramine 25mg tablets
95107996 Trimipramine 50mg capsules
95107998 Trimipramine 10mg tablets
96130998 Imipramine 25mg/5ml oral solution
96687992 Imipramine 100 mg tab
95155992 Imipramine 25mg tablets
97112997 Imipramine 25mg tablets
97593992 Imipramine hcl 12.5 mg inj
98136997 Trimipramine 25mg tablets
98140998 Imipramine hydrochloride 10mg tablets
98212992 Trimipramine 50mg capsules
99554990 Imipramine 10mg tablets
98140996 Imipramine hydrochloride 25mg/5ml syrup
99555990 Imipramine 10mg tablets
95156992 Imipramine 50 mg tab
97091998 Imipramine hydrochloride 10mg tablets
98136996 Trimipramine 50mg capsules
95107997 Trimipramine 25mg tablets
99554989 Imipramine 25mg tablets
99556989 Imipramine 25mg tablets
96265979 Imipramine 25mg tablets
98140997 Imipramine 25mg tablets

98136998 Trimipramine 10mg tablets
99555989 Imipramine 25mg tablets
95154992 Imipramine 75 mg tab
97112998 Imipramine 10mg tablets
98149990 Imipramine 25mg tablets
86996998 Duloxetine 60mg gastro-resistant capsules
86997998 Duloxetine 30mg gastro-resistant capsules
86998998 Duloxetine 60mg gastro-resistant capsules
87334998 Duloxetine 40mg gastro-resistant capsules
87335998 Duloxetine 20mg gastro-resistant capsules
87336998 Duloxetine 40mg gastro-resistant capsules
86999998 Duloxetine 30mg gastro-resistant capsules
87337998 Duloxetine 20mg gastro-resistant capsules
64642979 Venlafaxine 37.5mg/5ml oral solution
52700979 Venlafaxine 150mg modified-release capsules
64640979 Venlafaxine 75mg/5ml oral solution
79303978 Venlafaxine 37.5mg modified-release capsules
52165979 Venlafaxine 150mg modified-release tablets
52164979 Venlafaxine 75mg modified-release tablets
79304978 Venlafaxine 37.5mg modified-release capsules
80024978 Venlafaxine 150mg modified-release tablets
81506998 Venlafaxine 37.5mg modified-release tablets
81750998 Venlafaxine 75mg modified-release capsules
81930998 Venlafaxine 75mg modified-release capsules
82874998 Venlafaxine 150mg modified-release capsules
82191998 Venlafaxine 75mg modified-release capsules
82959998 Venlafaxine 225mg modified-release tablets
82962998 Venlafaxine 150mg modified-release tablets
83074998 Venlafaxine 150mg modified-release capsules
83145998 Venlafaxine 150mg modified-release capsules
83157998 Venlafaxine 150mg modified-release tablets
83162998 Venlafaxine 75mg tablets
83204998 Venlafaxine 150mg modified-release capsules
83114998 Venlafaxine 150mg modified-release capsules
83264998 Venlafaxine 150mg modified-release capsules
83217998 Venlafaxine 150mg modified release capsules
88755998 Venlafaxine 75mg modified-release capsules
86431998 Venlafaxine 37.5mg/5ml oral suspension
88776998 Venlafaxine 75mg modified-release capsules
92597990 Venlafaxine 37.5mg tablets
96023979 Venlafaxine 150mg modified-release capsules
83149998 Venlafaxine 150mg modified-release capsules
96033979 Venlafaxine 75mg modified-release capsules

83159998 Venlafaxine 150mg modified-release tablets
99896996 Venlafaxine 50mg tablets
99896998 Venlafaxine 37.5mg tablets
81505998 Venlafaxine 37.5mg modified-release tablets
96054979 Venlafaxine 75mg tablets
81929998 Venlafaxine 150mg modified-release capsules
82540998 Venlafaxine 75mg modified-release capsules
82961998 Venlafaxine 225mg modified-release tablets
83146998 Venlafaxine 75mg modified-release capsules
83163998 Venlafaxine 37.5mg tablets
83075998 Venlafaxine 75mg modified-release capsules
83218998 Venlafaxine 75mg modified release capsules
88755997 Venlafaxine 150mg modified-release capsules
92596990 Venlafaxine 75mg tablets
83158998 Venlafaxine 75mg modified-release tablets
98336997 Venlafaxine 75mg tablets
98336996 Venlafaxine 50mg tablets
99896997 Venlafaxine 75mg tablets
81749998 Venlafaxine 150mg modified-release capsules
82875998 Venlafaxine 75mg modified-release capsules
83115998 Venlafaxine 75mg modified-release capsules
83265998 Venlafaxine 75mg modified-release capsules
96022979 Venlafaxine 150mg modified-release capsules
83160998 Venlafaxine 75mg modified-release tablets
98336998 Venlafaxine 37.5mg tablets
82190998 Venlafaxine 150mg modified-release capsules
83150998 Venlafaxine 75mg modified-release capsules
88776997 Venlafaxine 150mg modified-release capsules
80023978 Venlafaxine 75mg modified-release tablets
83205998 Venlafaxine 75mg modified-release capsules
82963998 Venlafaxine 75mg modified-release tablets
96034979 Venlafaxine 75mg modified-release capsules
96029979 Venlafaxine 150mg modified-release capsules
69604979 Citalopram 20mg/5ml oral suspension
69605979 Citalopram 10mg/5ml oral suspension
82791998 Escitalopram 20mg/ml oral drops sugar free
69606979 Citalopram 10mg/5ml oral suspension
85970998 Escitalopram 10mg/ml drops
85971998 Escitalopram 10mg/ml oral drops sugar free
87662998 Escitalopram 5mg tablets
88285998 Escitalopram 10mg tablets
91380997 Citalopram 10mg tablets
91395998 Citalopram 20mg tablets

92172998 Citalopram 40mg/ml oral drops sugar free
91395996 Citalopram 40mg tablets
94880990 Citalopram 40mg tablets
93946990 Citalopram 40mg tablets
94894990 Citalopram 20mg tablets
94936990 Citalopram 40mg tablets
95269990 Citalopram 40mg tablets
95334990 Citalopram 20mg tablets
95418990 Citalopram 40mg tablets
95271990 Citalopram 10mg tablets
95421990 Citalopram 10mg tablets
95632990 Citalopram 20mg tablets
95666990 Citalopram 40mg tablets
95668990 Citalopram 10mg tablets
82790998 Escitalopram 20mg/ml oral drops sugar free
95704990 Citalopram 20mg tablets
93994990 Citalopram 10mg tablets
95995979 Citalopram 10mg tablets
91671998 Escitalopram 10mg tablets
91380998 Citalopram 20mg tablets
98088998 Escitalopram 20mg tablets
87663998 Escitalopram 5mg tablets
94893990 Citalopram 40mg tablets
93948990 Citalopram 10mg tablets
94937990 Citalopram 20mg tablets
95333990 Citalopram 40mg tablets
95420990 Citalopram 20mg tablets
95633990 Citalopram 10mg tablets
98561998 Escitalopram 20mg tablets
95703990 Citalopram 40mg tablets
91380996 Citalopram 40mg tablets
92174998 Citalopram 40mg/ml oral drops sugar free
95335990 Citalopram 10mg tablets
95667990 Citalopram 20mg tablets
94895990 Citalopram 10mg tablets
87251998 Citalopram 10mg tablets
93996990 Citalopram 20mg tablets
95631990 Citalopram 40mg tablets
95270990 Citalopram 20mg tablets
91395997 Citalopram 10mg tablets
95705990 Citalopram 10mg tablets
96345989 Fluvoxamine 100mg tablets
96493997 Fluvoxamine 100mg tablets

96492998 Fluvoxamine 50mg tablets
96492997 Fluvoxamine 100mg tablets
96810989 Fluvoxamine 100mg tablets
96493998 Fluvoxamine 50mg tablets
66183979 Sertraline 25mg/5ml oral suspension
66185979 Sertraline 20mg/5ml oral suspension
79261979 Sertraline 100mg/5ml oral suspension
66187979 Sertraline 150mg/5ml oral suspension
86159998 Sertraline 50mg/5ml oral suspension
92729990 Sertraline 100mg tablets
92728990 Sertraline 50mg tablets
93173998 Sertraline 50mg tablets
93174998 Sertraline 50mg tablets
93732990 Sertraline 100mg tablets
93842990 Sertraline 100mg tablets
93173997 Sertraline 100mg tablets
93694990 Sertraline 50mg tablets
93843990 Sertraline 50mg tablets
93749990 Sertraline 50mg tablets
93174997 Sertraline 100mg tablets
75904978 Fluoxetine 20mg dispersible tablets sugar free
84403998 Fluoxetine 20mg/5ml oral solution sugar free
76398978 Fluoxetine 20mg dispersible tablets sugar free
82367998 Fluoxetine 10mg tablets
84436998 Fluoxetine 20mg/5ml oral solution sugar free
90159998 Fluoxetine hydrochloride 20mg capsules
90814998 Fluoxetine 20mg capsules
94447996 Fluoxetine 60mg capsules
94447998 Fluoxetine 20mg capsules
94490997 Fluoxetine 20mg/5ml oral solution
93066990 Fluoxetine 20mg capsules
95610990 Fluoxetine 60mg capsules
95820990 Fluoxetine 20mg/5ml oral solution sugar free
95388990 Fluoxetine 20mg capsules
96162979 Fluoxetine 20mg capsules
96606990 Fluoxetine 20mg capsules
96272990 Fluoxetine 20mg capsules
96651990 Fluoxetine 20mg capsules
96659990 Fluoxetine 20mg capsules
99592998 Fluoxetine hydrochloride 20mg capsules
96709990 Fluoxetine 20mg capsules
91928990 Fluoxetine 20mg/5ml oral solution sugar free
94447997 Fluoxetine 20mg/5ml oral solution sugar free

95813990 Fluoxetine 20mg/5ml oral solution sugar free
94490998 Fluoxetine 20mg capsules
75905978 Fluoxetine 20mg dispersible tablets sugar free
96643990 Fluoxetine 20mg capsules
96654990 Fluoxetine 20mg capsules
96168979 Fluoxetine 20mg capsules
96729990 Fluoxetine 20mg capsules
93905990 Fluoxetine 20mg capsules
95426990 Fluoxetine 20mg/5ml oral solution sugar free
96281990 Fluoxetine 20mg capsules
96647990 Fluoxetine 20mg capsules
94490996 Fluoxetine hydrochloride 60mg capsules
96674990 Fluoxetine 20mg capsules
96155979 Fluoxetine 20mg/5ml oral solution sugar free
90766998 Fluoxetine hydrochloride 20mg/5ml oral liquid
96644990 Fluoxetine 20mg capsules
54494979 Paroxetine 10mg tablets
84807998 Paroxetine 10mg tablets
85382998 Paroxetine 10mg tablets
93487990 Paroxetine 30mg tablets
93489997 Paroxetine 30mg tablets
93490996 Paroxetine 10mg/5ml oral solution
95028990 Paroxetine 30mg tablets
93490998 Paroxetine 20mg tablets
95332990 Paroxetine 20mg tablets
93489996 Paroxetine 10mg/5ml oral suspension sugar free
93489998 Paroxetine 20mg tablets
95578990 Paroxetine 20mg tablets
95350990 Paroxetine 20mg tablets
95007990 Paroxetine 30mg tablets
93490997 Paroxetine 30mg tablets
96087990 Paroxetine 20mg tablets
95051990 Paroxetine 20mg tablets
54495979 Paroxetine 10mg tablets
92309998 Bupropion 150mg modified-release tablets
92311998 Bupropion 150mg modified-release tablets
65255979 Trazodone 25mg/5ml oral suspension
65253979 Trazodone 50mg/5ml oral solution sugar free
65263979 Trazodone 150mg/5ml oral suspension
65261979 Trazodone 250mg/5ml oral solution
95141997 Trazodone 150mg modified-release tablets
95142997 Trazodone 100mg capsules
95141998 Trazodone 50mg/5ml oral solution sugar free

95527990 Trazodone 150mg tablets
96422988 Trazodone 150mg tablets
96295989 Trazodone 100mg capsules
96422990 Trazodone 50mg capsules
96443989 Trazodone 100mg capsules
96726989 Trazodone 100mg capsules
98312997 Trazodone hydrochloride 150mg modified release tablets
98486996 Trazodone 150mg tablets
65249979 Trazodone 75mg/5ml oral solution
98486998 Trazodone 50mg capsules
95142998 Trazodone 50mg capsules
96295990 Trazodone 50mg capsules
96443988 Trazodone 150mg tablets
96726990 Trazodone 50mg capsules
98486997 Trazodone 100mg capsules
96295988 Trazodone 150mg tablets
96443990 Trazodone 50mg capsules
95142996 Trazodone 150mg tablets
98312998 Trazodone hydrochloride 50mg/5ml liquid
96422989 Trazodone 100mg capsules
58745979 Mirtazapine 45mg orodispersible tablets
58747979 Mirtazapine 15mg tablets
86982998 Mirtazapine 15mg tablets
87684998 Mirtazapine 45mg orodispersible tablets
86981998 Mirtazapine 45mg tablets
87685998 Mirtazapine 15mg orodispersible tablets
87687998 Mirtazapine 15mg tablets
87946998 Mirtazapine 30mg orodispersible tablets
87430998 Mirtazapine 15mg/ml oral solution sugar free
88717998 Mirtazapine 30mg tablets
90125979 Mirtazapine 15mg tablets
92903990 Mirtazapine 45mg orodispersible tablets
92813990 Mirtazapine 45mg tablets
92979990 Mirtazapine 45mg orodispersible tablets
92988990 Mirtazapine 15mg tablets
93178990 Mirtazapine 45mg orodispersible tablets
94035990 Mirtazapine 45mg tablets
92981990 Mirtazapine 15mg tablets
94126990 Mirtazapine 30mg tablets
94773990 Mirtazapine 30mg tablets
94400990 Mirtazapine 45mg tablets
87945998 Mirtazapine 30mg orodispersible tablets
90094979 Mirtazapine 30mg orodispersible tablets

94847990	Mirtazapine 30mg tablets
92814990	Mirtazapine 15mg tablets
92980990	Mirtazapine 30mg orodispersible tablets
92992990	Mirtazapine 45mg orodispersible tablets
94037990	Mirtazapine 15mg tablets
94401990	Mirtazapine 15mg tablets
87686998	Mirtazapine 45mg orodispersible tablets
92986990	Mirtazapine 45mg orodispersible tablets
94250990	Mirtazapine 15mg tablets
88715998	Mirtazapine 30mg tablets
92454990	Mirtazapine 15mg tablets
93180990	Mirtazapine 15mg tablets
94797990	Mirtazapine 30mg tablets
92906990	Mirtazapine 15mg tablets

COUNSELLING TREATMENT CODES

7L1a.00	Cognitive behavioural therapy
7L1a000	Cognitive behavioural therapy by unidisciplinary team
7L1a100	Cognitive behavioural therapy by multidisciplinary team
7L1ay00	Other specified cognitive behavioural therapy
7L1az00	Cognitive behavioural therapy NOS
8G1..00	General psychotherapy
8G10.00	Psychotherapy - behavioural
8G11.00	Psychotherapy - cognitive
8G12.00	Psychotherapy - psychodynamic
8G13.00	Cognitive-behaviour therapy
8G14.00	Cognitive analytic therapy
8G15.00	Computerised cognitive behavioural therapy
Z5...00	Psychotherapy
Z52..00	Cognitive and behavioural therapy
Z521.00	Cognitive - behaviour therapy
Z521.11	CBT - Cognitive - behaviour therapy
Z521.12	Cognitive-behavioural therapy approach
Z521.13	Cognitive-behaviour therapy
Z521100	Generic cognitive behavioural therapy
Z522.00	Behavioural psychotherapy
Z522.11	Behaviour therapy
Z522.13	Cognitive therapy approach
Z522.14	Cognitive approach
Z522.16	Structural psychotherapy
Z4I..00	Psychodynamic interventions relating to emotions
Z4I..11	Psychodynamic interventions relating to feelings
Z5A..00	Psychoanalytic and psychodynamic therapy
Z5A..11	Psychoanalytical - psychodynamic therapy

Z5A..12	Explorative psychotherapy
Z5A3.00	Psychodynamic psychotherapy
Z5A3100	Long-term psychodynamic psychotherapy
Z5A3400	Psychodynamic-interpersonal psychotherapy
Z5A4.00	Brief focal psychodynamic therapy
8G9Z.00	Other psychotherapy NOS
Z523.00	Cognitive therapy
Z523.11	Cognitive therapy approach
Z523.12	Cognitive approach
Z523100	Beck's cognitive therapy
Z523200	Rational emotive therapy
Z523211	Rational emotive therapy
Z523300	Cognitive restructuring

Appendix 4. Medline and Embase search strategy for predictors of adverse psychiatric effects from levetiracetam

1. (psychiatric or depress* or anxi* or mani* or psycho* or suicid*).tw
2. (levetiracetam or keppra).tw
3. (adverse effect*).tw
4. 1 and 2 and 3

Appendix 5. Questionnaire used to rank all 36 items considered important in predicting the risk of psychiatric adverse events in patients with epilepsy receiving levetiracetem.

Psychiatric adverse effects from levetiracetam: Delphi Consensus Exercise Round 1

PARTICIPANT DETAILS

Your code: [ ]

Medical specialty: [ ]

Number of years of practice in your specialty [ ]

INITIAL CHECKLIST: this first DELPHI survey is designed to gather opinion on what clinical features are important in determining whether a patient will develop psychiatric adverse effects following initiation of levetiracetam for epilepsy.

Indicate your opinion on each criterion using the following guide:

1: Criterion not important at all
2: Criterion not very important
3: Criterion of equivocal importance
4: Criterion somewhat important
5: Criterion very important
No judgement: No opinion on the criterion.

Please circle or bold your selection

Item Number	Feature	Rank					
DEMOGRAPHICS							
1	Patient age	1	2	3	4	5	No judgement
Additional comments							
2	Gender	1	2	3	4	5	No judgement
Additional comments							
MEDICAL AND PSYCHIATRIC HISTORY							
3	Duration of epilepsy	1	2	3	4	5	No judgement

Item Number	Feature	Rank					
Additional comments							
4	Drug resistant epilepsy	1	2	3	4	5	No judgement
Additional comments							
5	History of depression	1	2	3	4	5	No judgement
Additional comments							
6	History of an anxiety disorder	1	2	3	4	5	No judgement
Additional comments							
7	History of mania	1	2	3	4	5	No judgement
Additional comments							
8	History of psychosis	1	2	3	4	5	No judgement
Additional comments							
9	History of any other psychiatric disorder	1	2	3	4	5	No judgement
Additional comments							
10	History of a conversion disorder	1	2	3	4	5	No judgement
Additional comments							
11	Charlson Comorbidity Index Score*	1	2	3	4	5	No judgement
Additional comments							
12	Post-traumatic epilepsy	1	2	3	4	5	No judgement
Additional comments							
13	History of febrile seizures	1	2	3	4	5	No judgement
Additional comments							
14	History of status epilepticus	1	2	3	4	5	No judgement
Additional comments							

Item Number	Feature	Rank					
15	History of mild cognitive impairment or dementia	1	2	3	4	5	No judgement
Additional comments							
16	History of neurosurgery	1	2	3	4	5	No judgement
Additional comments							
17	Prolonged post-ictal state	1	2	3	4	5	No judgement
Additional comments							
MEDICATIONS							
18	Levetiracetam dose	1	2	3	4	5	No judgement
Additional comments							
19	Number of concurrent AEDs	1	2	3	4	5	No judgement
Additional comments							
20	Concurrent use of phenytoin	1	2	3	4	5	No judgement
Additional comments							
21	Concurrent use of phenobarbital	1	2	3	4	5	No judgement
Additional comments							
22	Concurrent use of valproic acid	1	2	3	4	5	No judgement
Additional comments							
23	Concurrent use of ethosuximide	1	2	3	4	5	No judgement
Additional comments							
24	Concurrent use of carbamazepine	1	2	3	4	5	No judgement
Additional comments							
25	Concurrent use of oxcarbazepine	1	2	3	4	5	No judgement
Additional comments							
26	Concurrent use of clobazam	1	2	3	4	5	No

Item Number	Feature	Rank					
							judgement
Additional comments							
27	Concurrent use of lamotrigine	1	2	3	4	5	No judgement
Additional comments							
28	Concurrent use of topiramate	1	2	3	4	5	No judgement
Additional comments							
29	Concurrent use of lacosamide	1	2	3	4	5	No judgement
Additional comments							
30	Concurrent use of perampanel	1	2	3	4	5	No judgement
Additional comments							
31	Levetiracetam daily dose	1	2	3	4	5	No judgement
Additional comments							
32	Current or previous prescription for any psychotropic medication	1	2	3	4	5	No judgement
Additional comments							
SOCIAL HISTORY							
33	Socioeconomic status as defined by the Townsend Deprivation Index**	1	2	3	4	5	No judgement
Additional comments							
34	Recreational drug use	1	2	3	4	5	No judgement
Additional comments							
HEALTH CARE UTILISATION							
35	Number of outpatient visits in the previous year	1	2	3	4	5	No judgement
Additional comments							
36	Number of ER visits in the last year	1	2	3	4	5	No judgement
Additional comments							

*Charlson Comorbidity Index Score was designed to predict a patient's ten-year mortality though it is often used for other outcomes aside from death. The components and weights of the scale are as follows: Myocardial infarction (1 point) Congestive heart failure (1 point), Peripheral vascular disease (1 point), Dementia (1 point), Mild cerebrovascular disease (1 point), Chronic lung disease (1 point), Connective tissue disease (1 point), Peptic ulcer disease (1 point), Mild chronic liver disease (1 point), Diabetes (1 point), Hemiplegia (2 points), Moderate to severe renal disease (2 points), Diabetes with end-organ damage (2 points), Tumour without metastases (2 points), Leukemia (2 points), Lymophoma (2 points), Moderate to severe chronic liver disease (3 points), Metastatic solid tumour (6 points), AIDS (6 points)

**The Townsend Deprivation Index is a measure of material deprivation that uses the following four variables: unemployment (as a percentage of those aged 16 and older who are economically active), non-car ownership (as a percentage of all households), non-home ownership (as a percentage of all households), and household overcrowding. This is commonly calculated for an area or region using census data specific to particular postal codes.

In your opinion are all relevant clinical characteristics included in this initial checklist?

Yes ☐ No ☐

If, in your opinion, there are important clinical characteristics missing please list them below:

Thank you for your help.