**Big data analysis of ASM retention rates and expert ASM algorithm: A comparative study**

Samuel Håkansson1,2,3 | Johan Zelano1,2,3

**Abstract**

**Objective:** Only 50% of patients with new-onset epilepsy achieve seizure freedom with their first antiseizure medication (ASM). A growing body of data illustrates the complexity of predicting ASM response and tolerability, which is influenced by age, sex, and comorbidities. Randomized data with sufficient resolution for personalized medicine are unlikely to emerge. Two potential facilitators of ASM selection are big data using real-world retention rates or algorithms based on expert opinion. We asked how these methods compare in adult-onset focal epilepsy.

**Methods:** ASM retention rates were determined by cross-referencing data from comprehensive Swedish registers for 37,643 individuals, with identified comorbidities. Eight fictive cases were created and expert advice was collected from the algorithm Epipick. We compared Epipick suggestions in representative patient subgroups, and determined whether ranking based on retention rate reflected expert advice.

**Results:** The Epipick algorithm suggested six ASM alternatives for younger patients and three ASM alternatives for older patients. In the real-world data, retention rates for the ASMs ranked as best options by Epipick were high; 65%–72% for young patients and 71%–84% for older patients. The lowest retention rate for Epipick suggestions was 42%–56% in younger cases, and 70%–80% in older cases. The ASM with the best retention rate was generally recommended by Epipick.

**Significance:** We found a large overlap between expert advice and real-world retention rates. Notably, Epipick did suggest some ASMs with more modest retention rates. Conversely, clearly inappropriate ASMs (not recommended by Epipick) had high retention rates in some cases, showing that decision systems should not rely indiscriminately on retention rates alone. In future clinical decision support systems, expert opinion and real-world retention rates could work synergistically.

**Keywords**

antiseizure medication, clinical decision support system, pharmacotherapy
SELECTING THE RIGHT ANTISEIZURE MEDICATION (ASM) FOR EACH PATIENT IS A MAJOR CHALLENGE IN EPILEPTOLOGY. ONLY 50% OF PATENTS ACHIEVE SEIZURE FREEDOM WITH THE FIRST ASM, AND THE TRIAL-AND-ERROR PROCESS OF FINDING THE RIGHT DRUG CAN EXTEND INTO YEARS. THE PROPORTION OF PERSONS WITH EPILEPSY WHO REMAIN ON A SUBOPTIMAL ASM AND HAVE SEIZURES OR SIDE EFFECTS AS A CONSEQUENCE IS UNKNOWN. A GROWING BODY OF EVIDENCE HINTS AT THE COMPLEXITY OF SELECTING THE OPTIMAL FIRST ASM; MULTIPLE FACTORS SUCH AS AGE, SEX, COMORBIDITIES, AND ETIOLOGY SEEM TO INFLUENCE RETENTION RATES.

Several strategies exist to improve ASM success rates: algorithms providing expert opinion, studies providing randomized evidence, and big data. There are pros and cons of all these approaches.

Randomized data provide a high level of evidence, but is not likely to provide personalized data. Registration-purpose randomized-controlled trials (RCTs) have heterogeneous study populations and evaluate antiseizure effect by measuring the proportions of participants with fewer seizures, but are less informative about whether a first monotherapy will provide seizure freedom. Investigator-initiated trials are another option, and large studies like Standard and New Antiepileptic Drugs (SANAD) and SANAD II are informative, but require enormous efforts, and the participant numbers allow only relatively crude stratification in subgroup analyses.

Niche RCTs, focusing on particular subgroups of patients, have proven very difficult. Even for poststroke epilepsy, the most common acquired epilepsy, trials frequently struggle to reach recruitment targets. RCTs for every patient group (30-year-old women with posttraumatic epilepsy, 65-year-old men with epilepsy after brain infection, and so on) are not feasible.

Big data may offer a complementary approach. We recently showed that tracking real-world ASM retention rates in large register-based data sets of patients with acquired epilepsy gave results very similar to SANAD and RCTs on poststroke epilepsy. In addition, we found that age, sex, and comorbidities influenced retention rates and that 14%–21% of patients did not start with the ASM most likely to succeed for their strata. Other investigators using machine learning on large data sets have come to similar conclusions regarding the potential for improvement.

If big data is to inform clinical practice, there must be at least some congruence with randomized evidence and expert opinion. We have already demonstrated that register-based big data can replicate randomized studies, but how they compare to expert opinion is not known. In the present study, we, therefore, compared the results of big data analytics to expert opinion. Based on eight fictive cases, we tracked ASM use on a nationwide scale for relevant patient groups and compared the results to expert opinion, represented by the Epipick algorithm.

DATA FROM SEVERAL COMPREHENSIVE SWEDISH HEALTH REGISTERS WERE CROSS-REFERENCED: THE NATIONAL PATIENT REGISTER (NPR), THE CAUSE OF DEATH REGISTER (CDR), AND THE DRUG REGISTER (DR). THE NPR WAS ESTABLISHED IN 1987, WITH EXPANDED OUTPATIENT COVERAGE FROM 2001, AND INCLUDES INFORMATION ON ALL DIAGNOSES REGISTERED IN IN- OR OUTPATIENT CARE. THE CDR CONTAINS THE DATE OF DEATH FOR ALL SWEDISH INHABITANTS. THE DR WAS ESTABLISHED IN 2005 AND CONTAINS INFORMATION ON ALL PRESCRIPTIONS IN SWEDEN. REPORTING TO THE NPR AND CDR IS MANDATORY FOR ALL HEALTH CARE PROVIDERS, AND THE DR CONTAINS ALL PRESCRIPTIONS IN SWEDEN. ALL REGISTERS ARE MANAGED BY THE NATIONAL BOARD OF HEALTH AND WELFARE, WHO ANONYMIZED THE DATA BEFORE WE WERE GIVEN ACCESS TO IT.

KEY POINTS

- National Patient Register and prescription data were cross-referenced to study antiseizure medication (ASM) retention rates in all adults in Sweden >30 years with epilepsy onset after 2007.
- Eight fictive cases were used to compare real-world ASM retention rates for subgroups defined by age, sex, and comorbidities, and expert advice in the Epipick tool.
- The ASM with the highest retention rate was among Epipick-recommended treatments in all eight cases.
- Epipick generally recommended drugs that patients are likely to retain, but some suggestions had more moderate retention rates.
- Combinations of expert opinion and big data analytics could provide more complete information for prescribers.
2.2 | Cohort

We ordered anonymized information on all individuals \((n = 94 \, 321)\) with a first International Classification of Diseases, Tenth Revision (ICD-10) code of epilepsy (G40) after 2007. For the purpose of this study, we included patients with a first epilepsy diagnosis after the age of 30 (presumed focal epilepsy) and dispensation of an ASM (Anatomical Therapeutic Chemical (ATC) code N03) at or after their first seizure (Figure 1). Individuals with a rare first ASM (confidence intervals wider than 50%) were excluded, resulting in a total of 37,643 individuals. An age limit to define focal epilepsy was used in the main analysis because the code G40.9 (unspecified epilepsy) is often used for practical reasons and onset of generalized epilepsy is rare after age 30. A more specific diagnosis of focal epilepsy was used in a sensitivity analysis, including individuals with an ICD-code for focal epilepsy G40.1, G40.2, G40.6, or unspecified epilepsy G40.9 with a previous diagnosis of stroke (I61, I62, I63, or I69) or traumatic brain injury (S00-S06 or S20.9), resulting in a total of 23,254 patients.

2.3 | Patient characteristics and ASM tracking

Based on the NPR, age at epilepsy onset, sex, and comorbidities were defined by register searchers. The following comorbidities were identified: stroke, traumatic brain injury, psychiatric conditions, dementia, multiple sclerosis, central nervous system (CNS) infection, and developmental disorders/intellectual disability based on relevant ICD-10 codes (Table S1). ASM retention was estimated with Kaplan-Meier calculations based on a prescription interval of 12 months, and each dispensation was sufficient for 3 months, as described previously. Briefly, treatment was assumed to continue until 1 year passed without renewal, and patients were censored at death or date of export (December, 31, 2019). Confidence intervals were calculated using Greenwood’s Exponential formula.

2.4 | Cases, retention rates, and Epipick

We created eight fictive cases of focal epilepsy (Table 2), representing a broad range of ages and etiologies. For these eight cases, we assessed retention rates in the data set for individuals matching the case age, sex, and comorbidities. For cases of unknown cause, we included all individuals, but in a sensitivity analysis we excluded patients with any comorbidity at all (only including G40 and R56.8, and excluding patients with stroke, trauma, multiple sclerosis, dementia, brain infection, intellectual disability, psychosis, depression, stress, personality disorder, mental development disorder, or behavioral and emotional disorders) (ICD codes are available in Table S1). For the cases of poststroke epilepsy, posttraumatic epilepsy, or epilepsy in dementia, we restricted the analyses to patients with these comorbidities.

Expert opinion was obtained from the online ASM guide Epipick (www.epipick.org). Epipick provides ranking of ASMs in three levels of prioritization: best, second best, and least desirable though still acceptable. We used the ASMs categorized as “best” as comparators for the real-life data.

**FIGURE 1** Study concept. Of all individuals with new-onset epilepsy \((n = 94 \, 321)\), at total of 37,643 were selected based on cross-referenced registers: the National Patient Register (NPR) provided medical variables, the Cause of Death Register (CDR) provided information on survival, and the Drug Register (DR) provided information on antiseizure medication (ASM) prescriptions. The ASM tracking was based on (1) retention-rate calculations using prescription (P) interval (double arrow) to detect treatment stop (S), and (2) selecting subgroups for estimates.
2.5  Ethical permission

The study was approved by the Ethics Review Authority, decision number 2020-04902. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

2.6  Data availability statement

The underlying register data are protected by Swedish confidentiality laws and cannot be shared by the authors. The Swedish registers are available to researchers upon request to the Swedish National Board of Health and Welfare.

3  RESULTS

3.1  Retention rates

We first analyzed retention rates in all individuals in the data set and in those with a more specific diagnosis of focal epilepsy (Table 1). Lamotrigine had the highest retention rate and levetiracetam had the second highest.

3.2  Epipick suggestions

Next, we used our fictive cases to assess retention rates in particular patient subgroups. The Epipick algorithm suggested six ASM alternatives for patients younger than 50 years, and three ASM alternatives for older patients (Table 2).

In the real-world data, we first assessed retention rates with a permissive approach, including all ASMs with a confidence interval <50%. The retention rates for the best Epipick options were high: 65%–72% for young patients and 71%–84% for older patients; the lowest retention rates among the best Epipick suggestions were 42%–56% in younger cases and 70%–80% in older cases (Figure 2A). If precision was increased by including only ASMs with more than 50 users (resulting in a smaller confidence interval) the results were almost identical (Figure 2B), the one difference being a reduced gap between the Epipick suggestion with the highest and the lowest demonstrated retention rate.

3.3  Retention rate–based rank

We next evaluated the reverse association: whether the drugs with the best retention rates were among those recommended by Epipick. The ASMs with the highest retention rates were generally recommended by Epipick. If ASMs with any number of users were included, the highest-ranking ASM was among the Epipick suggestions in six of eight cases (Figure 2A). If ASMs with more than 50 users were included, the highest-ranking ASM was among the Epipick suggestions in all cases (Figure 2B).

Finally, we asked whether retention-rate ranking could distill the same drugs as those suggested by Epipick. If ASMs with any number of users were included, ASMs not suggested by Epipick had the highest or second-highest retention rate in several cases. In some cases, a clearly inappropriate ASM had the highest retention rate (phenytoin in elderly patients

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**TABLE 1** Retention rates for all individuals in the data set and for individuals with codes specific for focal epilepsy

| Antiseizure medication | All with epilepsy onset >30 years | Specific codes for focal epilepsy |
|------------------------|---------------------------------|---------------------------------|
|                        | 1-year retention rate | 95% CI | N | 1-year retention rate | 95% CI | N |
| Lamotrigine            | 71                 | 69–72 | 5641 | 71                 | 69–72 | 3383 |
| Levetiracetam          | 68                 | 68–69 | 12 974 | 68                 | 67–69 | 7998 |
| Phenobarbital          | 66                 | 49–75 | 58 | 62                 | 34–70 | 32 |
| Valproate              | 62                 | 61–64 | 4272 | 62                 | 60–64 | 2651 |
| Lacosamide             | 61                 | 51–68 | 134 | 57                 | 46–67 | 91 |
| Carbamazepine          | 58                 | 58–59 | 11 844 | 59                 | 58–60 | 7578 |
| Oxcarbazepine          | 57                 | 52–61 | 478 | 56                 | 49–61 | 303 |
| Phenytoin              | 53                 | 49–57 | 619 | 52                 | 47–57 | 394 |
| Gabapentin             | 45                 | 41–48 | 943 | 45                 | 40–49 | 517 |
| Pregabalin             | 40                 | 36–45 | 528 | 40                 | 33–45 | 252 |
| Clobazam               | 39                 | 30–46 | 152 | 31                 | 20–41 | 75 |
| Topiramate             | 38                 | 28–46 | 115 | 40                 | 27–52 | 55 |
**Table 2** Case vignettes, Epipick suggestions, and register data results

| Case | Epipick best | Real world rank | All with epilepsy onset >30 years | Specific codes for focal epilepsy |
|------|--------------|----------------|----------------------------------|----------------------------------|
|      | Epipick best | Real world rank | 1-year retention rate | 95% CI | n | 1-year retention rate | 95% CI | n |
| 30-year-old female, epilepsy and traumatic brain injury (MRI lesion) | Cbz | ltg | 71 | 60–78 | 101 | 72 | 60–79 | 83 |
| | Esol | lev | 57 | 42–70 | 50 | 56 | 40–68 | 48 |
| | Lcm | cbz | 51 | 38–60 | 76 | 47 | 33–57 | 66 |
| | Ltg | pgb | 50 | 18–66 | 14 | NA | NA | NA |
| 30-year-old female, epilepsy of unknown cause | Cbz | oxc | 67 | 35–79 | 18 | NA | NA | NA |
| | Esl | ltg | 64 | 60–68 | 591 | 66 | 59–70 | 282 |
| | Lcm | lev | 53 | 47–57 | 387 | 47 | 40–54 | 193 |
| | Ltg | cbz | 52 | 47–56 | 433 | 54 | 47–60 | 261 |
| | Lev | tpm | 45 | 21–60 | 22 | NA | NA | NA |
| | Oxc | vpa | 43 | 33–51 | 111 | 48 | 33–59 | 54 |
| | Pgb | 33 | 21–46 | 55 | 44 | 24–62 | 25 |
| | Pht | 32 | 10–47 | 19 | 27 | 3–44 | 11 |
| 30-year-old male, epilepsy and traumatic brain injury (MRI lesion) | Cbz | ltg | 65 | 54–74 | 86 | 64 | 53–74 | 76 |
| | Esol | vpa | 60 | 45–69 | 62 | 59 | 43–69 | 56 |
| | Lcm | lev | 57 | 48–65 | 130 | 56 | 47–65 | 116 |
| | Ltg | cbz | 51 | 43–58 | 172 | 48 | 39–55 | 147 |
| | Lev | pgb | 43 | 25–60 | 29 | 41 | 18–56 | 23 |
| | Oxc | clb | 45 | 25–57 | 35 | 40 | 12–56 | 15 |
| 40-year-old male, epilepsy of unknown cause | Cbz | ltg | 68 | 64–71 | 577 | 67 | 62–72 | 319 |
| | Esol | oxc | 62 | 47–71 | 66 | 65 | 45–76 | 37 |
| | Lcm | lev | 60 | 57–63 | 1005 | 60 | 56–64 | 597 |
| | Ltg | vpa | 57 | 52–61 | 442 | 56 | 50–63 | 221 |
| | Lev | cbz | 56 | 53–59 | 1432 | 58 | 55–62 | 806 |
| | Oxc | clb | 45 | 25–57 | 35 | 40 | 12–56 | 15 |
| | Lcm | 42 | 10–59 | 12 | NA | NA | NA |
| | Pgb | 37 | 28–45 | 123 | 34 | 21–44 | 61 |
| | Gbp | 32 | 23–42 | 99 | 31 | 19–45 | 48 |
| | Tpm | 31 | 8–47 | 16 | NA | NA | NA |
| | Pht | 26 | 10–38 | 31 | NA | NA | NA |
| Case                                                      | Epipick best | Real world rank | All with epilepsy onset >30 years | Specific codes for focal epilepsy |
|-----------------------------------------------------------|--------------|----------------|-----------------------------------|-----------------------------------|
|                                                           |              |                | 1-year retention rate 95% CI n    | 1-year retention rate 95% CI n    |
| 45-year-old female, epilepsy of unknown cause              | cbz          | lcm            | 72 42–89 15                       | NA 59–68 508                      |
|                                                           | esl          | ltg            | 65 62–68 1051                     | 64 59–68 435                      |
|                                                           | lcm          | lev            | 58 54–61 849                      | 56 51–60 357                      |
|                                                           | ltg          | cbz            | 52 49–55 976                      | 53 49–57 573                      |
|                                                           | lev          | vpa            | 49 43–55 277                      | 50 41–58 136                      |
|                                                           | oxc          | oxc            | 45 28–57 42                       | 42 19–56 24                       |
|                                                           | tpm          |                | 38 21–50 40                       | 33 8–49 17                       |
|                                                           | gbp          |                | 38 26–46 92                       | 30 14–48 31                       |
|                                                           | pht          |                | 36 19–49 37                       | 30 8–46 18                       |
|                                                           | cbz          |                | 38 26–44 115                      | 39 23–54 39                       |
| 60-year-old male, epilepsy and stroke                     | lcm          | ltg            | 77 71–81 270                      | 78 72–82 242                      |
| (concomitant medications, MRI lesion)                     |              | lev            | 72 69–74 1054                     | 71 68–74 921                      |
|                                                           |              | vpa            | 68 62–72 338                      | 66 61–71 306                      |
|                                                           |              | cbz            | 66 63–68 1147                     | 64 61–67 1004                     |
|                                                           |              | oxc            | 57 40–71 39                       | 61 41–76 32                       |
|                                                           |              | pht            | 54 38–64 55                       | 51 34–62 47                       |
|                                                           |              | gpb            | 49 25–63 26                       | 54 25–67 22                       |
|                                                           |              |                | 35 21–46 56                       | 36 20–47 50                       |
| 65-year-old female, epilepsy and stroke                   | lcm          | ltg            | 71 63–76 199                      | 70 62–75 177                      |
| (concomitant medications, MRI lesion)                     |              | lev            | 70 66–74 521                      | 70 65–74 440                      |
|                                                           |              | vpa            | 68 59–74 158                      | 67 57–73 140                      |
|                                                           |              | pht            | 61 37–73 29                       | 61 34–74 24                       |
|                                                           |              | cbz            | 60 55–64 531                      | 59 54–63 484                      |
|                                                           |              | gbp            | 50 27–63 30                       | 52 27–66 27                       |
|                                                           |              | oxc            | 46 23–46 26                       | 42 19–56 24                       |
| Case                                                                 | Epipick best | Real world rank | All with epilepsy onset >30 years | Specific codes for focal epilepsy |
|---------------------------------------------------------------------|--------------|----------------|-----------------------------------|----------------------------------|
|                                                                     |              |                | 1-year retention rate 95% CI n    | 1-year retention rate 95% CI n   |
| 70-year-old male, epilepsy and traumatic brain injury (concomitant medications, MRI lesion) | lcm          | ltg            | 80                                | 74–84                            | 79                               | 73–83 246 |
|                                                                     |              | lev            | 73                                | 69–75                            | 72                               | 68–75 776 |
|                                                                     |              | vpa            | 71                                | 65–76                            | 70                               | 63–75 242 |
|                                                                     |              | cbz            | 69                                | 66–72                            | 67                               | 63–70 746 |
|                                                                     |              | oxc            | 64                                | 40–76                            | 54                               | 27–68 22  |
|                                                                     |              | gbp            | 62                                | 44–75                            | 63                               | 44–77 35  |
|                                                                     |              | pht            | 61                                | 41–73                            | 64                               | 41–75 34  |
|                                                                     |              | gbg            | 52                                | 22–66                            | 45                               | 15–60 17  |
| 70-year-old male, epilepsy and traumatic brain injury (concomitant medications, MRI lesion) | lcm          | ltg            | 81                                | 75–85                            | 79                               | 72–84 191 |
|                                                                     |              | pht            | 78                                | 53–87                            | 78                               | 50–87 24  |
|                                                                     |              | lev            | 72                                | 68–76                            | 70                               | 66–75 426 |
|                                                                     |              | cbz            | 66                                | 60–70                            | 64                               | 58–69 329 |
|                                                                     |              | oxc            | 66                                | 57–73                            | 63                               | 52–70 126 |
|                                                                     |              | gpx            | 59                                | 39–70                            | 55                               | 32–68 30  |
| 80-year-old male, dementia (concomitant medications) | lcm          | pht            | 84                                | 65–93                            | 82                               | 59–93 25  |
|                                                                     |              | lmg            | 84                                | 79–87                            | 82                               | 76–87 216 |
|                                                                     |              | lvg            | 80                                | 77–83                            | 80                               | 76–83 506 |
|                                                                     |              | oxc            | 79                                | 50–87                            | NA                               |          |
|                                                                     |              | cbz            | 78                                | 74–81                            | 77                               | 73–81 411 |
|                                                                     |              | vpa            | 75                                | 69–80                            | 75                               | 67–81 185 |
|                                                                     |              | gtp            | 55                                | 38–70                            | 64                               | 43–79 31  |
| 80-year-old female, dementia (concomitant medications) | lcm          | pht            | 81                                | 64–90                            | 73                               | 52–86 28  |
|                                                                     |              | lmg            | 80                                | 76–83                            | 79                               | 74–83 402 |
|                                                                     |              | lvg            | 79                                | 67–88                            | 80                               | 57–88 32  |
|                                                                     |              | oxc            | 73                                | 69–77                            | 73                               | 67–78 344 |

Note: Epipick settings used are indicated in parenthesis in the vignettes.
Abbreviations: cbz, carbamazepine; esl, eslicarbazepine acetate; lcm, lacosamide; oxc, oxcarbazepine; lmg, lamotrigine; lvg, levetiracetam; tpm, topiramate; gpg, pregabalin; vpa, valproic acid; pht, phenytoin.
FIGURE 2  Retention rates of the Epipick suggestion with the highest (gray area) and lowest (dashed) retention rate (large areas better). If all antiseizure medications (ASMs) with any number of individuals were included (A) some Epipick suggestions had low retention rates, but this was not seen if precision was increased by requiring 50 users (B). PTE = posttraumatic epilepsy, PSE = poststroke epilepsy.

FIGURE 3  Evaluation of whether retention rates identify expert choice. Top row (larger area better): If all antiseizure medications (ASMs) with any number of users were included, the ASM with the highest retention rate was recommended by Epipick in six of eight cases (A). Performance of retention rates was improved if 50 users were required; then the ASM with the highest retention rate was recommended by Epipick in all cases (B). Lower row (points closer to center better): With any number of users, some potentially inappropriate ASMs not recommended by Epipick had the highest retention rates (C). With >50 users, “inappropriate” ASMs ranked three or lower in all cases (D).

If the analysis was restricted to ASMs with more than 50 users, the ASM with the best and the second-best retention rates were suggested by Epipick for all cases (Figure 3).

3.4  Sensitivity analysis

For the main analysis, the three patients with unknown causes were represented by all patients. In a sensitivity...
analysis, we included patients with no comorbidity at all (Table S2). This analysis showed results that were similar to the main analysis: both top retention rate ASMs were recommended by Epipick for all cases.

4 | DISCUSSION

We evaluated the potential of national big data routinely collected in administrative health care registers to inform ASM selection by stratification on age, sex, and comorbidities by comparing the performance of big data analytics to that of expert opinion, as illustrated by Epipick. We aimed to evaluate the congruence between these approaches for facilitating ASM selection. The analysis resulted in several interesting conclusions, and it is hoped that they are helpful in furthering personalized medicine in epilepsy.

First of all, retention rate in prescription data on a national level seems to find relatively appropriate ASMs, although some restriction is needed to avoid inappropriate alternatives. Conversely, expert opinion illustrated by Epipick recommends drugs that patients in Swedish registers are likely to retain. Nonetheless, our investigation did demonstrate that some Epipick suggestions had higher retention rates than others. These results have several implications for the development of future clinical decision support systems, one being that combinations of expert opinion and big data analytics are likely to yield better results than either one. Expert opinion algorithms can be enhanced by providing retention rates for the possible alternatives to the user. Conversely, clinical decision systems should not rely indiscriminately on retention rates alone, since this can be high also for inappropriate ASMs.

There are other interesting findings in our material. To our knowledge, it is the first attempt to use administrative data to track ASM retention in patient subgroups based on data from an entire country. Our findings that lamotrigine has the highest retention rate in focal epilepsy is in excellent agreement with the SANAD and SANAD II studies. The results in our study are also similar to previously reported comparisons of Epipick and real-world retention rates in a smaller population. The ASMs suggested by Epipick had a significantly higher retention rate than many lower ranked ASMs.

Some inappropriate ASMs had high retention rates in our real-world data, indicating a potential problem with putting too much emphasis on retention rate in guiding treatment. High retention of inappropriate ASMs may arise for several reasons. Long-term adverse effects might not result in withdrawal until time points that are later than those analyzed by us, and low-quality epilepsy care may cause patients to continue taking less suitable or tolerated ASMs. For instance, sodium valproate was prescribed to women with epilepsy of childbearing age to a non-negligible extent in the study period, despite the now well-known risks and 2018 European Medicines Agency regulations.

There are drawbacks to our method. The register method relies on several assumptions. The epilepsy diagnosis has been validated and has a 90% positive predictive value. Similarly, the ASM tracking by Kaplan-Meier ignores competing risks. The real-world retention rates also represent clinical reality, meaning that the higher ASM retention rates in the older cases may well represent less-rigorous epilepsy care with fewer attempts at ASM revision or that patients have not survived long enough to change their treatment. The results may also be confounded by co-medication and seizure frequency, which is considered in Epipick but not in our data, potentially leading to a difference in retention rates among Epipick suggestions. For instance, the titration required for lamotrigine may lead to it being used in cases with less frequent seizures, which may also require a longer evaluation period and thereby delayed discontinuation of the drug.

Although our fictive cases represent many patients, our investigation does not cover the huge individual variability of epilepsy. With more data, the method can probably give more precise estimates for even more narrowly defined patient groups. Although we used prescription data from an entire country for over a decade, the selection of individuals with specific comorbidities, age, and sex resulted in relatively few patients using individual ASMs and relatively imprecise estimates of retention rates for these drugs. Multinational efforts could be one possible counter-effort. It would also be interesting to study ASM dosage, but extracting the doses actually used by patients from prescription register data is not possible.

A near step in personalized medicine of epilepsy is the use of artificial intelligence, to make even better use of big data accumulating in various health registers. Our study provides some clues on how expert opinion and big data analytics can interact to create even better outcomes.

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CONFLICT OF INTEREST

JZ reports speaker honoraria for unbranded educations from Eisai and UCB, and as employee of Sahlgrenska university (no personal compensation) being an
investigator/subinvestigator in clinical trials sponsored by UCB, GW Pharma, Bial, and SK life science. SH reports no disclosures.

**ORCID**

Samuel Håkansson [https://orcid.org/0000-0002-8681-0113](https://orcid.org/0000-0002-8681-0113)

Johan Zelano [https://orcid.org/0000-0001-9445-4545](https://orcid.org/0000-0001-9445-4545)

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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