# Machine learning and big data for personalized epilepsy treatment

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- But what is a girl addicted to fun supposed to do
Maddy Bishop

# ABSTRACT

Finding an effective anti-seizure medication (ASM) with minimal side effects is a challenge. Patient characteristics are used to guide treatment selection, but about half of the patients with epilepsy do not achieve seizure freedom with their first ASM. While randomized controlled trials are the gold standard for estimating treatment efficacy, they may not always be clinically relevant, especially for rare conditions. Registers are valuable sources of data because they can contain many patients, are accessible, and are updated regularly. The aim of the present research is to evaluate registers and develop machine learning algorithms for personalized medicine in epilepsy.

We used prescriptions, in- and outpatient data, and mortality data from national Swedish registers to model ASM use of patients. As a bundled estimation of efficacy and tolerability, retention rate was used as the measure of outcome.

The results indicate that using register data to estimate retention of ASMs is feasible and personalized ASM selection can potentially improve patient outcomes. Retention rates from registers are similar to that of RCTs and meta-analyses of RCTs. In an analysis of patients with epilepsy and comorbidities, there was a potential improvement of 14-21% of the 5-year retention rate for the initial ASM (Paper I). Ranking of ASMs for patient cases based on retention rates from register data is similar to suggestions based on expert advice (Paper II). We also studied ASM use in children, a group with limited evidence (Paper III). Specialized machine learning algorithms can potentially be a useful source of information for doctors for selecting ASMs (Paper IV).

In conclusion, this research highlights the potential of registers as a data source for personalized medicine. Machine learning trained on register data can be used to predict the efficacy of ASMs, but the methodology needs further development and clinical verification.



**Keywords**: anti-seizure medication, personalized treatment, machine learning

# SAMMANFATTNING PÅ SVENSKA

Epilepsi behandlas oftast med antiepileptika. Men att hitta rätt medicin som minskar risken för anfall och samtidigt ger så få biverkningar som möjligt är svårt. Val av antiepileptikum grundas på bland annat ålder, kön, typ av epilepsi och samjuklighet, men trots det blir hälften av alla patienter inte anfallsfria av första testade antiepileptikum. Randomiserade kontrollerade studier (RCT) anses vara det bästa underlaget för att bedömma effekt av mediciner, men det är inte alltid de är kliniskt relevanta, speciellt för ovanliga tillstånd eller syndrom. Register är värdefulla datakällor eftersom att de har information om många patienter, är tillgängliga, och uppdateras regelbundet. Målet med denna forskning är att utvärdera register som datakälla och utveckla maskininlärningsalgoritmer för precisionsmedicin inom epilepsi.

Vi har använt svenska nationella registerdata av recept, sluten- och öppenvård samt död för att modellera patienters användning av antiepileptika. Som ett aggregerat mått av effekt och tolerabilitet har vi använt retention som måttet på utfall av antiepileptika.

Resultaten i denna avhandling indikerar att det är möjligt att använda registerdata för att uppskatta retention och att patientanpassat val av antiepileptika kan öka retentionen. Retentionsgrader uppskattade genom registerdata liknar de av RCTer samt meta-analyser av RCTer. I en analys med patienter med komorbiditeter fann vi en potentiell ökning av retentionsgraden med 14-21% efter 5 år för första antiepileptikum. Att rangordna antiepileptika efter retentionsgrad ger liknande resultat som förslag baserade på expertråd. Maskininlärningsalgoritmer som är specialiserade för observationell registerdata kan bli användbart som beslutsunderlag för att välja bästa möjliga medicin.

Forskningen i denna avhandling belyser potentialen hos register som datakälla för precisionsmedicin. Maskininlärningsalgoritmer tränade på registerdata skulle kunna användas för att förutsäga utfallet av antiepileptika, men metodiken behöver vidareutvecklas och verifieras kliniskt.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Samuel Håkansson**, Markus Karlander, David Larsson, Zamzam Mahamud, Sara Garcia-Ptacek, Aleksej Zelezniak, Johan Zelano.
Potential for improved retention rate by personalized antiseizure medication selection: A register-based analysis
*Epilepsia* 2021; 62(9): 2123-2132.
https://doi.org/10.1111/epi.16987.

II. **Samuel Håkansson**, Johan Zelano.
Big data analysis of ASM retention rates and expert ASM algorithm: A comparative study
*Epilepsia* 2022; 63(6): 1553-1562.
https://doi.org/10.1111/epi.17235.

III. **Samuel Håkansson**, Ronny Wickström, Johan Zelano.
Selection and continuation of antiseizure medication in children with epilepsy in Sweden 2007-2020.
*Pediatric Neurology* 2023; 144: 19-25.
https://doi.org/10.1016/j.pediatrneurol.2023.03.016

IV. **Samuel Håkansson**, Fredrik D. Johansson, Aleksej Zelezniak, Johan Zelano.
Personalized anti-seizure medication selection using counterfactual time-to-event machine learning: a national retrospective study.
*Manuscript*.

# CONTENT

# ABBREVIATIONS

| | |
|---|---|
| ASM | Anti-seizure medication |
| CDAUC | Cumulative/Dynamic Area Under Curve |
| CDR | Cause of Death Register |
| CI | Concordance index |
| EEG | Electroencephalography |
| ICD | International Classification of Diseases |
| ILAE | International League Against Epilepsy |
| ML | Machine learning |
| MRI | Magnetic resonance imaging |
| MS | Multiple sclerosis |
| NPDR | National Prescribed Drug Register |
| NPR | National Patient Register |
| RCT | Randomized Controlled Trial |
| SUDEP | Sudden unexpected death in epilepsy |

# INTRODUCTION

Epilepsy is a neurological condition in which the affected has an enduring predisposition for seizures [1]. It is most often treated with anti-seizure medications (ASMs), with the goal of achieving seizure freedom with as few side effects as possible. Finding the right medication for patients with epilepsy is difficult. Approximately 50% of patients need to try more than one ASM and about 30% never achieve seizure freedom [2]. A common reason for ASM failure is side effects. When a new ASM regime is initialized, treatment evaluation can take time. One reason is that it can be difficult to determine the correct target dose; doses are usually increased after seizures, making titration an extended process if seizures are sparse. Another reason is that epilepsies can be selectively responsive to different ASMs. If patients could try an ASM with a high likelihood of success, they could conceptually become seizure-free faster, and experience fewer side effects during ASM tryouts.

Seizures and ASM side effects are important contributors to the burden of epilepsy. The annual global cost of epilepsy is estimated at $119 billion [3]. In Sweden, the direct healthcare cost per person is estimated to be $2403 per year and indirect costs are estimated to be $13 632 per year [3]. Direct costs include drugs, hospitalizations, contact with physicians, time spent by patients and families in the process of care, and social and educational services [4]. Indirect costs are estimates of foregone earnings from lost work and lost value due to fewer years of life [4]. Loss of independence is another example of a risk for patients with recurrent seizures. In a study with 81 adult patients with moderately severe epilepsy from southern USA, the most important concern was the ability to drive [5]. A study on outcomes after surgery found that the ability to drive was a major factor influencing employment post-surgery [6].

Since epilepsy is very heterogenous and there are more than 30 ASMs, performing randomized controlled trials (RCT) to identify the relative treatment effects of one or more ASMs is difficult, and such trials rarely contain enough patients for stratification of e.g. etiology. Instead, the use of systematically collected data, such as register data, is an interesting

alternative or supplement. Registers are a potential data source with plenty of patients, are relatively easily accessible, follow patients for a long time, and are updated systematically.

The hope for personalized medicine has increased in recent years owing to the development of machine learning (ML) methods in combination with an abundance of healthcare data. Two of the main advantages of using ML are the ability to obtain patient-specific recommendations, rather than stratified ones, and the ability to analyze complex and big data.

The focus of this thesis is to (1) investigate the viability of registers as a data source for personalized ASM selection, and (2) develop and evaluate machine learning methods trained on register data to suggest an optimal ASM for patients.

# BACKGROUND

## EPILEPSY AND ANTI-SEIZURE MEDICATIONS

Epilepsy is a common brain disorder, with a lifetime prevalence of 0.76% worldwide [7]. Epilepsy is usually diagnosed after two unprovoked seizures or after a single unprovoked seizure together with a high risk of experiencing more seizures [8]. The most common way to treat epilepsy is to use anti-seizure medications (ASMs). There are approximately 30 different ASMs, each with a different mechanism of action and potential side effects. Epilepsy can start at any age, but the incidence is U-shaped with more onsets in youths and older individuals. Genetic causes are more common in younger ages, whereas certain acquired epilepsies after brain damage such as a stroke become more common with advancing age.

There are two types of seizure onset: focal and generalised, and in some cases, unknown. Focal-onset refers to a seizure that starts within a single brain region and implies a focal disturbance of brain function that can be genetic or acquired. Awareness can be either retained or impaired during a seizure, even if the person is immobile [9]. Generalised onset refers to seizures that start in both hemispheres simultaneously. Focal-onset seizures may spread to other parts of the brain. For example, a seizure starting in a single part of the brain and then propagating to the other hemisphere, manifesting as a tonic-clonic seizure, can be classified as a focal to bilateral tonic-clonic seizure [9]. Seizure onset defines the type of epilepsy; focal seizures occur in focal epilepsies [10]. The type of epilepsy is important for ASM selection; some ASMs are selectively effective in focal epilepsies and may even aggravate generalised ones [11, 12]. Focal epilepsy can start at any age, whereas onset of generalised epilepsy is rare after age 25-30.

It is important to find a suitable ASM early on to avoid seizures and their consequences such as head injuries, fractures, and drowning [13, 14]. Some patients never find an appropriate ASM. Drug-resistant epilepsy is defined as the failure of two appropriately chosen and adequately tried ASMs, either as monotherapy or in combination [15]. The mortality rate is 4-7 times higher for people with drug-resistant epilepsy, and injury rates range from one per 20 to one per 3 person-years [16].

## ASM SELECTION AND SIDE EFFECTS

When selecting a suitable ASM, many factors may need to be considered. ILAE suggests taking into account epilepsy syndrome, age, gender, genetics, and comorbidities, to name a few [17]. It is also important to consider the patient's preferences.

ASMs may have long-term side effects [18] such as cardiac adverse effects [19] and valproic acid and pregnancy [20-22]. While it is important to treat seizures, misdiagnosing epilepsy, for example for cardiac arrest, and starting epilepsy treatment can be disastrous. Some medications are associated with side effects that are related to specific genes. Carbamazepine is the main cause of Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN) in Southeast Asian countries [23]. SJS-TEN causes high fever, malaise, exanthema, and mucosal involvement.

A modified version of the WHO classification of adverse effects has been used to describe side effects of ASMs (Table 1) [24]. Types A and C are more likely than the other types to be found during short clinical trials, whereas types B, D, and E sometimes require a longer follow-up time to be discovered and understood.

**Table 1** Classification of adverse effects of ASMs. Adapted from [24]

| | Description of adverse effects |
|---|---|
| Type A | Related to the known mechanism of action of the drug; common or very common; dose-dependent; acute; predictable; reversible |
| Type B | Related to individual vulnerability; first few weeks of treatment; uncommon; high morbidity and mortality; reversible |
| Type C | Related to the cumulative dose of the drug; common; chronic; mostly reversible |
| Type D | Related to prenatal exposure to the drug; uncommon; delayed; dose-dependent; irreversible |
| Type E | Adverse drug interactions; common; reversible |

ASMs often require slow titration to avoid severe side effects. The titration periods differ for ASMs (Table 2) [25]. The difference in titration time can

make it challenging to compare ASMs since a longer time to maintenance means that patients stay on an ASM for a longer duration without it necessarily being a better medication. On the contrary, a longer titration might mean that a patient has seizures while on a low dose of the medication and thus change treatment even though the medication itself was not inadequate, but the dose was insufficient.

**Table 2** Time to maintenance dose for ASMs. Adapted from [25]

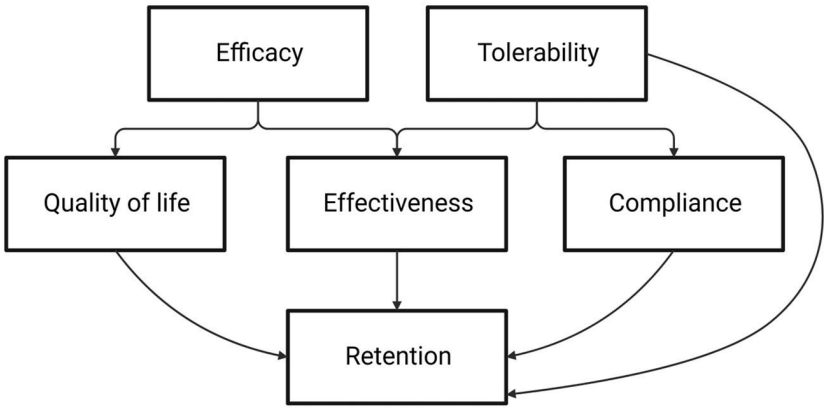
| ASM | Median time to the maintenance dose (weeks) |
|---|---|
| Carbamazepine | 5.4 |
| Lacosamide | 5.1 |
| Lamotrigine | 8.1 |
| Levetiracetam | 4.7 |
| Phenytoin | 3.3 |
| Topiramate | 6.1 |
| Valproate | 5.1 |

While ASMs are the primary treatment for epilepsy, for patients with drug-resistant epilepsy (13.7-36.3% of patients with epilepsy [7]), there are alternatives such as brain surgery [26], vagus nerve stimulation [27], and ketogenic diet [28].

## MEASURING THE OUTCOME OF ASMS

Several different outcomes can be evaluated for an ASM in clinical trials: percentage of seizure reduction, responder rate (>50% seizure reduction), quality of life [29], time to first seizure, adverse events, retention rate, and compliance [30]. Retention is the time to treatment failure for any reason and is an integrated measure of efficacy and tolerability (Figure 1). The European Medicines Agency encourages the use of retention rate as a secondary measure of outcome in monotherapy trials [31]. The main disadvantages of using retention rate as an outcome measure are that it requires a longer trial duration, a larger sample size, and has less historical data to compare to [30].

**Figure 1** Retention is an aggregated measure of efficacy and tolerability. Adapted from [30]. Created with BioRender.com




## CLINICAL TRIALS OF ASMS

The current literature illustrates the difficulties in determining the relative efficacy of ASMs in a clinically meaningful manner. Traditional methods include RCTs, uncontrolled trials, and observational studies. The benefits and problems of these strategies and the limitations in answerable research questions of relevance for personalized medicine are discussed below.

One suggestion of the hierarchy of evidence for selecting initial ASM for a patient is [32]:

1. Individual patient data meta-analysis
2. Systematic review and meta-analysis of large RCTs
3. Large RCTs
4. Systematic reviews of small RCTs
5. Small RCTs
6. The consensus of expert opinion
7. Individual expert opinion
8. Case series
9. Individual case report

Randomized controlled trials (RCT) are the gold standard for evaluating epilepsy treatments. However, these trials are often conducted for regulatory reasons with placebo or a single comparator as reference [33]. The eligibility criteria in clinical trials can be very restrictive to avoid exposing groups such as elderly or pregnant patients to potential side effects [34], making it challenging to extrapolate the efficacy of treatments to all patients. Furthermore, regulatory study protocols leave little or no flexibility in dosing schemes, which may affect the generalizability of the study to clinical practice and the interpretation of drug efficacy.

Trials may also be too short to determine the optimal dose for patients. For example, pregabalin was found to be inferior to lamotrigine, possibly because the initial maintenance dose of pregabalin was ineffective, and the duration of the trial did not allow for the comparison of effectiveness at higher doses [35]. Clinical trials with 3-6 months follow-up are of limited applicability to general practice because the effectiveness of the drug is difficult to determine in such a short time frame [30]. Controlled trials in epilepsy are difficult to implement due to high costs and ethical difficulties, whereas uncontrolled studies tend to provide misleading estimates of both efficacy and adverse effects due to confounders [33]. Non-regulatory trials are sometimes biased towards the sponsor's product by choosing the eligibility criteria, choice of formulation, target doses, titration rates, or interpreting the results in a certain way [34, 36]. ASMs are often tested as adjunctive treatment in trials with patients with uncontrolled seizures [37, 38]. Oftentimes, these are the only data on efficacy available to clinicians when a new ASM is released to the market. Clinicians must then be cautious about the optimal use of the drug, especially if it is used as monotherapy.

Few trials in epilepsy are regarded as high-quality evidence of treatment efficacy. In 2006, 33 eligible trials of adults with focal seizures were analyzed. Two of them were rated as class I (the highest rating in terms of quality of evidence), one as class II, and 30 as class III (the lowest rating). All the trials in adults with generalised tonic-clonic or other generalised seizure types achieved class III rating [17, 39]. In a systematic review of randomized placebo-controlled adjunctive therapy trials, only 3 of the 63 trials conducted in adults with focal epilepsy reported the proportion of

patients who completed the trial successfully, that is, those who had a >50% reduction in seizure frequency and were able to complete the trial [40].

As different drugs have different levels of evidence of efficacy in clinical trials, the International League Against Epilepsy (ILAE) has graded the medications according to the level of evidence of efficacy as initial monotherapy for focal-onset epilepsy (Table 3). Many ASMs lack high-quality evidence of efficacy and none of the drugs obtained an increase in evidence level in the updated version. In summary, the ILAE finds evidence for the effectiveness of different ASMs, but this is of little use to clinicians contemplating which ASM to use first.

**Table 3** ILAE guidelines for adults with newly diagnosed or untreated focal-onset epilepsy. Level A suggests that the ASM is established as an efficacious initial monotherapy, B is probably efficacious, C is possibly efficacious, and D is potentially efficacious

| ASM | Effectiveness, evidence level 2006 [17] | Effectiveness, evidence level 2013 [41] |
|---|---|---|
| Carbamazepine | A | A |
| Gabapentin | C | C |
| Lamotrigine | C | C |
| Oxcarbazepine | C | C |
| Phenobarbital | C | C |
| Phenytoin | A | A |
| Topiramate | C | C |
| Valproic acid | B | B |
| Vigabatrin | C | C |
| Clonazepam | | D |
| Levetiracetam | | A |
| Primidone | | D |
| Zonisamide | | A |

The ILAE guidelines concluded the following concerns: (a) trials were not designed and powered as noninferiority trials because the main goal of many trials is to get a medication approved for market; (b) they were too short to produce clinically relevant information; (c) titration schedules were fixed and forced, and could be biased favouring the sponsor's product; (d) the trials had a heterogeneous patient group with multiple age groups and seizure types;

and (e) the design, conduct, and analysis of the trials were by industry [17, 32].

Some RCTs have tried to use multiple arms. Two of the largest phase 4 randomized controlled trials on ASM efficacy are the Standard and New Antiepileptic Drugs (SANAD) trials on focal epilepsy [42, 43]. The two trials included 1721 and 990 patients, respectively. Patients aged 5 years or older with at least two unprovoked seizures were eligible for recruitment and they were followed-up for 12 months. Patients were excluded if they had known progressive neurological diseases, had acute symptomatic seizures, or were currently taking an ASM.

A few trials conducted in Europe have been designed to provide information comparing a new drug and previously established treatment options in terms of efficacy and tolerability [33]. Although they have been criticized with concerns of assay sensitivity [38, 44, 45], i.e. the ability to distinguish an effective treatment from a less effective one. The U.S. Food and Drug Administration (FDA) requires evidence of the efficacy of a drug to demonstrate its superiority over a comparator. This comparator cannot be a placebo administered to patients with active epilepsy due to ethical concerns, but it is also improbable for a new drug to show significantly superior efficacy compared to the best standard ASM [44]. This led to a trial design of conversion to monotherapy with a sub-optimally dosed comparator [38, 46]. This design is also problematic because it allocates patients with uncontrolled seizures to a deliberately suboptimal treatment. Patients included in the study are pharmacoresistant, which is different from the intended monotherapy population. Efficacy is established by demonstrating a reduced risk of seizures, not clinical improvement, and the full dose is typically higher than the optimal dosing range in the clinical setting [36, 38, 44, 47, 48].

Some trials use placebo as a baseline for epilepsy treatment. One way to make trials easier to perform would be to remove the placebo group, which would be a valid strategy if the magnitude of the placebo response would be consistent over time, across trials, and in any geographic setting [33]. However, the proportion of responders to placebo ranged from <5% to almost 40% in a systematic review of all RCTs conducted in adults with focal epilepsy between 1960 and 2009 [40]. Most RCTs of ASMs are conducted

for regulatory purposes, where a product is deemed efficacious and safe if it is “better than nothing” [44]. In contrast, for clinicians to make informed decisions about drug selection, they would need to know how the drugs compare to previously established treatment options, preferably on the same population, titration schedule, etc. To make matters worse, placebo has seen a rising response in the last few years, making it more difficult to compare studies [40]. Placebo has also been linked to a 6-fold increase in the risk of sudden unexpected death in epilepsy (SUDEP) [49], showing the potential danger of trials with placebo. Because it is problematic to compare trials, one could seek information from head-to-head trials. However, these may not be available for many years after release to the market, or in some cases not at all [34].

While the SANAD results suggest that drugs performing better than placebo for generalised and focal seizures should be considered broad-spectrum ASMs, another suggestion of the definition of broad-spectrum is to depend on the demonstration of equivalence or superiority of efficacy against the existing first-choice agents [32]. The SANAD studies were not sufficiently large to alloy much stratification regarding age, sex, and comorbidities.

## OBSERVATIONAL STUDIES OF ASMS

Prescription data is important for understanding adverse effects and other drug-related problems. Use of ASMs in other disorders, changes in prescription patterns, and combination of drugs are examples of usages of prescription data from registers or electronic health records [50]. Registers have been used to study ASM use and its effect on pregnancy in Finland [51], the effect of ASMs on the risk of cancer in Denmark [52], general trends of ASM use in Germany [53], changes in ASM use in children and adolescents in Norway [54], epilepsy and ASMs, and the relationship to transport accidents in Sweden [55], and combined data from Nordic countries to study the risk of autism and intellectual disability from ASMs [56].

Although RCTs are considered the best evidence of treatment efficacy, observational studies may be superior to clinical trials for some purposes. Observational studies provide better evidence than RCTs for serious idiosyncratic reactions, chronic adverse events, or teratogenicity [32].

# TIME-TO-EVENT STATISTICS

When the outcome of a data point has a fixed lower limit but no upper limit, the outcome is right-censored. For example, this often arises in studies where the survival of patients is of interest, hence, it is commonly referred to as survival analysis. Patients who lived longer than the study period will be censored; it is known that they lived at least until the end of the study. The data of the studies in this thesis were right-censored either because the patient used the ASM until the end of the study or until they were deceased. Left-censoring was not dealt with in the studies of this thesis but could be incorporated if patients with unknown ASM start dates were included. The Kaplan-Meier estimator is a popular estimation method for right-censored data and it was used in all studies in this thesis.

# ESTIMATING TREATMENT EFFECT FROM OBSERVATIONAL DATA

Regulatory-grade clinical trials for drugs are expensive, with a median cost of about $19 million in 2015-2016 [57]. They could also be difficult to perform, especially for ASMs where the patient would potentially have to give up another option, which at the time is considered a better choice. Real-world data, such as registers and electronic health records, are alternative data sources for drugs released on the market. However, estimating the causal effects of ASMs using register data is not straightforward, mainly because the assignment of drugs by a doctor is non-random [58]. The probability of an individual being assigned a treatment is called the propensity score [59]. The propensity score can be used to adjust the regression models to estimate the causal effect of a treatment on a subject.

# MACHINE LEARNING FOR PERSONALIZED TREATMENT SELECTION

Using biomarkers to train machine learning models for personalized medicine has the potential advantages of better medication effectiveness, risk reduction of adverse events, lower healthcare costs, early diagnosis and prevention of disease, improved disease management, and smarter clinical trial designs

[60]. Many different data sources are considered biomarkers, for example, electronic health records, biological high-throughput data, bio-images such as MRT and CT scans, and data from wearable sensors and mobile health applications [60].

In vanilla supervised machine learning, the labels of the input data are known. The performance of the model was estimated by splitting the dataset into a training set and a test set (possibly also into a validation set). However, when estimating the treatment effect, it is rare to know the outcomes of all treatments for all patients. This makes it more difficult to evaluate the trained models because the evaluation of the test set will show how well the model will perform on the treatments assigned to the patients. Instead, a policy evaluation method can be used [61]. The goal of policy evaluation is to compare different policies, such as the treatment choices of a doctor or a machine learning model. This is essentially done by weighing the data points in the test set based on how commonly the treatment is assigned to that type of patient.

When estimating the effect of an action on an outcome, an assumption about the relationship between the features of the dataset is sometimes required. A simple example is the estimation of the effect of altitude on temperature. We know that the altitude of a place might affect the temperature, and we know that the temperature does not affect the altitude. However, if we have a dataset with place, altitude, and temperature, it is impossible from the data alone to determine the causal relationship between altitude and temperature without additional assumptions. Nonetheless, with assumptions or additional input data, it is possible to deduce the relation between the variables [62].

# MACHINE LEARNING IN EPILEPSY

Epilepsy is a disease with difficult and diverse challenges, some of which have been attempted to be untangled with ML. ML has been used in epilepsy for image analysis for the classification of epilepsies, detecting lesions, and predicting seizure outcomes [63], seizure detection in EEG [64], seizure forecasting [65], and identifying regions of interest for epilepsy surgery [66].

# AIM

The overall aim of this thesis is to deepen the knowledge about the use of ASMs, how the ASM retention rate is affected by patient characteristics and to investigate the possibility to use this data to train machine learning models to inform the decision of selecting a personalized ASM.

| Paper | Aim | Rationale |
|---|---|---|
| I Potential for improved retention rate by personalized ASM selection | To estimate the retention and retention rate gap of ASMs using registers. | Data on ASM efficacy is sparse. Registers are potential sources of data. |
| II Comparison of ASM retention rates and expert ASM algorithm | To describe the similarity in ASM ranking of ASM retention rates and an ASM expert knowledge tool. | Expert knowledge tools for selecting ASMs have been shown to be useful. How does it compare to real-world data? |
| III Selection and continuation of ASM in children with epilepsy | To describe the use and retention of ASMs for children in Sweden. | Evaluating ASM efficacy for children is challenging. |
| IV Personalized ASM selection using machine learning | To develop and test novel machine learning models for selecting personalized ASMs. | Clinicians could potentially improve patient outcome with a tool for personalized ASM treatment. |

# METHODS

## NATIONAL REGISTERS

The Swedish National Board of Health and Welfare maintains registers for in- and outpatient hospital visits, prescribed medications, and death dates. It is mandatory for caregivers to report cases to the registers. For this thesis, the National Patient Register (NPR), the National Prescribed Drug Register (NPDR), and the Cause of Death Register (CDR) were used in all studies while the Swedish Stroke register, the Swedish dementia register, and the Swedish MS register were used only in Paper I.

### NATIONAL PATIENT REGISTER (NPR)

The NPR contains diagnose codes using the International Classification of Diseases (ICD) and dates for inpatient care since 1987 and specialized outpatient care since 2001 in Sweden [67]. An epilepsy diagnosis with the ICD code G40 has a positive predictive value of approximately 90% when compared to patient charts [68]. For comorbidities, the positive predictive values are stroke, 94% [69]; MS, 93% [70]; trauma (open tibial fracture), 87% [71]; and dementia: 81.3% [72]. Brain tumours had a sensitivity of 78% compared to the Swedish Cancer Register [73]. There are no validated studies of traumatic brain injury (TBI) but a study on brain concussion found the PPV to be 100%, though with only 18 cases [67].

### NATIONAL PRESCRIBED DRUG REGISTER (NPDR)

The NPDR contains all prescriptions and dispensations by pharmacies in Sweden since the 1$^{st}$ of July 2005 [74]. Drugs are registered by their Anatomical Therapeutic Chemical code (ATC) with ASMs starting the ATC code with N03. The register has been shown to have negligible loss and measurement error [75].

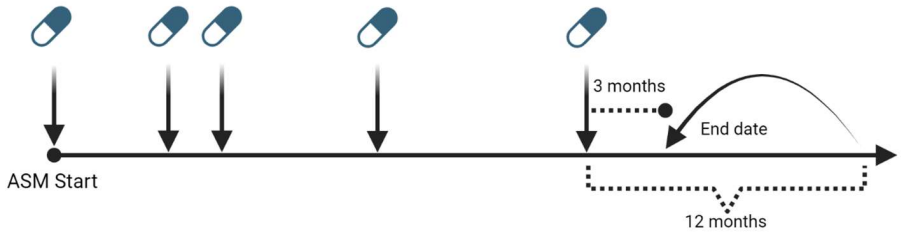
### CAUSE OF DEATH REGISTER (CDR)

The CDR contains dates and ICD codes of the underlying causes of death since 1961 for all deceased Swedish residents.

# PATIENT MODELING

All prescriptions of ASMs for a patient were collected with ATC codes. The start date for an ASM for a patient started at the initial dispensation date. The last date for an ASM was 3 months after the last dispensation. The last date for an ASM was set when there had been at least 12 months without a new dispensation (Figure 2). It is assumed that patients quit an ASM only because it was inadequate.

**Figure 2** Modeling of patient data. Patients retrieve prescriptions, when a new prescription is dispensed, 3 months of ASM use is added. If 12 months pass without a new dispensation, the medication was stopped 3 months after the last retrieval. Created with BioRender.com




For Paper I, polytherapy was allowed, while in Paper II, III, and IV only monotherapy was allowed. This means that in Paper II, III and IV there is an additional stopping rule for the duration of the first ASM if another medication is initiated. A difference between these two approaches is if the optimization is for finding the best monotherapy, or the best monotherapy including the potential to add more drugs. These two goals will yield different choices of personalized ASM if, e.g., drug A is in general used for a long time as monotherapy while drug B is often started with and then used with add-on therapy.

The duration of ASM use is censored if a patient uses the medication at the end of study, or if the patient dies while on the medication. If a patient starts a second medication, the duration of the first medication is not censored.

# ETHICAL CONSIDERATIONS

All studies were approved by the Ethics Review Authority. Paper and approval numbers; Paper I: 2020–01829, Paper II and IV: 2020-04902, Paper

III: 2020-04902/2022-00312. Register-based research does not impose any physical risks for patients, but precautions must be made such that data is securely stored. The data was anonymized before being given to the authors and the data was handled with confidentiality.

# RESULTS

## POTENTIAL FOR IMPROVED ASM RETENTION RATE (PAPER I)

### KEY POINTS

**Question** Based on register data, is there room for improvement in the retention rate of an initial ASM?

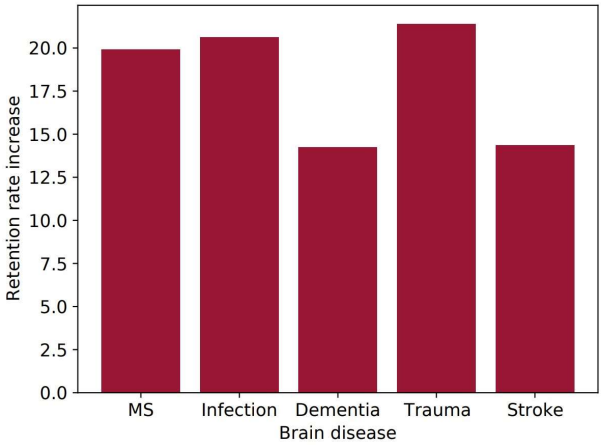
**Findings** The potential for improvement of 5-year retention of the first ASM was between 14-21% depending on the comorbidity.

**Implications** Personalized ASM selection could improve the retention rate of the first ASM.

A total of 6380 patients with acquired epilepsy after one of the comorbidities stroke (number of patients: 5024, 78.7%), dementia (699, 11.0%), trauma (265, 4.2%), brain infection (243, 3.8%), or MS (149. 2.3%) were collected using data from the NPR, NPDR, CDR, and the national stroke, dementia, and MS registers [76]. The usability of registers as a data source for calculating retention rates was explored by stratifying the cohort by demographics, comorbidities, and ASM history, as well as quantifying the potential improvement in retention rate for the initial ASM.

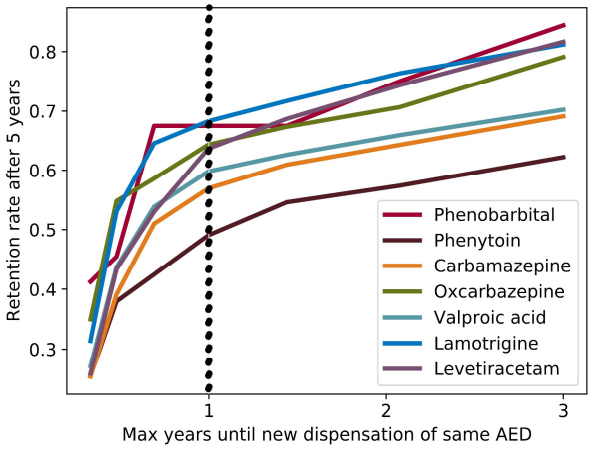
Kaplan-Meier analysis of the 5-year retention rate showed a difference of 20% for MS, 14% for dementia, 21% for trauma, and 14% for stroke between the best ASM per comorbidity, age and sex strata, and the rest of the ASMs (Figure 3). The optimal age and sex stratification for each comorbidity were calculated by finding the stratification that had the largest increase in retention rate while still having at least 10 patients per retention rate estimation.

**Figure 3** Potential improvement in retention rate (in percentage points) if each stratum had been assigned the ASM with the highest retention




To validate the method, the retention rates of carbamazepine, lamotrigine, and topiramate were compared to a randomized trial (SANAD).

**Figure 4** Sensitivity analysis of the maximum allowed time between dispensations




In a sensitivity analysis, we investigated how the retention rate is affected by changing the max time between two dispensations (Figure 4). The chosen

time was 1 year because it is the validity time for a prescription and the retention rates were more stable from that point.

It was also found that the failed first ASM could provide useful information when deciding the subsequent treatment. For patients with poststroke epilepsy, lamotrigine had a higher 1-year retention rate, 84% (95% CI = 80–87) than levetiracetam 78% (95% CI = 75–82), p = .03. However, for the patients who used valproic acid as their initial ASM, levetiracetam had a higher retention rate, 93% (95% CI = 86–97) than lamotrigine, 73% (95% CI = 61–82), p = .002.

# COMPARISON OF RETENTION RATES AND EXPERT ALGORITHM (PAPER II)

## KEY POINTS

**Question** How do the retention rate statistics from national registers compare to an expert-based algorithm?

**Findings** The ASM with the highest retention rate was recommended by the expert-based algorithm in all eight test cases if at least 50 patients were used to estimate the retention rate.

**Implications** Clinical decision support systems could work and be implemented with both real-world retention rates and expert opinions.

To further evaluate the applicability of registers as data sources for ASM efficacy we compared the ranking of ASMs based on their retention rates to the ranking according to an expert tool named EpiPick [77].

The NPR, NPDR, and CDR were cross-referenced and patients over 30 years of age at epilepsy onset and a common ASM (confidence interval <50%) were included, resulting in a population of 37643 patients [78].

The retention rates for all individuals were calculated using the Kaplan-Meier statistic. Lamotrigine and levetiracetam had the highest retention rates, and levetiracetam and carbamazepine were the most common treatments (Table 4).

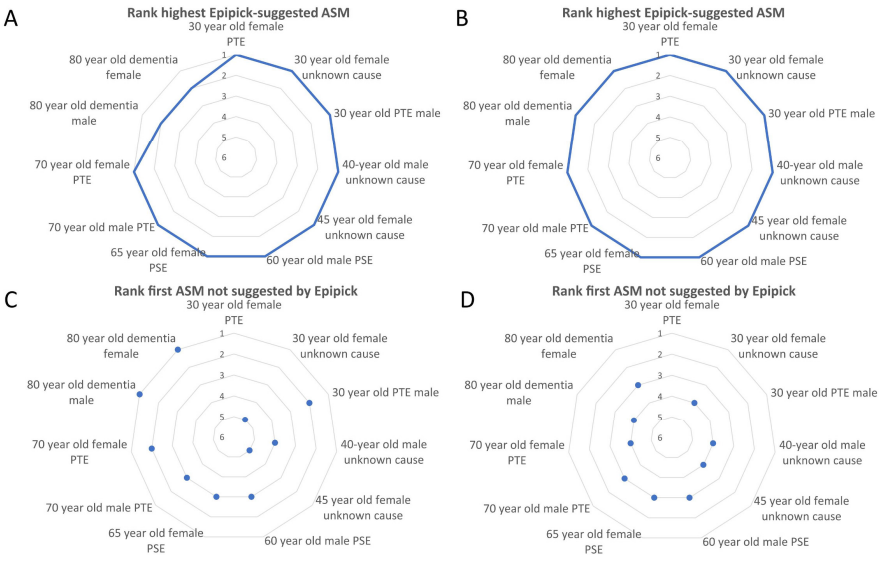
To verify that the retention rates and rankings were not confounded by different epilepsy diagnoses, a sensitivity analysis was performed where only patients with focal epilepsy were included. For the most common ASMs; levetiracetam, carbamazepine, lamotrigine, and valproate, the retention rates were almost exactly the same even though approximately 40% of patients had been removed from the cohort.

**Table 4** Retention rates for all patients 30 years and older

| ASM | 1-year retention rate, % (95% CI) | Number of patients |
|---|---|---|
| Lamotrigine | 71 (69-72) | 5641 |
| Levetiracetam | 68 (68-69) | 12974 |
| Phenobarbital | 66 (49-75) | 58 |
| Valproic acid | 62 (61-64) | 4272 |
| Lacosamide | 61 (51-68) | 134 |
| Carbamazepine | 58 (58-59) | 11844 |
| Oxcarbazepine | 57 (52-61) | 478 |
| Phenytoin | 53 (49-57) | 619 |
| Gabapentin | 45 (41-48) | 943 |
| Pregabalin | 40 (36-45) | 528 |
| Clobazam | 39 (30-46) | 152 |
| Topiramate | 38 (28-46) | 115 |

Eight patient cases were constructed to test the overlap between Kaplan-Meier retention rates and EpiPick. When more than 50 patients were used per medication, the ASM with the highest retention rate was recommended by EpiPick in all cases (Figure 5). At least two ASMs with the highest retention rates were recommended by EpiPick in all cases.

**Figure 5** Comparison of ranking ASMs according to retention rate versus ranking according to EpiPick. Subfigures B and D show rankings of retention rates with at least 50 patients per ASM. Figures A and B show the EpiPick-ranking of the ASM with the highest retention rate. Figures C and D show the highest retention-based ranked ASM not recommended by EpiPick



# SELECTION AND CONTINUATION OF ASM IN CHILDREN (PAPER III)

## KEY POINTS

**Question** Which ASMs are prescribed to children with epilepsy and what are the retention rates?

**Findings** The most common treatments had high retention rates. Off-label use is common but does not seem to be associated with lower retention. Valproic acid is rarely prescribed to females of childbearing age since the implementation of restrictions.

**Implications** Clinicians can be confident in following clinical practice rather than relying on formal registrations of ASMs.

Children and adolescents are generally not included in clinical trials, which makes it more difficult to assess treatment efficacy for young patients [79]. Sweden has generous off-label rules, allowing doctors to prescribe medications outside strict regulatory approval. The retention of ASMs in children is also less affected by e.g. the cost of medications because of the universal coverage of healthcare costs in Sweden. A similar Swedish study investigated the prescription patterns of ASMs in children with epilepsy and other diagnoses [80]. The main contribution in this work beyond including more recent data is a retention rate analysis and a pathway analysis.

Evaluating ASM efficacy for children using retention rate is presumably not as reliable as for adults since, e.g., children may have more difficulties conveying side effects, and the epilepsy may resolve. Nonetheless, studying the prescribing patterns of ASMs in pediatric patients is an important step to evaluate ASMs using routinely collected register data.

One-year monotherapy retention rate analysis and pathway selection analysis of ASMs was performed to investigate prescription patterns. Patients were divided into strata of 1 month to 1 year, 1-5 years, 5-12 years, 12-18 years female, and 12-18 years male. Neonatal patients up to one month old were

not included in the study because the group may contain both severe epilepsies and acute provoked neonatal seizures, variables not available in our dataset.

For patients age 1 month to 1 year, oxcarbazepine and valproic acid had the highest retention rate at 60% and 51%, respectively (Figure 6). Patients aged 1-5 years had oxcarbazepine, valproic acid, and levetiracetam at the highest retention rate at 62%, 61%, and 59%, respectively. Valproic acid is not indicated for this age group, suggesting that medications without pediatric indication are still retained by patients. For patients aged 5-12 years, lamotrigine, oxcarbazepine, and carbamazepine had the highest retention rates at 71%, 69%, and 68%, respectively. Males of age 12-18 had the highest retention rate with lamotrigine, valproic acid, and oxcarbazepine at 74%, 73%, and 72%, respectively. For females, lamotrigine, ethosuximide, and levetiracetam had the highest retention rates at 68%, 64%, and 63%, respectively.

**Figure 6** Retention rates of children of different age and sex groups (A-E)

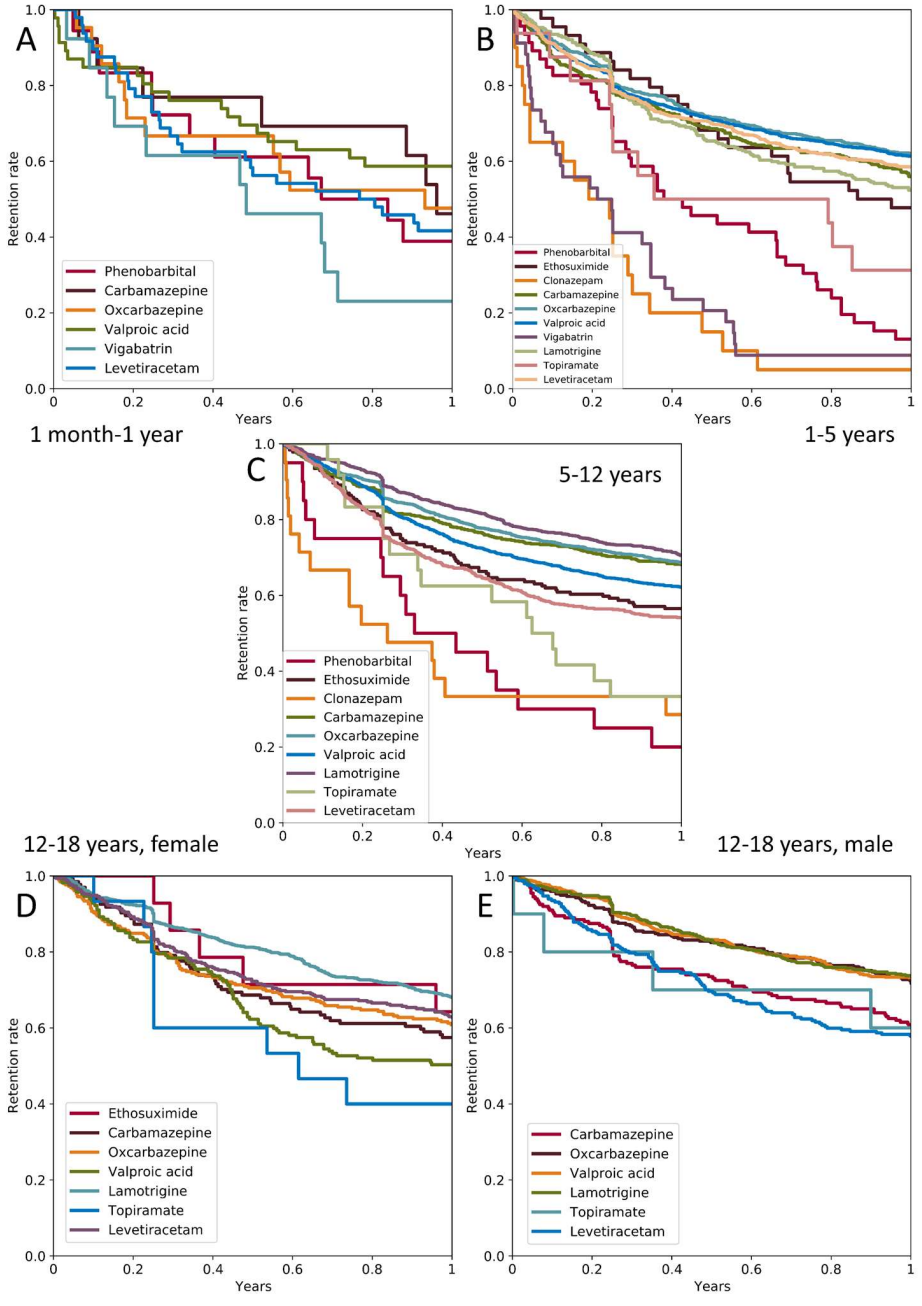
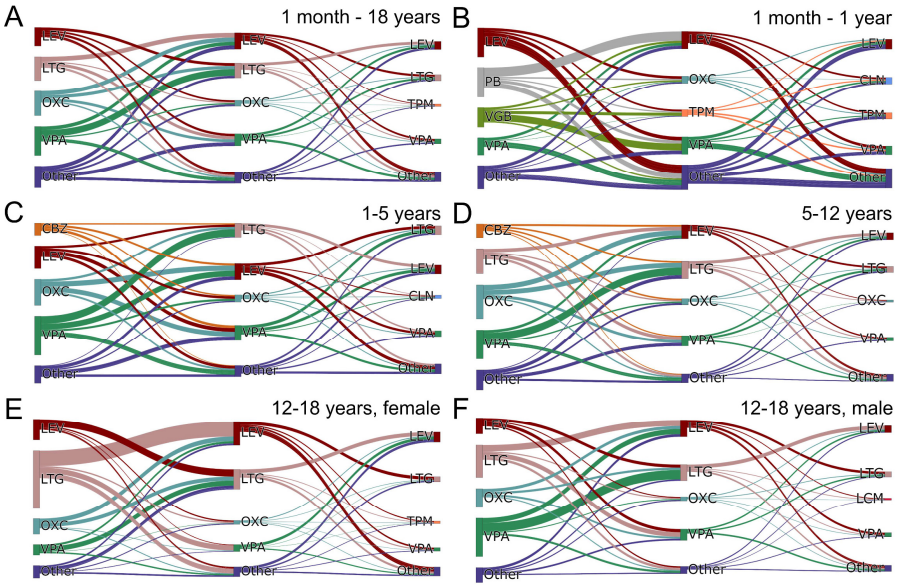


**Figure 7** Pathways of ASMs for children for the four most common ASMs and the rest of the medications grouped as "other". Abbreviations: CBZ, carbamazepine; CLN, clonazepam; CM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; TPM, topiramate; VPA, valproic acid; VGB, vigabatrin




The most common pathways for up to the third treatment were analyzed. The most common pathway per group was: 1 month to 1 year; phenobarbital followed by levetiracetam, 1-5 years, valproic acid followed by lamotrigine; 5-12 years, valproic acid followed by lamotrigine; 12-18 years males, valproic acid followed by lamotrigine; 12-18 years females, lamotrigine followed by levetiracetam.

# PERSONALIZED ASM SELECTION USING MACHINE LEARNING (PAPER IV)

## KEY POINTS

**Question** Can registers be used to train specialized machine learning algorithms to predict a good ASM for a patient?

**Findings** Our novel ML models performed better than the benchmark ML methods on the real data set.

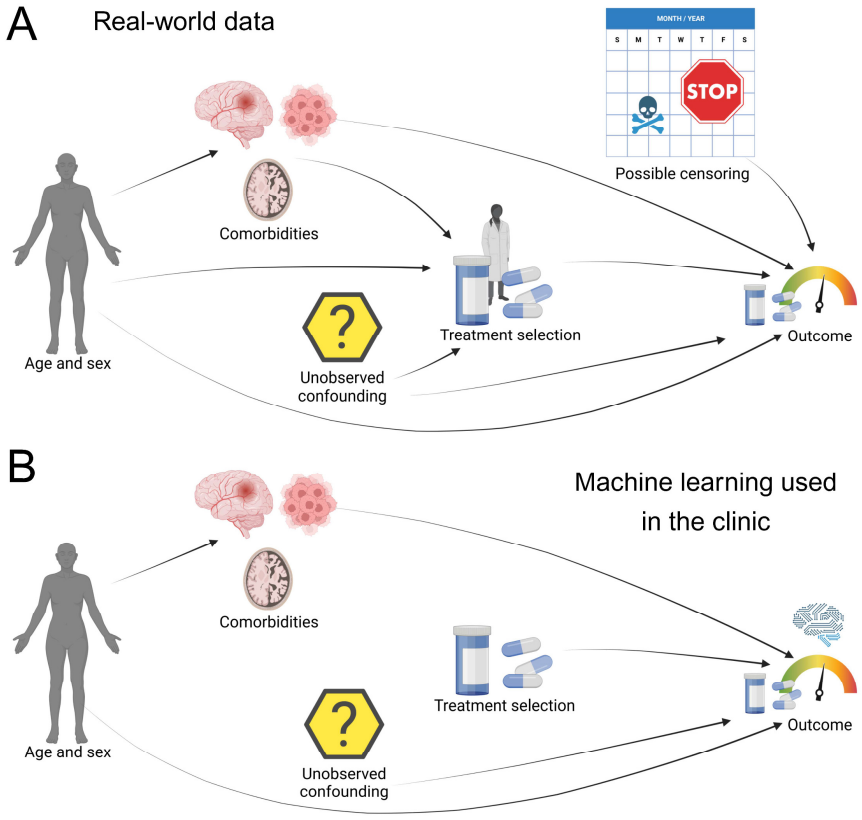
**Implications** The novel ML models show promising results, suggesting that they may be useful tools for clinicians.

If doctors had a tool to help select ASMs, patients could have a higher likelihood of finding an adequate treatment. Using register data to train machine learning algorithms, we wanted to investigate if it could be a useful clinical support system for doctors. The register data has two major difficulties: (1) the duration of ASM use is sometimes censored and (2) the data is observational, meaning that estimations of treatment effect are subjected to confounding bias if confounding is not adjusted for. A model that handled confounding from observational data on multiple treatments with survival data was not available in the literature, and thus two existing models were further developed.

The two models that were further built upon were [81] (CSA) and [82] (SurvCI). Both models are neural networks comprised of a base network connected to treatment arms (which also are neural networks). The idea is that the first layer constructs a representation of a patient such that it resembles a patient from an RCT, i.e. all patient groups having the same age, sex, and prevalence of the different comorbidities. This method is similar to that of using propensity score to weigh patients differently in an analysis. The resulting multi-armed version of the previous models were called Multi-CSA and Multi-SurvCI.

A synthetic patient dataset was created to investigate the performance impact of training the ML model with observational data and then applying the model in the clinic. The synthetic dataset was created to resemble the real-world dataset. A causal graph was created to visualize how the synthetic dataset was made (except for the unobserved confounding) (Figure 8).

**Figure 8** Causal graphs of the relation between variables. Created with BioRender.com




The baseline model Componentwise Gradient Boosting Survival Analysis (CGB Survival) had the best performance both using the Concordance index (CI) metric and Cumulative/Dynamic Area Under Curve (CDAUC) (Table 5). CGB Survival, Multi-CSA, and Multi-SurvCI all had small changes in performance from the observational dataset to the randomized one. The

median retention rate had a lot lower performance than CGB Survival, Multi-CSA, and Multi-SurvCI.

**Table 5** Performance of models on synthetic data

| | Concordance index | | Area Under Curve | |
|---|---|---|---|---|
| **Model** | Observational | Randomized | Observational | Randomized |
| Multi-CSA | 0.693 (0.003) | 0.702 (0.002) | 0.834 (0.002) | 0.793 (0.002) |
| Multi-SurvCI | 0.698 (0.004) | 0.685 (0.003) | 0.804 (0.003) | 0.774 (0.004) |
| CGB Survival | 0.714 (0.008) | 0.707 (0.010) | 0.844 (0.005) | 0.804 (0.009) |
| Survival forest | 0.610 (0.017) | 0.570 (0.012) | 0.727 (0.013) | 0.632 (0.015) |
| Median retention | 0.587 (0.027) | 0.637 (0.011) | 0.629 (0.036) | 0.676 (0.013) |

Multi-CSA had the highest performance, both with CI and CDAUC on the real-world dataset (Table 6). Note that this evaluation is of the observational dataset (Figure 8A) and not how it would be used in the clinic i.e. randomized dataset (Figure 8B).

**Table 6** Performance of models on real-world patient data

| Model | CI | CDAUC |
|---|---|---|
| Multi-CSA | 0.706 (0.005) | 0.750 (0.007) |
| Multi-SurvCI | 0.664 (0.005) | 0.708 (0.007) |
| CGB Survival | 0.651 (0.004) | 0.614 (0.020) |

An estimation of the ML methods' performance compared to the current treatment regime was conducted using a doubly robust balanced policy evaluation [83]. The ML models were compared to clinicians, random policy, and single treatment policy (same ASM given to all patients). Three different versions of the policy evaluation were conducted. CGB Survival and Random Survival Forest (RSF) were used to estimate the duration for censored patients and a balanced method and a K-Nearest Neighbours (KNN) method was used to estimate the policy evaluation weights. In the balanced policy evaluation with CGB, oxcarbazepine single treatment policy had the highest value (1023.1, SD: 4.8) followed by Multi-SurvCI (976.2, SD: 15.0) and Multi-CSA (955.1, SD: 26.0) (Table 7). It is important to note that the

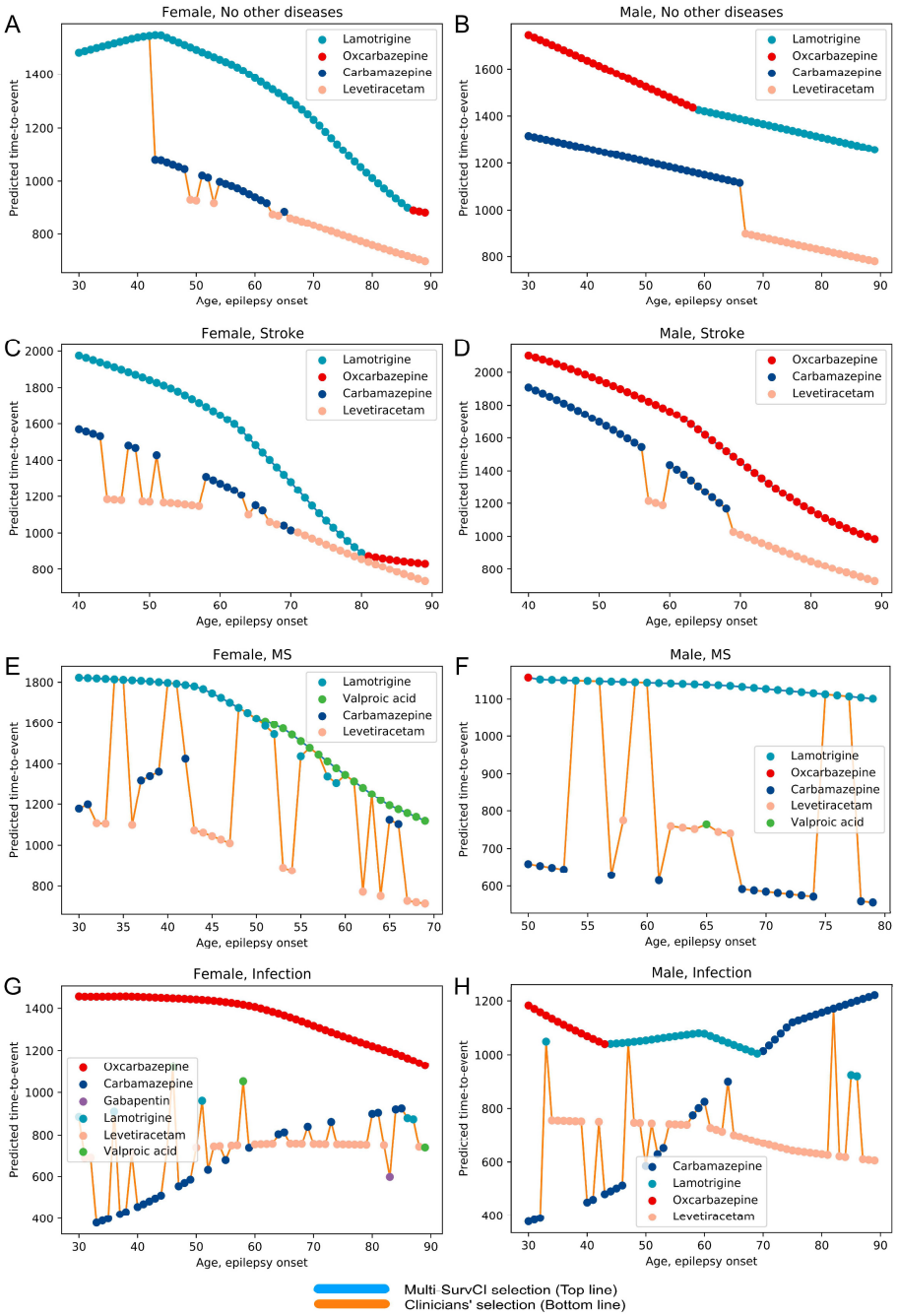
algorithms are trained for a slightly different target than the policy evaluation since censored patients must be estimated by a separate survival model.

**Table 7** Policy evaluation of the novel ML algorithms, clinicians, random, and single-treatment policy. In square brackets are details of the method; the first abbreviation is the method used to estimate the censored data points, and the second abbreviation describes how the weights are computed. CGB = Componentwise gradient boosting survival analysis, RSF = Random Survival Forest, balanced = doubly robust balanced policy evaluation, KNN = K-nearest neighbours

| Policy | Value [CGB+Balanced] | Value [CGB+KNN] | Value [RSF+KNN] |
|---|---|---|---|
| Clinicians | 881.1 (4.6) | 903.9 (60.6) | 814.5 (32.6) |
| Random policy | 824.7 (3.9) | 828.3 (9.2) | 854.8 (10.1) |
| Multi-SurvCI | 976.2 (15.0) | 979.1 (21.4) | 1091.7 (25.3) |
| Multi-CSA | 955.1 (26.0) | 963.2 (34.9) | 1007.5 (29.9) |
| Carbamazepine | 875.8 (3.9) | 880.9 (24.3) | 814.9 (15.2) |
| Oxcarbazepine | 1023.1 (4.8) | 1019.0 (23.7) | 1152.2 (13.4) |
| Valproic acid | 756.9 (2.3) | 767.5 (22.4) | 791.6 (15.3) |
| Lamotrigine | 949.9 (2.3) | 959.3 (16.6) | 1000.7 (21.1) |
| Gabapentin | 626.6 (8.0) | 632.4 (23.3) | 729.3 (15.1) |
| Levetiracetam | 905.3 (3.1) | 909.1 (17.4) | 777.9 (9.6) |
| Pregabalin | 628.7 (6.8) | 635.4 (16.8) | 697.3 (13.4) |

Another question that was asked in this study was: what if the suggestions from the ML algorithms could be used to improve the current treatment policy of clinicians? The current treatment policy was estimated by selecting the most common treatment for each of the 13 comorbidities and age +- 2 years, e.g., the most common treatment for females aged 78-82 with a previous stroke is levetiracetam. The result is shown in Figure 9, where the ASM with highest retention according to Multi-SurvCI is compared to the Multi-SurvCI-estimation of the most common selection according to the current treatment policy of clinicans.

**Figure 9** Comparison of clinician's context averaged choice and the highest ranked ASM according to Multi-SurvCI



# DISCUSSION

This thesis has investigated the use and retention of ASMs in adults and children, explored the suitability of routinely collected register data as a data source for informing ASM selection, and developed machine learning methods to determine the optimal ASM.

Conclusions of this thesis that will be discussed:

1. Register data approximate retention rates and relative retention of ASMs in manners that are similar to the results of previous clinical trials.
2. There is likely room for improvement in retention rate through personalized ASM selection based on patient features.
3. Prediction of personalized ASM based on register data resembles suggestions obtained through expert advice, showing potential clinical relevance.
4. Machine learning trained on register data might be a useful tool for selecting optimal ASM.

1. In an analysis in Paper I, it was found that the Kaplan-Meier retention rates of register data showed similar 5-year retention rates as that of SANAD I [76]. Our study also yielded similar results as a meta-analysis of RCTs. The 1-year retention of carbamazepine was 58% in our data. In a meta-analysis of 30 RCTs with carbamazepine, the 1-year retention was 61% (95% CI:54-68%) [84]. However, in contrast to our study, this meta-analysis included focal and generalized seizures of both children and adults. In a network meta-analysis of RCTs with carbamazepine as the baseline, it was found that lamotrigine and levetiracetam were better than carbamazepine for treatment failures for any reason and due to adverse events [85]. Carbamazepine was better than gabapentin for treatment failures for any reason and lack of efficacy, but gabapentin was better for treatment failures due to adverse events.

When ranking the ASMs according to the hazard ratio (HR) from the network analysis [85], the result shows similar tendencies to that of ranking according to retention rate from our data: lamotrigine and levetiracetam have higher

retention, lacosamide, carbamazepine, oxcarbazepine, and valproic acid have medium retention, and phenytoin, topiramate, and gabapentin have low retention (Table 8). Phenobarbital stands out as the retention rate is high, but the HR is low. This is likely to be at least partly because of the low number of patients in the Kaplan-Meier retention rate estimation, 58. The network study included both children and adults while our study in Paper II only included adults >30 years of age. The difference in age in the two studies might be of significance because older populations often have higher retention rates, see for example [78].

**Table 8** Comparison of ASM ranking according to retention rates (Paper II) and a network analysis [85]. Pregabalin and clobazam were not included in the network analysis. Light orange means few patients for estimation of retention rate (<200). HR=Hazard ratio

| ASM | 1-year retention rate, % (CI) | Network analysis by Nevitt et. al. HR (95% CI) | Network analysis ranking |
|---|---|---|---|
| Lamotrigine | 71 (69-72) | 0.79 (0.69-0.91) | 1 |
| Levetiracetam | 68 (68-69) | 0.80 (0.69-0.93) | 2 |
| Phenobarbital | 66 (49-75) | 1.56 (1.18-2.07) | 10 |
| Valproic acid | 62 (61-64) | 1.08 (0.88-1.31) | 6 |
| Lacosamide | 61 (51-68) | 0.95 (0.74-1.22) | 3 |
| Carbamazepine | 58 (58-59) | 1.00 (-) | 4 |
| Oxcarbazepine | 57 (52-61) | 1.03 (0.82-1.30) | 5 |
| Phenytoin | 53 (49-57) | 1.14 (0.90-1.44) | 7 |
| Gabapentin | 45 (41-48) | 1.21 (1.01 to 1.45) | 9 |
| Pregabalin | 40 (36-45) | - | - |
| Clobazam | 39 (30-46) | - | - |
| Topiramate | 38 (28-46) | 1.19 (0.99-1.43) | 8 |

The SANAD I and II trials have some of the most prominent evidence of ASM efficacy. In SANAD I, lamotrigine had a longer time to treatment failure than carbamazepine, gabapentin, and topiramate, with a non-significant advantage over oxcarbazepine [42]. In SANAD II, the primary outcome was time to 12 month-remission divided into two analyses, an intention-to-treat (ITT) which included all patients, and a per-protocol (PP)

one which excluded patients with major protocol deviations and patients who subsequently were diagnosed as not having epilepsy [43]. The authors found that levetiracetam was inferior to lamotrigine in both the ITT and PP analyses while zonisamide was inferior only in the PP analysis. In Paper II, we also found that lamotrigine had the highest retention in adults with presumed focal epilepsy.

There have been several studies utilizing prescription data to estimate retention of ASMs. A study conducted on focal epilepsy in Japan using a health insurance claims database found that lacosamide had a higher 1-year retention rate (73.0%, n=141 patients) than levetiracetam (58.3%, n=530), lamotrigine (57.5%, n=80), and perampanel (54.7%, n=75) [86]. As in Paper II, levetiracetam and lamotrigine showed similar retention, even though the number of patients was quite low in this study, especially for lamotrigine.

2. In Paper I, the room for retention rate improvement was estimated to be 14-21% depending on the comorbidity. In a similar analysis in Paper IV, a policy evaluation score was calculated for the novel machine learning methods as well as the current treatment policy by clinicians. While the policy evaluation showed unexpected results such as oxcarbazepine assigned to all patients got the highest score of the evaluated policies, it still might give a hint about the size of the treatment gap. Compared to clinicians, there was a 16.1% increase for oxcarbazepine, a 10.8% increase for Multi-SurvCI and an 8.4% increase for Multi-CSA (using the CGB+Balanced variant). Note that the two methods from Paper I and Paper IV differ in cohort, unit, and adjustment of confounding.

A study using machine learning to predict the optimal ASM for patients based on electronic health records estimated a 22 percentage points (pp) increase (0.4 to 0.62, estimated from viewing the plot) in the probability of treatment-related survival ($p<0.001$) with the model-predicted regimen compared to the current treatment regime [87]. In a validation study of EpiPick, it was found that the 1-year retention rate could increase by 12 pp, from 67% to 79% ($p=0.005$) [42]. The validation study included 425 patients and evaluated retention rates, seizure freedom rates, and adverse effects leading to treatment discontinuation. A sensitivity analysis on a sub-cohort with propensity scoring yielded similar results.

3. In Paper II, we found that there is a large agreement between retention rates and the expert-based algorithm tool EpiPick in all eight test cases. A validation study of EpiPick invited 24 experts to select the optimal ASM for 25 patient cases and compared it to the choice of the EpiPick app [88]. There was a fair agreement between the experts and the app, with 73% agreement on the highest ranked selections of the app and 95% of experts found that no incorrect ASMs were ranked highest by EpiPick [88]. Since experts support the suitability of EpiPick for use by healthcare providers [88] and EpiPick ranks and retention rate ranks are similar, it is likely that retention rates ranks are of clinical relevance.

4. To evaluate the novel machine learning methods in Paper IV, they were compared to baseline methods, including a Kaplan-Meier median retention method. This KM method is based on the results in Paper II. For all test cases, the retention rates showed similar results as the tool EpiPick [89] if 50 patients were used in the population to estimate the retention rate. The median retention rate method had a concordance index of 0.587 on the synthetic dataset while Multi-CSA and Multi-SurvCI had 0.693 and 0.698, respectively. If the median retention rate method is approximately equally as good as EpiPick, the novel machine learning methods may have equal or better performance than EpiPick.

In the policy evaluation in Paper IV, oxcarbazepine had the highest score of all policies. It would be expected to have an ML method, optimized towards the target, to have the highest score. The policy evaluation and the training data have slightly different targets. This exposes a weakness in either the policy evaluation method, e.g. that estimation of time-to-events and weights are off, or that the novel ML methods do not optimize towards the correct goal (or possibly both).

In a previous study using ML to predict ASM retention, the most common suggestions by the model were, in order of prevalence, levetiracetam, lamotrigine, pregabalin, and oxcarbazepine [87]. Levetiracetam was by far the most recommended ASM by the model, which is considerably different from the suggestions made by the ML models in this study, e.g. shown in Figure 9. Valproic acid was not included in this previous study.

# STRENGTHS AND LIMITATIONS

Here, the methodology of the studies will be discussed with its advantages and potential points of improvement compared to similar studies.

A potential flaw of modelling the drug used retrospectively, i.e. the 12 months gap allowance, is that the treatment use length might be biased [90]. For example, if a drug is commonly used by old people who are more likely to decease i.e. the outcome is censored, then the censoring might happen without the possibility of a prescription. More concretely, if a patient decides to quit a medication and dies 10 months after their last prescription, we assume that the patient used the medication for all 10 months, while if the patient would have lived for at least 2 more months, the patient would not have retrieved new medication and the treatment use length would have stopped at 3 months after the last dispensation. This is only a potential problem for the decision-making of selecting ASM if some drugs are used more by patients who are more likely to die, meaning that the relative outcome between ASMs is changed.

Drug adherence is another potential confounder. Patients might dispense the medication but not take it. However, it is seemingly unlikely that patients would retrieve medication and not use it. It is also unlikely that some medications more than others would be retrieved and not used, which would be a problem since the relative adherence would differ between the ASMs. Note that there is a strength in using dispensations, which are ASMs actually picked up by the patient, and not just a prescription by the doctor.

Our data may be missing important variables for the optimal selection of ASM. The ILAE suggests considering, except age, sex, and comorbidities (which are available in our data) seizure syndrome, dose-dependent adverse effects, idiosyncratic reactions, chronic toxicities, teratogenicity, carcinogenicity, pharmacokinetics, interaction potential, formulations, genetics, comedications, and ability to swallow pills in the decision-making [17]. The guidelines also mention insurance coverage, relative wealth, and ASM cost as variables, which may be less important to consider in a Swedish context since the healthcare system is to a large extent funded by the

government. Missing variables might cause dubious results due to unobserved confounding [91].

A systematic review of validation studies of administrative data to identify cases of epilepsy suggests that algorithms with the combination of ICD-10 code G40 (epilepsy) and one or more ASMs can be used confidently to identify people with epilepsy [92]. The approach had the highest positive predictive value compared to alternative approaches of using the G40 code alone, ICD-code R568 (seizure) and the use of ASM, and the use of ASM alone.

The titration time might affect the outcome of the ASMs. As shown in Table 2, titration times differ for different drugs. ASMs with longer titration times need a longer time to be evaluated, which means that patients stay on those drugs for a longer time, and the duration of use is thus artificially increased. On the other hand, a patient might have seizures during the titration period, causing a switch of medication to a more fast-acting ASM. In this case, the drug was not necessarily bad, it was just not the right dose. Lamotrigine has the longest titration time, meaning that its retention might be more difficult to estimate.

The quality of care differs between different hospitals and providers. If some healthcare providers have an insufficient clinical follow-up of patients and also prescribe some medications more than others, our analysis of the treatment effect might be skewed. An American study found that prescriptions for second-generation ASMs were more commonly prescribed by clinicians practising near an epilepsy centre [93]. Thus, training the ML models on only patients who e.g. received care from neurologists could be an alternative approach to achieve data points with higher quality.

National registers have some advantages compared to medical claims when used as a data source. Medical claims have been used to retrieve a large cohort of patients with epilepsy for the use of machine learning to select ASM [87]. The data source was the IMS Health Surveillance Data Incorporated medical claims database (SDI) which aggregates patient information from multiple provider sources. A drawback with SDI is that all claims for an individual might not be obtained if providers not submitting to

SDI were used [87]. To control for potentially lost data, the authors required at least 80% continuous monthly eligibility, in 1-year windows, in any of the databases. At least 2 years of data were required for each patient. Excluding patients with lost information removes data points but could also introduce selection bias if, for example, young patients are more likely to have healthcare providers that do not report to SDI. In Swedish registers, all healthcare providers except primary care are obligated to report in- and outpatient visits, meaning that diagnoses for e.g. high blood pressure, diabetes type 2, and heart failure have relatively low sensitivity.

Survival analysis is difficult to evaluate because of incomplete information from the censoring. In the work in this thesis, the duration of treatment has been used as the outcome. An alternative approach could have been to use a rule to define a binary outcome for each ASM that a patient used. For example: keeping medication for a year would suggest that the ASM was adequate, and conversely, if the medication is stopped earlier, it was inadequate. This approach is used in [87], where an ASM was assumed to be successful if a medication was used for more than 12 months, unsuccessful if used for 1-12 months, and invalid if used for less than 1 month. The results from the accuracy tests and policy evaluation in Paper IV could have been more reliable with this method because of the full information on the labels. However, if there is insight in e.g. if a patient used a medication for 3 months or 9 months in terms of how good the ASM was, a simplification of the outcome could potentially lead to worse performance on real patients if a machine learning model trained on the simplified data would be used in the clinic. One could also argue that the censoring could simply be ignored, and thus assume that patients quit a medication at the end of the study or at death, but this would likely skew outcomes of medications, and medications commonly prescribed at the end of the study would seem worse. Another question that could be asked is: what if patients with censored outcomes were removed from the cohort? That could possibly skew the outcomes as well since older patients and patients with epilepsy-onset close to the end of the study would more often be removed. Since patients would be removed non-randomly from the study, not only would the number of patients decrease, but selection bias would also be introduced.

Studies using machine learning to predict the outcome of ASMs similar to that of Paper IV have been conducted (Table 9). The advantage of the methodology in Paper IV compared to the other studies in Table 9 is the number of patients and the causal inference approach.

**Table 9** Studies of machine learning for prediction of ASM efficacy

| Study | Number of patients | Number of ASMs | Patient variables | Treatment outcome |
|---|---|---|---|---|
| Paper IV | 38830 | 7 | Age, sex, 13 comorbidities | Length of ASM use |
| **[94]** | 1798 | 7 | Age, sex, 3 comorbidities, 8 clinical variables, type of epilepsy, EEG and MRI, and previous ASMs | Complete seizure freedom for the first year of ASM treatment |
| **[87]** | 34990 | 10 and combinations of ASMs (52 regimens in total) | Age, sex, comorbidities, other drugs, | No change in ASM regimen or withdrawal of any ASM in the subsequent 1-12 months after change |
| **[95]** | 235 | 1 | Age, sex, genetics, previous ASMs, EEG, seizures, epilepsy type, demographics, clinical variables | >50% seizure frequency reduction 12 weeks after study baseline |
| **[96]** | 287 | 1, any monotherapy | Age, sex, seizure type, clinical variables, demographics, EEG, MRI | Early remission, late remission, and never remission |
| **[97]** | 46 | 1 | Age, MRI, epilepsy type, clinical variables | 3 years of seizure freedom |
| **[98]** | Mice | 4 | EEG features | Binary response |

In the ML for ASM studies [94] and [95], the previous ASMs of a patient are used as variables. While this might seem like a good idea, it might cause trouble. The reason is not because the variable is not informative. It is, as exemplified in Paper I, showing that lamotrigine had the highest retention rate as initial ASM, but for patients starting with valproic acid, levetiracetam had the highest retention. However, the reason it is a dubious variable is that the distribution of covariates might differ between the patients who had a previous ASM and those who did not. This stems from the doctor using the information of the previous treatment when the new medication was selected.

Even though the developed machine learning models in Paper IV account for training on observational data, it is important to note that the causal effect estimation performed by the models is not the same as causal decision-making [99]. The reason the models are optimized for effect estimation and not decision-making is because of the structure of the training data. To optimize for decision-making, we would have to know which medications worked for a patient. While this could have been estimated by a hard rule, it is probably difficult to specify a rule such that the decision-making error would be less than by using causal effect estimation.

Another potentially improbable but not impossible scenario arises from the difficulty for the clinician to evaluate an ASM for a patient. If a particular ASM has the property that patients have fewer seizures but are more aware while having the seizures, they might think a new medication is worse even though they might have fewer seizures. A solution to this problem is to record seizures using devices such as EEG headsets, wearables, or cameras.

# FUTURE PERSPECTIVES

The underlying cause of epilepsy is heterogeneous among patients, and is complex to understand, which makes the disease process itself difficult to target when developing ASMs [100]. Prognostic models from e.g. the SANAD studies show that EEG and brain imaging, among other clinical measures, are informative when predicting the outcome after a first seizure or an epilepsy diagnosis. However, the precision of EEG and brain imaging has shown to be insufficient for use in drug development [101]. Cellular and molecular biomarkers such as RNA, microRNA, protein, and metabolites extracted from blood [102] and cerebrospinal fluid [103] could be used to understand and predict the outcome of treatment [104]. Gathering data on biological biomarkers and the outcome of ASMs and using machine learning to predict a suitable treatment would further help to decrease the number of patients with drug-resistant epilepsy.

In a study using electronic health records from the US, the identification of patients with epilepsy was performed with ICD codes, ASMs, age, sex, and text features derived from doctors' notes [105]. The model had a very high accuracy, misclassifying only 1.46% of the test cases. While age and sex did not increase the accuracy, using text features did. Thus, using doctors' notes in addition to the ICD codes and ASMs could help identify patients with epilepsy and remove patients without. The same technique could also be used to better identify the specific type of epilepsy.

Future research on personalized medicine should be focused on developing machine learning techniques and evaluation methods with the clinical setting in mind. While this may sound obvious, sometimes it may be tempting to model problems by simplifying them to fit an existing algorithm. The problem arises when the evaluation is simplified as well, and the resulting methodology loses clinical relevance. In addition, validating ML algorithms in clinical trials is important to verify the assumptions made in all steps of the procedure.

The methodology discussed in this thesis applies to more areas than selecting a medication for epilepsy. It can be used in any setting with similar available data and assumptions i.e. users keep the treatment for a duration of time, the

time corresponds to the outcome of the treatment, and the treatment is only stopped if it was bad (or only if it was good, if the problem is to find the treatment with the earliest time-to-event).

# CONCLUSIONS

This thesis investigated the viability of register data as a data source for evaluating and predicting ASM suitability for patients. Using statistical methods and machine learning to handle real-world big data, we have shown that it is possible to approximate retention and estimate treatment effect of ASMs. The machine learning methodology was developed and evaluated with a causal inference approach to increase the amount of information yielded from the data and improve the chance for clinical application.

## KEY POINTS

- Register data is an interesting complement to clinical studies of ASM outcomes.
- Treatment gap estimations suggest room for improvement in ASM selection.
- The failure of a first specific ASM could provide information about which ASM to try next.
- Kaplan-Meier retention rates of register data are comparable to EpiPick suggestions.
- Off-label use of ASMs in children in Sweden is common but not associated with lower retention.
- Specialized machine learning algorithms trained on register data are likely to provide useful information to clinicians, but further methodological development and evaluation are necessary.

The goal of the research was to help patients to become seizure-free faster, potentially at all, and could especially aid those with rare syndromes and comorbidities. Ultimately, machine learning trained on registers has the potential to improve the lives of people living with epilepsy.

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