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Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016

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ABSTRACT

Objective To assess the evolution of antiepileptic drug (AED) treatment patterns and seizure outcomes in England from 2003 to 2016.

Design, setting and participants Retrospective cohort study of electronic medical records from Clinical Practice Research Datalink and NHS Digital Hospital Episode Statistics databases. Patients newly diagnosed with epilepsy were identified and followed until end of data availability. Three eras were defined starting 1 April 2003 (first NICE guideline); 1 September 2007 (SANAD publication); 1 January 2012 (second NICE guideline).

Outcome measures Outcomes were time from diagnosis to first AED; AED sequence; time from first AED to first 1-year remission period (no new AED attempts and no seizure-related healthcare events); and time from first AED prescription to refractoriness (third AED attempt regardless of reason). Kaplan-Meier was used to analyse time-to-event variables.

Results 4388 patients were included. Mean follow-up was 6.8, 4.2, and 1.7 years by era. 84.6% of adults (≥16 years), 75.5% of children (<16), and 89.1% of elderly (65+) received treatment within 1 year; rates were generally stable over time. Treatment trends included reduced use of carbamazepine (adult first-line, era 1: 34.9%; era 3: 10.7%) and phenytoin, earlier-line and increased use of levetiracetam (adult first-line, era 1: 2.6%; era 3: 26.2%) and lamotrigine, particularly in adults and elderly, and a larger number of different AEDs used overall. Valproate use shifted somewhat to later lines. Rates of 1-year remission within 2 years of starting treatment increased in adults (era 1: 71.9%; era 3: 81.4%) and elderly (era 1: 76.1%; era 3: 81.7%). Overall, 55.5% of patients relapsed after achieving 1-year remission. Refractoriness rates remained stable over the eras (~26% of adults within 5 years).

Conclusion Treatment trends often were not aligned with era-relevant guidance. However, our results suggest a slight improvement in epilepsy treatment outcomes over the 13-year period.

ARTICLE SUMMARY

Strengths and limitations of this study

- Use of the Clinical Practice Research Datalink and NHS Digital Hospital Episode Statistics databases allowed access to a large national pool of patients for identification of those newly diagnosed with epilepsy.
- Treatment eras were delineated by epilepsy guideline updates to allow capture of changes in antiepileptic drug treatment practice.
- The stringency of diagnostic criteria may limit the generalisability of the data.
- The nature of the data is prone to incomplete or incorrect medical records and coding, lack of specificity, and capture prescriptions but not prescription fills.
- The definition of remission was based on health care consultations, with 1 year possibly too short to be considered for remission; and drug resistance was based on switching antiepileptic drugs without taking into account the reasons for treatment changes, which were unknown but likely driven by lack of effect and poor tolerability.

INTRODUCTION

The introduction of new antiepileptic drugs (AEDs) since 2003 has been accompanied by studies of the comparative efficacy, safety, and tolerability of older and newer AEDs,[1-3] as well as by evolving clinical practice guidelines that incorporate newer medications into recommendations for epilepsy treatment.[4-6] Treatment patterns would be expected to reflect the latest guidance for individual AEDs in epilepsy management, but scant information is available to assess alignment in clinical practice. A number of studies have reported an increase in the use of newer AEDs prescribed for first-line treatment in new-onset epilepsy in UK primary care settings[7, 8] and across European Union countries.[9]

Use of newer AEDs with reported similar or improved efficacy and better tolerability than older AEDs would be expected to benefit overall epilepsy treatment success and patient outcomes. However, literature suggests that there has been no meaningful improvement in epilepsy treatment-related outcomes[1, 10-12] and a notable portion of patients still fail first-line AED therapy.[13, 14] The objective of this study was to evaluate AED treatment patterns and seizure outcomes in England over three time periods from 2003 to 2016, using electronic medical record data, to provide further insights into the management of patients newly diagnosed with epilepsy.

METHODS

Study design

This was an exploratory, retrospective cohort analysis of primary care electronic medical records from the UK Clinical Practice Research Datalink (CPRD) and secondary care electronic medical records from the National Health Service (NHS) Digital Hospital Episode Statistics (HES) databases. The CPRD contained over 4 million active patient records (and more than 11 million overall) drawn from 674 UK primary care practices, representing approximately 7% of the UK population, in 2015

[15]; these numbers have since grown.[16] The HES database contains details of all secondary care admissions, outpatient appointments, and Accident & Emergency attendances at NHS hospitals in England.[17]

AED treatment patterns and seizure outcomes in England were assessed over three 4.5-year eras. Era 1 (first guideline era) included dates from 1 April 2003 to 31 August 2007 and encompassed the publication of the first National Institute for Health and Care Excellence (NICE) epilepsy guidance.[4, 18, 19] These guidelines recommended carbamazepine (CBZ) or sodium valproate (VPA) as first-line treatment for focal (partial-onset) and generalised seizures. Era 2 (intermediate era) was defined as 1 September 2007 to 31 December 2011, and captured updated guidance that recommended lamotrigine (LTG) or CBZ as first line for focal (partial-onset) seizures and VPA for generalised seizures based on a large randomized pragmatic trial (SANAD).[1] Era 3 (newer guideline era) spanned the timeframe from 1 January 2012 to 31 May 2016, with the second NICE epilepsy guidance recommending CBZ or LTG as first-line treatment for focal seizures, VPA for generalised seizures, and advice to be given to women of childbearing potential regarding foetal risks of malformation and neurodevelopmental impairments with VPA.[6, 20] A 2015 update warned against prescribing VPA to pregnant women and those of childbearing potential unless other AEDs were ineffective or not tolerated (in 2018 guidelines, VPA is contraindicated in girls and women of childbearing potential).[21]

Cohort selection

Patients with epilepsy newly diagnosed between 1 April 2003 and 31 May 2016 (date of last available CPRD practice data) were included in the study. Diagnosis was operationalised as an incident epilepsy diagnosis code (online supplementary table S1) at or near a neurologist visit, as assessed in HES outpatient data or primary care referral data using June 2016 data sets, and constituted the index date. Those who had started an AED attempt less than 3 months prior to a diagnosis were included. An AED attempt was defined on the start date of an AED prescription that a patient had never used before, and maintained for at least 31 days, as identified in primary

care records. A pre-index period of at least 2 years was required with their practice's data flagged as up-to-standard. Patients were excluded if they had an epilepsy diagnosis at any time before the index date, or AED treatment during the 2-year pre-index period. Included patients were followed until data were no longer available, owing either to death or to leaving their general practitioner practice or date of last CPRD data (31 May 2016).

Three age cohorts were considered: adults aged ≥16 years, children ≥2 to <16 years of age, and the elderly, ≥65 years of age (a subset of adult patients).

Outcome measures

The primary outcome was time to 1-year remission from seizures for all treated patients, starting from the time of first AED attempt until first 1-year period of remission. One-year remission was defined as having no new AED attempts, and the absence of all seizure-related healthcare events and quality outcomes framework data and read codes indicating a seizure at any time for at least 1 year (online supplementary table S2). A subsequent occurrence of any of these events is defined as a relapse. Outcomes also included time from diagnosis to first AED prescription (all patients); treatment patterns by era, age, and sex cohort; and time from first AED prescription to refractoriness (treated patients only), which was defined as a third distinct AED attempt as identified in primary care records. The end of AED exposure and treatment as poly/monotherapy were not assessed.

Statistical analysis

Descriptive statistics were used to summarise both continuous variables and categorical variables such as mean, standard deviation (SD), median, and percentages. Analyses were conducted on unmatched cohorts and reported results are unadjusted. Outcomes were evaluated using Kaplan-Meier analysis.

The protocol for this study was reviewed and approved by the Independent Scientific Advisory Committee, the CPRD scientific/ethics committee.

Patient involvement statement

This research was conducted without patient involvement in the design or interpretation of this study, or in the writing and editing of this document.

RESULTS

Study participants

Overall, of 137,267 patients with an epilepsy diagnosis code in the data, 4388 patients (adults n=3861; children n=527) met the study inclusion criteria and were available for analysis. Mean follow-up was 6.8 years (era 1), 4.2 years (era 2), and 1.7 years (era 3). Baseline characteristics were largely as expected for diagnosed patients (overall population: mean age at diagnosis, 41.4 years; 85.0% of patients with ≥1 AED treatment; 78.4% with unspecified epilepsy) (table 1). There appeared to be higher rates of comorbidities, reflected by epilepsy-specific comorbidity index scores, and lower rates of unspecified epilepsy diagnosis in era 3 compared with era 1. There were minor changes in the regional make-up of CPRD data, with the number of practices participating in CPRD generally decreasing in eastern regions and increasing in London and southern regions over time (eg, London made up 13.7% of practices in 2005 and 19.0% in 2015).

Table 1 Baseline characteristics of the sample population.

	Adults (≥16 years) n=3861	Children (<16 years) n=527	Elderly* (≥65 years) n=876

Age at diagnosis, years, mean (SD)	45.9 (20.4)	8.5 (4.0)	74.7 (7.0)
Female, n (%)	1845 (47.8)	244 (46.3)	372 (42.5)
No. diagnosed (%)			
Era 1, n (% of era)	1276 (33.0)	133 (25.2)	260 (29.7)
Era 2, n (% of era)	1452 (37.6)	248 (47.1)	322 (36.8)
Era 3, n (% of era)	1133 (29.3)	146 (27.7)	294 (33.6)
Germaine-Smith epilepsy-specific comorbidity index, mean (SD)	0.8 (1.9)	0.3 (1.0)	2.1 (2.5)
Era 1, n (% of era)	0.6 (1.5)	0.3 (1.0)	1.4 (2.3)
Era 2, n (% of era)	0.8 (1.8)	0.2 (0.7)	2.0 (2.3)
Era 3, n (% of era)	1.1 (2.4)	0.4 (1.2)	2.7 (2.9)
Epilepsy type			
Generalised, n (%)	324 (8.4)	72 (13.7)	65 (7.4)
Era 1, n (% of era)	91 (7.1)	15 (11.3)	15 (5.8)
Era 2, n (% of era)	119 (8.2)	44 (17.7)	22 (6.8)
Era 3, n (% of era)	114 (10.1)	13 (8.9)	28 (9.5)
Focal (partial-onset), n (%)	475 (12.3)	76 (14.4)	114 (13.0)
Era 1, n (% of era)	162 (12.7)	15 (11.3)	46 (17.7)
Era 2, n (% of era)	153 (10.5)	31 (12.5)	29 (9.0)
Era 3, n (% of era)	160 (14.1)	30 (20.5)	39 (13.3)
Unspecified	3062 (79.3)	379 (71.9)	697 (79.6)
Era 1, n (% of era)	1023 (80.2)	103 (77.4)	199 (76.5)

Era 2, n (% of era)	1180 (81.3)	173 (69.8)	271 (84.2)
Era 3, n (% of era)	859 (75.8)	103 (70.5)	227 (77.2)
At least one AED treatment, n (%)	3313 (85.8)	417 (79.1)	783 (89.4)
Total follow-up, patient-years†	16,483.92	2363.94	3257.28
Mean follow-up, years	4.3	4.5	3.7
Era 1, n (% of era)	6.7	7.3	6.0
Era 2, n (% of era)	4.1	4.6	3.7
Era 3, n (% of era)	1.7	1.8	1.7

Era 1, 1 April 2003 to 31 August 2007 (first NICE guidance); era 2, 1 September 2007 to 31 December 2011 (SANAD); era 3, 1 January 2012 to study 31 May 2016 (second NICE guidance).

*Elderly patients are a subset of the adult patient population.

†Total follow-up, patient-years: calculated by adding the follow-up time for all patients.

AED, antiepileptic drug.

Many patients (n=4456) who met inclusion criteria were excluded owing to pre-diagnosis AED use, primarily with AEDs that have multiple indications (eg, valproate, carbamazepine, lamotrigine). Because of the required 2-year baseline period, no 0- or 1-year-old children were included in the sample.

Time from diagnosis to first AED prescription

Kaplan-Meier estimates revealed that 84.6% of adults, 75.5% of children, and 89.1% of the elderly received AED treatment within 1 year of index date (figure 1). Treatment rates from era 1 to era 3 appeared to increase slightly in adults (82.3% to 86.6%) and the elderly (86.3% to 90.8%), and to decrease slightly in children (77.4% to 69.2%).

Treatment patterns over time

Analysis of treatment patterns over time in adults shows a large shift away from CBZ (adult first-line share, era 1: 34.9%; era 3: 10.7%) and phenytoin (PHT; adult first-line share, era 1: 7.6%; era 3: 2.1%), and toward earlier and increased use of levetiracetam (LEV; adult first-line share, era 1: 2.6%; era 3: 26.2%) (figure 2A). The use of first-line VPA remained relatively stable over eras 1 and 2, and decreased in era 3. AED treatment patterns appeared to be far more stable in children than adults, with use of first-line VPA remaining high over time (first-line share: in children, era 1: 49.0%; era 3: 49.6%; in adults, era 1: 29.0%; era 3, 49.0%; figure 2B). Nevertheless, the use of CBZ decreased in favour of earlier use of LEV (CBZ first-line share, era 1: 30.8%; era 3: 15.4%; LEV first-line share, era 1: 0%; era 3: 15.4%). These AED patterns were consistent for second-line treatment in children. Treatment pattern changes in the elderly population were similar but more pronounced than in the overall adult patient population. In the elderly, CBZ use fell in all treatment lines (first-line share, era 1: 36.3%; era 3: 9.1%; second-line share, era 1: 23.9%; era 3: 5.7%; third-line share, era 1: 16.7%; era 3: 4.7%) in favour of earlier and increased use of lamotrigine (LTG) and LEV (LTG first-line share, era 1: 8.5%; era 3: 27.4%; LEV first-line share, era 1: 4.0%; era 3: 31.2%; figure 2C).

Analysis of treatment patterns by sex indicated that in adults, women were prescribed first-line VPA and CBZ less often and LTG more often than men—a finding that remained stable over time (women vs men, era 1: VPA, 22.7% vs 35.2%; CBZ, 30.7% vs 39.2%, LTG, 31.4% vs 11.9%; era 3: VPA, 11.8% vs 26.1%; CBZ, 8.4% vs 12.8%; LTG, 42.6% vs 26.7%; figure 3). The trends in VPA and LTG use were mostly intact through third-line AED (figure 3). In children, generally LEV and LTG were more common and VPA less common for girls than boys across eras as well as through second-line AED (supplemental figure 1). In the elderly subgroup, first-line treatment patterns were comparable between men and women (supplemental figure 2).

One-year remission rates

One-year remission rates, within 1 or 2 years of treatment initiation, increased somewhat over time in adults and the elderly, but were more variable in children (table 2). The percentage of patients achieving a 1-year period of remission within 1 year of starting treatment increased from era 1 to era 3 in all three age cohorts. The most substantial increase (era 1 to era 3) was observed in the elderly (31.5% to 47.3%; a 50.3% increase from era 1). The percentage of adults and the elderly achieving 1-year remission within 2 years of starting treatment was higher than within 1 year and increased over time (era 1 to era 3: 71.9% to 81.4% adults; 76.1% to 81.7% elderly). In children, there was a slight decrease in remission rates within 2 years of treatment from era 1 to era 3 (table 2). Overall, 55.5% of patients relapsed after achieving 1-year remission.

Table 2 Treatment outcomes by study population and era

	Adults (≥16 years) n=3313	Children (<16 years) n=417	Elderly (≥65 years) n=783
Rate of 1-year remission within 1 or 2 years of treatment			
Patients with at least one period of 1-year remission,* n (%)	2430 (73.3)	317 (76.0)	536 (68.5)
Of these patients, at least one relapse,* n (%)	1362 (56.0)	163 (51.4)	310 (57.8)
1-year period of remission 1 year from treatment start (KM estimate)	35.2%	40.1%	36.3%
Era 1†	31.6%	36.4%	31.5%
Era 2†	34.7%	41.9%	32.8%
Era 3†	42.0%	40.8%	47.3%

1-year period of remission within 2 years of treatment start (KM estimate)	75.3%	75.9%	78.4%
Era 1†	71.9%	73.0%	76.1%
Era 2†	75.3%	78.3%	78.2%
Era 3†	81.4%	72.8%	81.7%
Rate of refractoriness within 3 years of starting first AED treatment			
Patients refractory 3 years from start of treatment (KM estimate)	17.5%	23.8%	11.9%
Era 1†	17.3%	20.8%	11.1%
Era 2†	17.4%	24.3%	13.4%
Era 3†	17.6%	(n<10)	11.2%

Era 1, 1 April 2003 to 31 August 2007 (first NICE guidance); era 2, 1 September 2007 to 31 December 2011 (SANAD); era 3, 1 January 2012 to study 31 May 2016 (second NICE guidance).

*Raw figures, not adjusted for differential follow-up between eras.

†Number of patients diagnosed in era 1, 2, and 3, respectively, and received treatment: adults, n=1097, 1254, and 962; children, n=110, 204, and 103; elderly, n=234, 291, and 258.

AED, antiepileptic drug; KM, Kaplan-Meier estimate.

Time from first AED treatment to refractoriness

Overall, a similar percentage (about 17% to 18%) of adult patients became refractory within 3 years of first starting treatment across the different eras (table 2). Approximately 25% to 26% of adults were treatment refractory after 5 years (data not shown). Elderly patients were less likely to become treatment refractory than all adults or children (table 2).

DISCUSSION

The results of this analysis suggest that there has been some improvement in epilepsy outcomes, reflected by shorter times to 1-year remission (no new AED attempts or seizure-related healthcare events for at least 1 year) over the 13-year period. Various reasons may contribute to this observation, including improved diagnosis of epilepsy and differential diagnosis of non-epilepsy disorders, more active epilepsy management with personalised treatment, and wider use of newer, better-tolerated AEDs, particularly to replace enzyme-inducing drugs in the elderly population who are most susceptible to risks associated with enzyme induction.[22] Although our study assessed treatment patterns by age group and sex, it did not assess whether prescribing is targeted based upon other patient characteristics.

The observed major changes in prescription trends are at odds with NICE guidelines during era 3, which suggest prescribing CBZ or LTG as first-line treatment in children and adults with newly diagnosed focal seizures, and VPA for those newly diagnosed with generalised seizures.[6] Analysis of first-line treatment patterns over time shows a reduction in VPA use in era 3, a large shift away from CBZ and PHT in all treatment lines, and a trend toward earlier and increased usage of LEV in adults, particularly the elderly.[6] Although the sharp decrease in PHT aligns with 2012 NICE guidelines,[6] possibly reflecting a change in AEDs used in acute settings or a shift to non-enzyme active AEDs (nEAAEDs) in older patients, the decrease in CBZ and increase in LEV do not align with treatment guidelines.

For elderly patients, 2012 NICE guidelines recommend CBZ as an extended release formulation.[6] Preferential use of CBZ in older patients was reported in a study of CPRD data from 2001 to 2010, which found that patients receiving enzyme-inducing AEDs (EIAEDs: CBZ, 63.3%; PHT, 35.3%) were older and had more comorbid illness; the study also reported the use of EIAEDs resulted in higher healthcare costs compared with nEAAEDs.[22] Our findings also show that CBZ was most often prescribed for the elderly population during era 1 (2003-2007). Given the higher susceptibility to risks associated with enzyme induction, as well as increased costs, a shift to nEAAEDs would appear a rational change that is reflected in era 3 prescribing trends.

In children, treatment patterns were more stable, which may reflect the situation that fewer new AEDs have become available for this population. Limited choices may be related to the more stringent criteria necessary for drug approval, with more complex trial designs and challenges in recruitment. The stability of VPA use in children may be related to its broad spectrum activity when diagnosis is uncertain.

In women, use of VPA greatly diminished across eras, lending support to a database study in the US that reported decreased VPA use among adult women.[23] These findings are perhaps not surprising given the teratogenic profile of VPA and increased warnings associated with VPA in girls and women of childbearing potential. In 2018, the Medicines and Healthcare products Regulatory Agency advised against the use of VPA in girls and women of childbearing potential;[24] thus, one might anticipate further declines in its use going forward.

A longitudinal cohort study describing seizure freedom rates over 30 years reported a virtually unchanged seizure-freedom rate, and a decrease in the probability of achieving seizure freedom with each unsuccessful AED regimen prescribed.[11] The study reported 61% to 64% of patients achieved 1-year seizure freedom over time.[11] Study authors concluded that despite changing treatment patterns and greater use of newer AEDs, as observed in the present study, no meaningful improvements in long-term outcomes had occurred. In contrast, our study found an improvement in outcomes, with a higher proportion of patients entering remission, nearly half of whom subsequently relapsed. Across eras, an increasing proportion of patients achieved 1-year remission (eg, 71.9% to 81.4% for adult subgroup). There are a number of differences that may explain the discrepancy in results between these studies. First, the prior study assessed 1-year seizure freedom before study end (thus excluding those who were seizure-free for ≥12 months who relapsed before study end), whereas our study assessed 1-year remission from AED initiation. Because patients with longer follow-up also have more time and opportunity to relapse, in the prior study 1-year seizure freedom favours patients with shorter follow-up (ie, those diagnosed in later eras), which is not the case in the current study. By using Kaplan-Meier methods to adjust for this differential follow-up time between eras, we found increasing remission rates over

time in adult and elderly subgroups. Other notable differences include time periods of the study cohorts (1982–2012 vs 2003–2012), available AEDs, reported study population (overall vs age-specific subgroups), settings (single epilepsy centre in Glasgow vs general practitioner practices across England), and data source (medical records and notes vs structured electronic medical records). It is possible that reporting outcomes for an overall population may have masked trends in the adult population, as our study found treatment patterns and remission rates in children were relatively stable over time periods.

The proportion of patients who were refractory within 3 years of first starting AED treatment was similar across eras, although percentages varied somewhat according to age group. The trend for increasing remission rates and stable refractoriness rates would appear to be a contradiction. A possible explanation may be that patients progress through 3 AEDs treatments via more active management. Although these patients would meet the definition for refractory epilepsy, the AEDs may represent more specifically chosen, better tolerated treatments that lead to improved remission rates.

Study interpretation is limited by a number of factors. The conservative, stringent diagnostic criteria may have limited the generalisability of the data, as the study selection rate was approximately 25% to 30% of the expected incidence rate.[25] The accuracy of electronic medical records data is limiting, as instances whereby a seizure or epilepsy code was used after a non-seizure event could be present. The requirement for a neurologist visit as part of our epilepsy diagnosis criteria was intended to maximise the accuracy of the diagnosis. Additionally, the epilepsy type was not usually discernible from medical record recording practices in our study, with 70% to 80% of patients having been classified as having an unspecified epilepsy diagnosis. Because patient characteristics by AED were not assessed, the accuracy of selected AED(s) is not known (all prescriptions reflect data from general practitioners).

Outcome definitions may also contribute to limitations. Our definition of remission was based on healthcare consultations, and it could be argued that the 1-year time period was insufficient to be considered as ‘remission’,[26] or that basing

remission on healthcare encounters rather than information about seizure frequency may be unspecific. Further, the definition of seizure freedom has evolved, with the ILAE proposing a 'rule of three', including the absence of seizures for at least the previous 12 months OR for three times the longest pre-treatment interval between seizures, whichever is greater.[27] In our study, drug resistance (refractoriness) was based on switching AEDs and did not take into account the reasons for treatment changes, which were unknown (eg, adverse events/tolerability, pregnancy) but likely were predominantly driven by a combination of lack of efficacy and poor tolerability. This definition differs from that proposed by the ILAE in 2010: 'Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.'[27]

Our study is also limited by incomplete information regarding prescribing data from general practitioners, particularly lack of information regarding patient adherence and the appropriateness of AED selection based on patient characteristics. Shifts in the make-up of practices supplying data to CPRD (eg, reflected by capture of higher rates of comorbidities and specified epilepsy diagnosis, and shifts in the regional make up of CPRD data, which may be associated with regional treatment practices) over time may have introduced unmeasured bias in patient baseline characteristics. Changes to data availability and accuracy over eras may have affected results, with a prior study noting the improved accuracy of administrative or registry data in later years.[28] A crucial limitation is that cohorts are unmatched and analyses unadjusted; thus, there is no statistical basis for comparisons between outcomes. As such, our findings are exploratory in nature and should be interpreted with caution.

Despite these potential limitations, our study suggests an evolution of AED treatment patterns and AED effectiveness over a 15-year period in clinical practice in England. Major changes in treatment patterns, particularly a reduction in CBZ and PHT use in favour of earlier and increased use of LEV, were observed. Although our study did not assess the use of particular AEDs based on patient characteristics or appropriateness, we generally found a reduction in the use of EIAEDs in the elderly and VPA in women, in keeping with newer treatment recommendations. In contrast

to other studies reporting no meaningful improvement in the overall epilepsy population,[10, 11] we found an increase in 1-year remission rates following AED initiation in adults, which, given the limitations of the current study, will need to be further studied. Although some improvement in epilepsy treatment outcomes was observed, a sizable proportion of patients with epilepsy remain uncontrolled on first- and second-line treatment, indicating a continued need for innovations for patients living with poorly controlled epilepsy.

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Contributors GP and SB conceived of the study and had a role in study design. JL and VK conducted data collection, extraction, and analysis of the data. GP, SB, and JL contributed to data interpretation. All authors contributed to the review and revision of the manuscript and approved of the final manuscript for publication.

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Competing interests G Powell is a paid medical consultant for UCB Pharma. J Logan and V Kiri are paid consultants for UCB Pharma. S Borghs is an employee of UCB Pharma.

Patient consent for publication Not required.

Data sharing statement The CPRD and HES datasets used in this study are available from the National Institute for Health Research, the Medicines & Healthcare products Regulatory Agency, and NHS Digital, respectively.

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FIGURE LEGENDS

Figure 1 Time from first diagnosis to first AED prescription in A) adults (n=3861), B) children (n=527), and C) elderly (n=876).

AED, antiepileptic drug.

Figure 2 Treatment patterns by AED attempt in A) adults, B) children, and C) elderly.*

*AEDs accounting for ≥1% of attempts in any patient group in any era.

ACZ, acetazolamide; AED, antiepileptic drug CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; ESL, eslicarbazepine; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHB, phenobarbital; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

Figure 3. Treatment patterns in adult men and women for A) first-line, B) second-line, and C) third-line treatment.*

*AEDs accounting for ≥1% of attempts in any patient group in any era.

AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

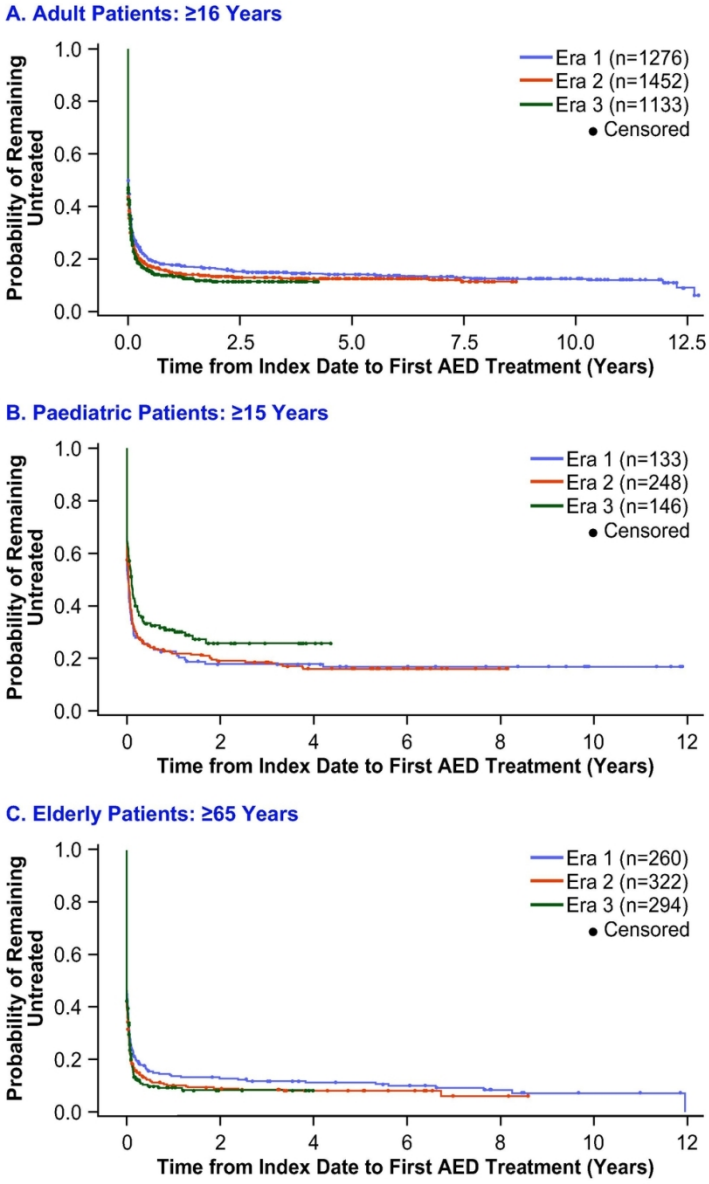

Figure 1. Time from first diagnosis to first AED prescription in A) adults (n=3861), B) children (n=527), and C) elderly (n=876).

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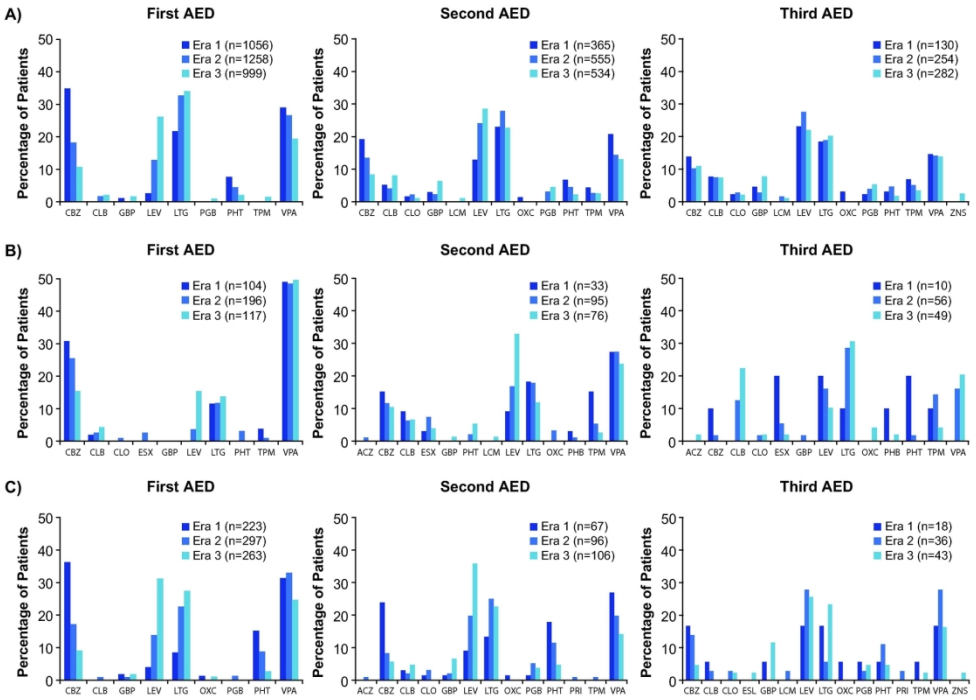

Figure 2. Treatment patterns by AED attempt in A) adults, B) children, and C) elderly.*

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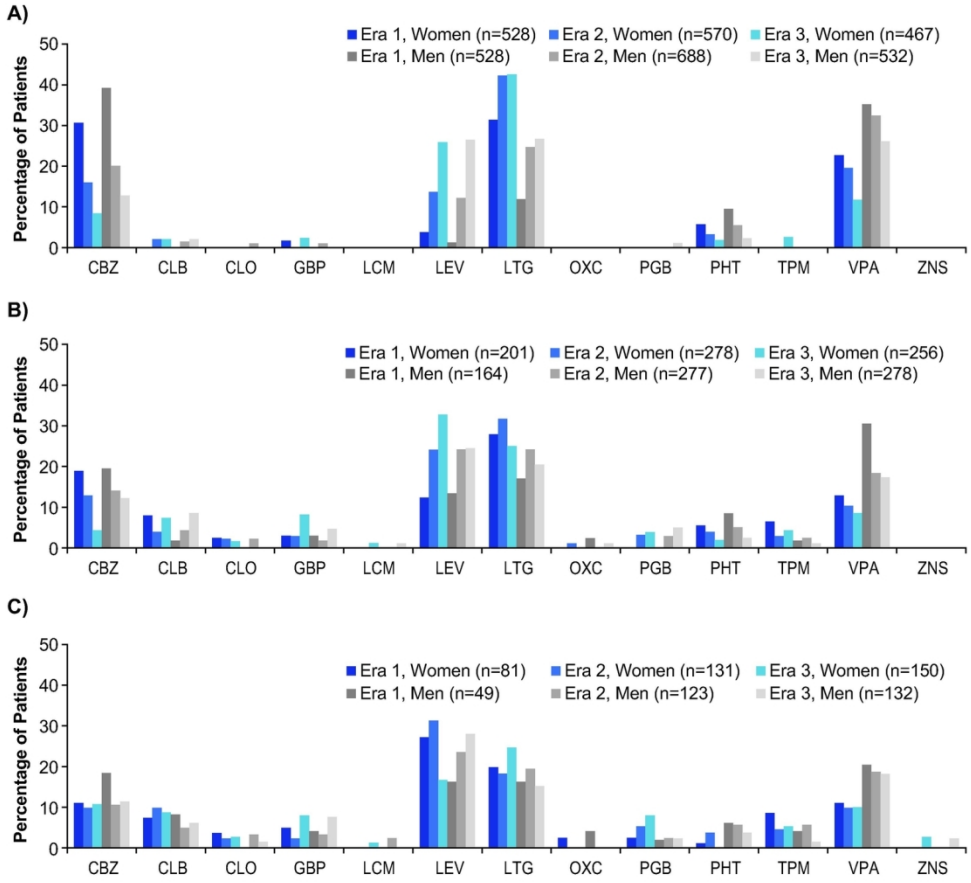


Figure 3. Treatment patterns in adult men and women for A) first-line, B) second-line, and C) third-line treatment.*

139x125mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016

Graham Powell, John Logan, Victor Kiri, Simon Borghs

Supplemental Tables

Supplementary Table S1 Diagnostic codes for epilepsy

CODES	TERM	EPILEPSY TYPE
International Classification of Diseases, Tenth Revision (ICD-10)		
G40	Epilepsy	Unspecified
G40.0	Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset	Partial
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	Partial
G40.2	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures	Partial
G40.3	Generalized idiopathic epilepsy and epileptic syndromes	Generalised
G40.4	Other generalized epilepsy and epileptic syndromes	Generalised
G40.5	Special epileptic syndromes	Unspecified
G40.6	Grand mal seizures, unspecified (with or without petit mal)	Generalised
G40.7	Petit mal, unspecified, without grand mal seizures	Unspecified
G40.8	Other epilepsy	Unspecified
G40.9	Epilepsy, unspecified	Unspecified
READ codes		
1O30.00	Epilepsy confirmed	unspecified
667B.00	Nocturnal epilepsy	unspecified
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]	mixed
Eu84200	[X]Rett's syndrome	generalised
F035200	Rasmussen syndrome	partial
F130600	Aicardi Goutieres syndrome	mixed
F132100	Progressive myoclonic epilepsy	generalised
F132111	Unverricht - Lundborg disease	generalised
F25..00	Epilepsy	unspecified
F250.00	Generalised nonconvulsive epilepsy	generalised
F250000	Petit mal (minor) epilepsy	unspecified
F250100	Pykno-epilepsy	generalised
F250400	Juvenile absence epilepsy	generalised
F250500	Lennox-Gastaut syndrome	generalised
F250y00	Other specified generalised nonconvulsive epilepsy	generalised
F250z00	Generalised nonconvulsive epilepsy NOS	generalised
F251.00	Generalised convulsive epilepsy	generalised
F251000	Grand mal (major) epilepsy	generalised
F251011	Tonic-clonic epilepsy	generalised

CODES	TERM	EPILEPSY TYPE
F251100	Neonatal myoclonic epilepsy	generalised
F251111	Otohara syndrome	mixed
F251500	Tonic-clonic epilepsy	generalised
F251y00	Other specified generalised convulsive epilepsy	generalised
F251z00	Generalised convulsive epilepsy NOS	generalised
F254.00	Partial epilepsy with impairment of consciousness	partial
F254000	Temporal lobe epilepsy	partial
F254100	Psychomotor epilepsy	partial
F254200	Psychosensory epilepsy	unspecified
F254300	Limbic system epilepsy	partial
F254z00	Partial epilepsy with impairment of consciousness NOS	partial
F255.00	Partial epilepsy without impairment of consciousness	partial
F255000	Jacksonian, focal or motor epilepsy	partial
F255011	Focal epilepsy	partial
F255012	Motor epilepsy	partial
F255100	Sensory induced epilepsy	unspecified
F255200	Somatosensory epilepsy	partial
F255300	Visceral reflex epilepsy	unspecified
F255311	Partial epilepsy with autonomic symptoms	partial
F255400	Visual reflex epilepsy	unspecified
F255500	Unilateral epilepsy	partial
F255y00	Partial epilepsy without impairment of consciousness OS	partial
F255z00	Partial epilepsy without impairment of consciousness NOS	partial
F256.00	Infantile spasms	generalised
F256.11	Lightning spasms	generalised
F256.12	West syndrome	generalised
F256100	Salaam attacks	generalised
F256z00	Infantile spasms NOS	generalised
F259.00	Early infant epileptic encephalopathy wth suppression bursts	mixed
F259.11	Ohtahara syndrome	mixed
F25A.00	Juvenile myoclonic epilepsy	generalised
F25B.00	Alcohol-induced epilepsy	unspecified
F25C.00	Drug-induced epilepsy	unspecified
F25D.00	Menstrual epilepsy	unspecified
F25E.00	Stress-induced epilepsy	unspecified
F25F.00	Photosensitive epilepsy	mixed
F25G.00	Severe myoclonic epilepsy in infancy	generalised
F25G.11	Dravet syndrome	generalised

CODES	TERM	EPILEPSY TYPE
F25y.00	Other forms of epilepsy	unspecified
F25y000	Cursive (running) epilepsy	partial
F25y100	Gelastic epilepsy	partial
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset	partial
F25y400	Benign Rolandic epilepsy	partial
F25y500	Panayiotopoulos syndrome	partial
F25yz00	Other forms of epilepsy NOS	unspecified
F25z.00	Epilepsy NOS	unspecified
Fyu5000	[X]Other generalized epilepsy and epileptic syndromes	generalised
Fyu5100	[X]Other epilepsy	unspecified
P228300	Aicardi syndrome	mixed
PK61.00	Sturge-Weber syndrome	partial
PKyz511	Angelman syndrome	generalised
PKyz700	Angelman's syndrome	generalised
PKyz711	Angelman syndrome	generalised
SC20000	Traumatic epilepsy	partial
ZS82.11	Landau-Kleffner syndrome	mixed

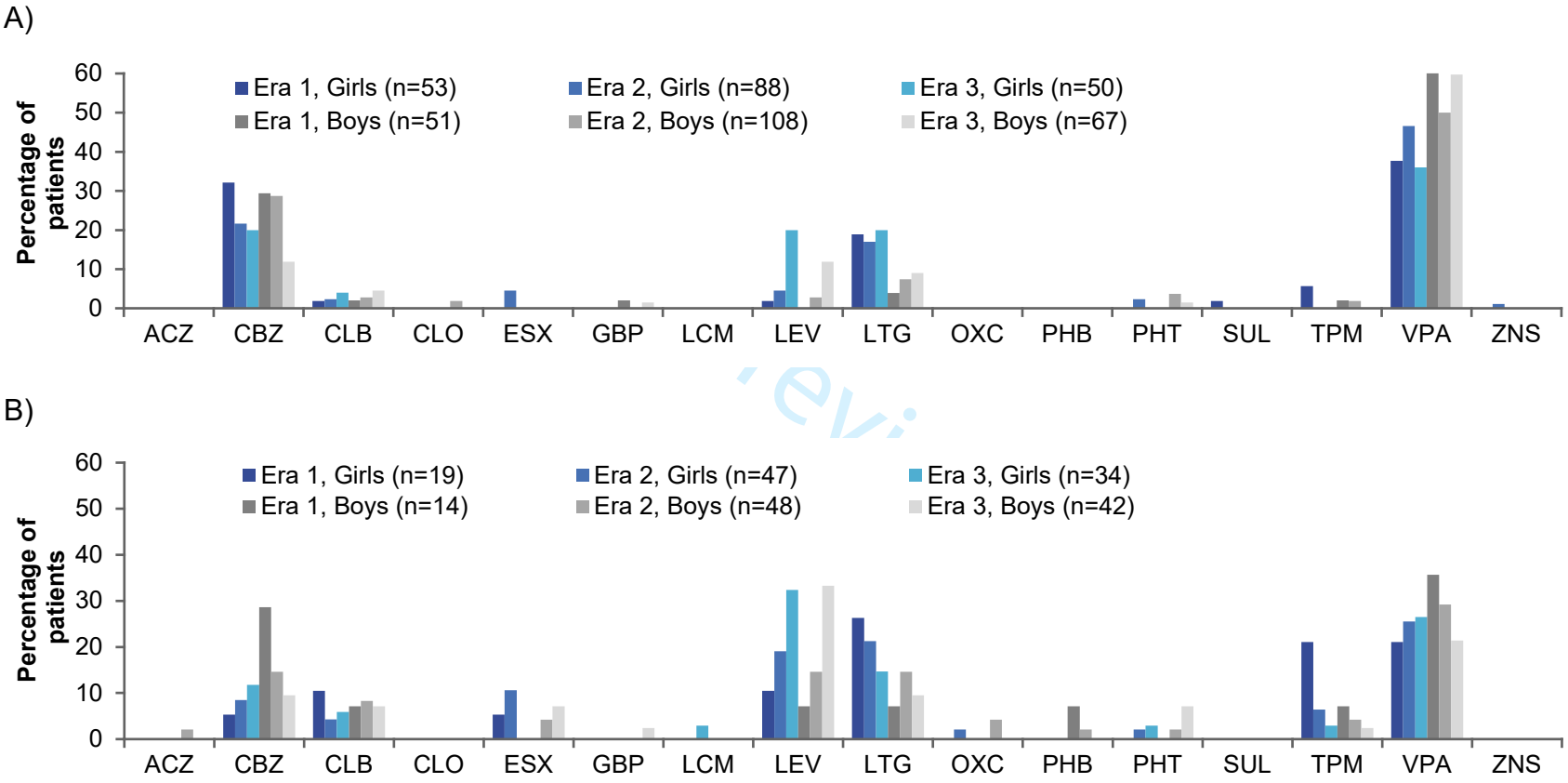
Supplementary Table S2 READ codes used to capture the primary outcome

CODE	TERM
Active epilepsy and seizures	
1B1W.00	Transient epileptic amnesia
1B27.00	Seizures in response to acute event
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
1B6B.00	Febrile convulsion
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..13	O/E - a seizure
2827	O/E - febrile convulsion
2828	Absence seizure
282Z.00	O/E - fit/convulsion NOS
667D.00	Epilepsy control poor
667Q.00	1 to 12 seizures a year
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	Daily seizures
667V.00	Many seizures a day
667W.00	Emergency epilepsy treatment since last appointment
F132z12	Myoclonic seizure
F250011	Epileptic absences
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251600	Grand mal seizure
F253.11	Status epilepticus
F254400	Epileptic automatism
F254500	Complex partial epileptic seizure
F255600	Simple partial epileptic seizure
F25H.00	Generalised seizure
F25X.00	Status epilepticus, unspecified
F25y300	Complex partial status epilepticus
F25z.11	Fit (in known epileptic) NOS
Fyu5200	[X]Other status epilepticus
Fyu5900	[X]Status epilepticus, unspecified

CODE	TERM
Q480.00	Convulsions in newborn
Q480.12	Seizures in newborn
R003.00	[D]Convulsions
R003000	[D]Convulsions, febrile
R003011	[D]Pyrexial convulsion
R003100	[D]Convulsions, infantile
R003400	[D]Nocturnal seizure
R003y00	[D]Other specified convulsion
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS
Ryu7100	[X]Other and unspecified convulsions
1B63.00	Had a fit
1B63.11	Fit - had one, symptom
282..12	O/E - a fit
2822	O/E - grand mal fit
2823	O/E - petit mal fit
2824	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2825	O/E - psychomotor fit
Q480.11	Fits in newborn
R003200	[D]Fit
F252.00	Petit mal status
F253.00	Grand mal status
F256.00	Infantile spasms
F256.11	Lightning spasms
F256z00	Infantile spasms NOS
F256100	Salaam attacks

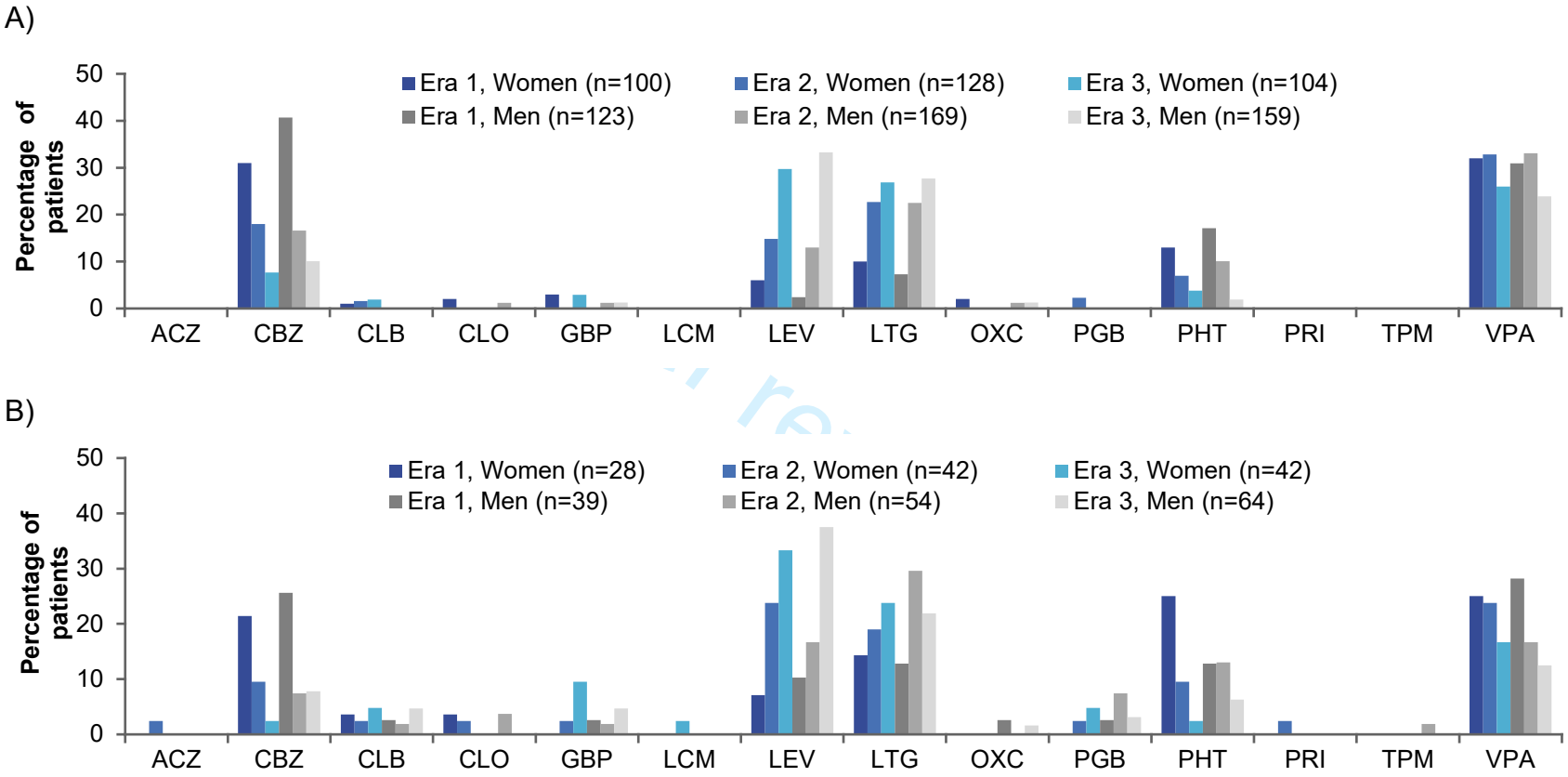
Supplementary Figures

Supplementary Figure S1 AED trends in boys and girls (<16 years of age) in A) first-line and B) second-line treatment.



ACZ, acetazolamide; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate.

Supplementary Figure S2 AED trends in elderly men and women (≥65 years of age) in A) first-line and B) second-line treatment.



ACZ, acetazolamide; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016: a retrospective cohort study using electronic medical records

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	General practice / Family practice, Medical management
Keywords:	drug resistance, refractoriness, remission, Epilepsy < NEUROLOGY, seizure freedom, treatment patterns

Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016: a retrospective cohort study using electronic medical records

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Tables/Figures: 5 (Supplemental items: 2 tables, 2 figures)

References: 32

Keywords: Drug resistance; refractoriness; remission; epilepsy; seizure freedom; treatment patterns

ABSTRACT

Objective To assess the evolution of antiepileptic drug (AED) treatment patterns and seizure outcomes in England from 2003 to 2016.

Design, setting and participants Retrospective cohort study of electronic medical records from Clinical Practice Research Datalink and National Health Service Digital Hospital Episode Statistics databases. Patients newly diagnosed with epilepsy were identified and followed until end of data availability. Three eras were defined starting 1 April 2003 (first National Institute for Health and Care Excellence [NICE] guideline); 1 September 2007 (Standard and New Antiepileptic Drugs publication); 1 January 2012 (second NICE guideline).

Outcome measures Time from diagnosis to first AED; AED sequence; time from first AED to first 1-year remission period (no new AED attempts and no seizure-related healthcare events); time from first AED to refractoriness (third AED attempt regardless of reason); Kaplan-Meier analysis of time-to-event variables.

Results 4388 patients were included (mean follow-up: 6.8, 4.2, and 1.7 years by era). 84.6% of adults (≥16 years), 75.5% of children (<16), and 89.1% of elderly subgroup (65+) received treatment within 1 year; rates were generally stable over time. Treatment trends included reduced carbamazepine use (adult first-line, era 1: 34.9%; era 3: 10.7%) and phenytoin, earlier-line and increased levetiracetam use (adult first-line, era 1: 2.6%; era 3: 26.2%) and lamotrigine (particularly adults and elderly subgroup), and larger number of different AEDs used. Valproate use shifted somewhat to later lines. Rates of 1-year remission within 2 years of starting treatment increased in adults (era 1: 71.9%; era 3: 81.4%) and elderly (era 1: 76.1%; era 3: 81.7%). Overall, 55.5% of patients relapsed after achieving 1-year remission. Refractoriness rates remained stable over time (~26% of adults within 5 years).

Conclusion Treatment trends often were not aligned with era-relevant guidance. However, our results suggest a slight improvement in epilepsy treatment outcomes over the 13-year period.

ARTICLE SUMMARY

Strengths and limitations of this study

- Use of the Clinical Practice Research Datalink and National Health Service Digital Hospital Episode Statistics databases allowed access to a large national pool of patients for identification of those newly diagnosed with epilepsy.
- Treatment eras were delineated by epilepsy guideline updates to allow capture of changes in antiepileptic drug treatment practice.
- The stringency of diagnostic criteria may limit the generalisability of the data.
- The nature of the data is prone to incomplete or incorrect medical records and coding, lack of specificity, and captures prescriptions but not prescription fills.
- The definition of remission was based on health care consultations, with 1 year possibly too short to be considered for remission; and drug resistance was based on switching antiepileptic drugs without taking into account the reasons for treatment changes, which were unknown but likely driven by lack of effect and poor tolerability.

INTRODUCTION

The introduction of new antiepileptic drugs (AEDs) since 2003 has been accompanied by studies of the comparative efficacy, safety, and tolerability of older and newer AEDs,[1-3] as well as by evolving clinical practice guidelines that incorporate newer medications into recommendations for epilepsy treatment.[4-6] Treatment patterns would be expected to reflect the latest guidance for individual AEDs in epilepsy management, but scant information is available to assess alignment in clinical practice. A number of studies have reported an increase in the use of newer AEDs prescribed for first-line treatment in new-onset epilepsy in UK primary care settings[7, 8] and across European Union countries.[9]

Use of newer AEDs with reported similar or improved efficacy and better tolerability than older AEDs would be expected to benefit overall epilepsy treatment success and patient outcomes. However, literature suggests that there has been no meaningful improvement in epilepsy treatment-related outcomes[1, 10-12] and a notable portion of patients still fail first-line AED therapy.[13, 14] The objective of this study was to evaluate AED treatment patterns and seizure outcomes in England over three time periods from 2003 to 2016, using electronic medical record data, to provide further insights into the management of patients newly diagnosed with epilepsy.

METHODS

Study design

This was an exploratory, retrospective cohort analysis of primary care electronic medical records (EMRs) from the UK Clinical Practice Research Datalink (CPRD) and secondary care claims data from the National Health Service (NHS) Digital Hospital Episode Statistics (HES) databases. The CPRD contained over 4 million active patient records (and more than 11 million overall) drawn from 674 UK primary care practices, representing approximately 7% of the UK population, in 2015

[15]; these numbers have since grown.[16] Data that may be captured in the CPRD primary care data include general practitioner (GP) prescriptions, diagnoses, procedures, and referrals, coded as Read codes (a system of clinical terms used in UK primary care EMRs),[17-19] as well as UK Quality and Outcomes Framework (QOF) indicators, which were designed to reward quality care by GPs and may offer additional clinical information (in the case of epilepsy, the indicators concern seizure frequency). The HES database contains details of all secondary care admissions, outpatient appointments, and Accident & Emergency attendances at NHS hospitals in England.[20] Within this database, diagnoses are coded using the *International Classification of Diseases, Tenth Edition* (*ICD-10*) and procedures are coded using the *Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures, Fourth Revision*.

AED treatment patterns and seizure outcomes in England were assessed over three 4.5-year eras. Era 1 (first guideline era) included dates from 1 April 2003 to 31 August 2007 and encompassed the publication of the first National Institute for Health and Care Excellence (NICE) epilepsy guidance.[4, 21, 22] These guidelines recommended carbamazepine (CBZ) or sodium valproate (VPA) as first-line treatment for focal (partial-onset) and generalised seizures. Era 2 (intermediate era) was defined as 1 September 2007 to 31 December 2011, and captured updated guidance that recommended lamotrigine (LTG) or CBZ as first line for focal (partial-onset) seizures and VPA for generalised seizures based on a large randomized pragmatic trial (Standard and New Antiepileptic Drugs [SANAD]).[1] Era 3 (newer guideline era) spanned the timeframe from 1 January 2012 to 31 May 2016, with the second NICE epilepsy guidance recommending CBZ or LTG as first-line treatment for focal seizures, VPA for generalised seizures, and advice to be given to women of childbearing potential regarding foetal risks of malformation and neurodevelopmental impairments with VPA.[6, 23] A 2015 update warned against prescribing VPA to pregnant women and those of childbearing potential unless other AEDs were ineffective or not tolerated (in 2018 guidelines, VPA is contraindicated in girls and women of childbearing potential).[24]

Cohort selection

Patients with epilepsy newly diagnosed between 1 April 2003 and 31 May 2016 (date of last available CPRD practice data) were included in the study. Diagnosis was operationalised as an incident epilepsy diagnosis code (online supplementary table S1), with evidence of a neurologist visit on the same date or in the preceding 3 months, as assessed in HES data or primary care referral data using June 2016 data sets, and constituted the index date. Patients were assigned to a treatment era based upon their index date (ie, the index date fell within one of the three defined treatment guideline eras). Those who had started an AED attempt less than 3 months prior to a diagnosis were included. An AED attempt was defined on the start date of an AED prescription that a patient had never used before, and maintained for at least 31 days, as identified in primary care records. A pre-index period of at least 2 years was required with their practice's data flagged as up-to-standard. Patients were excluded if they had an epilepsy diagnosis at any time before the index date, or AED treatment during the 2-year pre-index period. Included patients were followed until data were no longer available, owing either to death or to leaving their general practitioner practice or date of last CPRD data (31 May 2016).

Three age cohorts were considered: adults aged ≥16 years, children ≥2 to <16 years of age, and the elderly, ≥65 years of age (a subset of adult patients).

Outcome measures

The primary outcome was time to 1-year remission from seizures for all treated patients, starting from the time of first AED attempt until the first 1-year period of remission. One-year remission was defined as having no new AED attempts, and the absence of all seizure-related healthcare events (ie, seizure-related hospitalisation or seizure-related GP or outpatient visit; for instance a GP visit with a diagnosis recorded as '1B64.00 – had a convulsion'), QOF data and Read codes (online supplementary table S2) indicating a seizure at any time for at least 1 year. A subsequent occurrence of any of these events is defined as a relapse. Outcomes also included time from diagnosis to first AED prescription (all patients); treatment

patterns by era, age, and sex cohort; and time from first AED prescription to refractoriness (treated patients only), which was defined as a third distinct AED attempt as identified in primary care records. The end of AED exposure and treatment as poly/monotherapy were not assessed.

Statistical analysis

Descriptive statistics were used to summarise both continuous variables and categorical variables such as mean, standard deviation (SD), median, and percentages. Analyses were conducted on unmatched cohorts and reported results are unadjusted. Outcomes were evaluated using Kaplan-Meier analysis.

The protocol for this study was reviewed and approved by the Independent Scientific Advisory Committee, the CPRD scientific/ethics committee.

Patient involvement statement

This research was conducted without patient involvement in the design or interpretation of this study, or in the writing and editing of this document.

RESULTS

Study participants

Overall, of 137,267 patients with an epilepsy diagnosis code in the data, 4388 patients (adults n=3861; children n=527) met the study inclusion criteria and were available for analysis. Mean follow-up was 6.8 years (era 1), 4.2 years (era 2), and 1.7 years (era 3). Baseline characteristics were largely as expected for diagnosed patients (overall population: mean age at diagnosis, 41.4 years; 85.0% of patients with ≥1 AED treatment; 78.4% with unspecified epilepsy) (table 1). There appeared to be higher rates of comorbidities, reflected by epilepsy-specific comorbidity index scores, and lower rates of unspecified epilepsy diagnosis in era 3 compared with era

1. There were minor changes in the regional make-up of CPRD data; for example in England, the number of practices participating in CPRD generally decreased in eastern regions and increased in London and southern regions over time (ie, in the study data set, London-based practices represent 13.7% of practices contributing data for 2005 whereas they represent 19.0% of those contributing for 2015); other regions remained relatively stable.

Table 1 Baseline characteristics of the sample population.

	Adults (≥16 years) n=3861	**Children (<16 years) n=527**	**Elderly subgroup* (≥65 years) n=876**
Age at diagnosis, years, mean (SD)	45.9 (20.4)	8.5 (4.0)	74.7 (7.0)
Female, n (%)	1845 (47.8)	244 (46.3)	372 (42.5)
No. diagnosed (%)			
Era 1, n (% of era)	1276 (33.0)	133 (25.2)	260 (29.7)
Era 2, n (% of era)	1452 (37.6)	248 (47.1)	322 (36.8)
Era 3, n (% of era)	1133 (29.3)	146 (27.7)	294 (33.6)
Germaine-Smith epilepsy-specific comorbidity index, mean (SD)	0.8 (1.9)	0.3 (1.0)	2.1 (2.5)
Era 1, n (% of era)	0.6 (1.5)	0.3 (1.0)	1.4 (2.3)
Era 2, n (% of era)	0.8 (1.8)	0.2 (0.7)	2.0 (2.3)
Era 3, n (% of era)	1.1 (2.4)	0.4 (1.2)	2.7 (2.9)
Epilepsy type			

Generalised, n (%)	324 (8.4)	72 (13.7)	65 (7.4)
Era 1, n (% of era)	91 (7.1)	15 (11.3)	15 (5.8)
Era 2, n (% of era)	119 (8.2)	44 (17.7)	22 (6.8)
Era 3, n (% of era)	114 (10.1)	13 (8.9)	28 (9.5)
Focal (partial-onset), n (%)	475 (12.3)	76 (14.4)	114 (13.0)
Era 1, n (% of era)	162 (12.7)	15 (11.3)	46 (17.7)
Era 2, n (% of era)	153 (10.5)	31 (12.5)	29 (9.0)
Era 3, n (% of era)	160 (14.1)	30 (20.5)	39 (13.3)
Unspecified	3062 (79.3)	379 (71.9)	697 (79.6)
Era 1, n (% of era)	1023 (80.2)	103 (77.4)	199 (76.5)
Era 2, n (% of era)	1180 (81.3)	173 (69.8)	271 (84.2)
Era 3, n (% of era)	859 (75.8)	103 (70.5)	227 (77.2)
At least one AED treatment, n (%)	3313 (85.8)	417 (79.1)	783 (89.4)
Total follow-up, patient-years†	16,483.92	2363.94	3257.28
Mean follow-up, years	4.3	4.5	3.7
Era 1, n (% of era)	6.7	7.3	6.0
Era 2, n (% of era)	4.1	4.6	3.7
Era 3, n (% of era)	1.7	1.8	1.7

Era 1, 1 April 2003 to 31 August 2007 (first NICE guidance); era 2, 1 September 2007 to 31 December 2011 (SANAD); era 3, 1 January 2012 to study 31 May 2016 (second NICE guidance).

*Elderly patients are a subset of the adult patient population.

†Total follow-up, patient-years: calculated by adding the follow-up time for all patients.

AED, antiepileptic drug.

Many patients (n=4456) who met inclusion criteria were excluded owing to pre-diagnosis AED use, primarily with AEDs that have multiple indications (eg, valproate, carbamazepine, lamotrigine). Because of the required 2-year baseline period, no 0- or 1-year-old children were included in the sample.

Time from diagnosis to first AED prescription

Kaplan-Meier estimates revealed that 84.6% of adults, 75.5% of children, and 89.1% of the elderly subgroup received AED treatment within 1 year of index date (figure 1). Treatment rates from era 1 to era 3 appeared to increase slightly in adults (82.3% to 86.6%) and the elderly subgroup (86.3% to 90.8%), and to decrease slightly in children (77.4% to 69.2%).

Treatment patterns over time

Analysis of treatment patterns over time in adults shows a large shift away from CBZ (adult first-line share, era 1: 34.9%; era 3: 10.7%) and phenytoin (PHT; adult first-line share, era 1: 7.6%; era 3: 2.1%), and toward earlier and increased use of levetiracetam (LEV; adult first-line share, era 1: 2.6%; era 3: 26.2%) (figure 2A). The use of first-line VPA remained relatively stable over eras 1 and 2, and decreased in era 3. AED treatment patterns appeared to be far more stable in children than adults, with use of first-line VPA remaining high over time (first-line share: in children, era 1: 49.0%; era 3: 49.6%; in adults, era 1: 29.0%; era 3, 19.4%; figure 2B). Nevertheless, the use of CBZ decreased in favour of earlier use of LEV (CBZ first-line share, era 1: 30.8%; era 3: 15.4%; LEV first-line share, era 1: 0%; era 3: 15.4%). These AED patterns were consistent for second-line treatment in children. Treatment pattern changes in the elderly subgroup were similar but more pronounced than in the overall adult patient population. In the elderly subgroup, CBZ use fell in all treatment lines (first-line share, era 1: 36.3%; era 3: 9.1%; second-line share, era 1: 23.9%; era

3: 5.7%; third-line share, era 1: 16.7%; era 3: 4.7%) in favour of earlier and increased use of lamotrigine (LTG) and LEV (LTG first-line share, era 1: 8.5%; era 3: 27.4%; LEV first-line share, era 1: 4.0%; era 3: 31.2%; figure 2C).

Analysis of treatment patterns by sex indicated that in adults, women were prescribed first-line VPA and CBZ less often and LTG more often than men—a finding that remained stable over time (figure 3). The trends in VPA and LTG use were mostly intact through third-line AED (figure 3). In children, generally LEV and LTG were more common and VPA less common for girls than boys across eras as well as through second-line AED (supplemental figure 1). In the elderly subgroup, first-line treatment patterns were comparable between men and women (supplemental figure 2).

One-year remission rates

One-year remission rates, within 1 or 2 years of treatment initiation, increased somewhat over time in adults and the elderly subgroup, but were more variable in children (table 2). The percentage of patients achieving a 1-year period of remission within 1 year of starting treatment increased from era 1 to era 3 in all three age cohorts. The most substantial increase (era 1 to era 3) was observed in the elderly subgroup (31.5% to 47.3%; a 50.3% increase from era 1). The percentage of adults and the elderly subgroup achieving 1-year remission within 2 years of starting treatment was higher than within 1 year and increased over time (era 1 to era 3: 71.9% to 81.4% adults; 76.1% to 81.7% elderly). In children, there was a slight decrease in remission rates within 2 years of treatment from era 1 to era 3 (table 2). Overall, 55.5% of patients relapsed after achieving 1-year remission.

Table 2 Treatment outcomes by study population and era

	Adults (≥16 years)	Children (<16 years)	Elderly subgroup* (≥65 years)

	n=3313	n=417	n=783
Rate of 1-year remission within 1 or 2 years of treatment			
Patients with at least one period of 1-year remission,† n (%)	2430 (73.3)	317 (76.0)	536 (68.5)
Of these patients, at least one relapse,† n (%)	1362 (56.0)	163 (51.4)	310 (57.8)
1-year period of remission 1 year from treatment start (KM estimate)	35.2%	40.1%	36.3%
Era 1‡	31.6%	36.4%	31.5%
Era 2‡	34.7%	41.9%	32.8%
Era 3‡	42.0%	40.8%	47.3%
1-year period of remission within 2 years of treatment start (KM estimate)	75.3%	75.9%	78.4%
Era 1‡	71.9%	73.0%	76.1%
Era 2‡	75.3%	78.3%	78.2%
Era 3‡	81.4%	72.8%	81.7%
Rate of refractoriness within 3 years of starting first AED treatment			
Patients refractory 3 years from start of treatment (KM estimate)	17.5%	23.8%	11.9%
Era 1‡	17.3%	20.8%	11.1%
Era 2‡	17.4%	24.3%	13.4%
Era 3‡	17.6%	(n<10)	11.2%

Era 1, 1 April 2003 to 31 August 2007 (first NICE guidance); era 2, 1 September 2007 to 31 December 2011 (SANAD); era 3, 1 January 2012 to study 31 May 2016 (second NICE guidance).

*Elderly patients are a subset of the adult patient population.

†Raw figures, not adjusted for differential follow-up between eras.

‡Number of patients diagnosed in era 1, 2, and 3, respectively, and received treatment: adults, n=1097, 1254, and 962; children, n=110, 204, and 103; elderly subgroup, n=234, 291, and 258.

AED, antiepileptic drug; KM, Kaplan-Meier estimate.

Time from first AED treatment to refractoriness

Overall, a similar percentage (about 17% to 18%) of adult patients became refractory within 3 years of first starting treatment across the different eras (table 2). Approximately 25% to 26% of adults were treatment refractory after 5 years (data not shown). The subgroup of elderly patients was less likely to become treatment refractory than all adults or children (table 2).

DISCUSSION

The results of this analysis suggest that there has been some improvement in epilepsy outcomes, reflected by shorter times to 1-year remission (no new AED attempts or seizure-related healthcare events for at least 1 year) over the 13-year period. Various reasons may contribute to this observation, including improved diagnosis of epilepsy and differential diagnosis of non-epilepsy disorders, more active epilepsy management with personalised treatment, and wider use of newer, better-tolerated AEDs, particularly to replace enzyme-inducing drugs in the elderly subgroup who are most susceptible to risks associated with enzyme induction.[25] Although our study assessed treatment patterns by age group and sex, it did not assess whether prescribing is targeted based upon other patient characteristics.

The decreasing adherence of prescribing to treatment guidelines over the time course of this study suggests guidelines are not keeping up with clinical practice and a possible issue in guideline writing. The nature of evidence that contributes to guidelines might play a role here. In epilepsy, the reliance of guidelines primarily on

randomized controlled trials, which are scarce, may have led to relevant information being ignored. The observed major changes in prescription trends during era 3 are at odds with NICE guidelines, which suggest prescribing CBZ or LTG as first-line treatment in children and adults with newly diagnosed focal seizures, and VPA for those newly diagnosed with generalised seizures.[6] Analysis of first-line treatment patterns over time showed a reduction in VPA use in era 3, a large shift away from CBZ and PHT in all treatment lines, and a trend toward earlier and increased usage of LEV in adults, particularly the elderly subgroup.[6] Although the sharp decrease in PHT aligns with 2012 NICE guidelines,[6] possibly reflecting a change in AEDs used in acute settings or a shift to non-enzyme active AEDs (nEAAEDs) in older patients, the decrease in CBZ and increase in LEV do not align with treatment guidelines.

For elderly patients, 2012 NICE guidelines recommend CBZ as an extended release formulation.[6] Preferential use of CBZ in older patients was reported in a study of CPRD data from 2001 to 2010, which found that patients receiving enzyme-inducing AEDs (EIAEDs: CBZ, 63.3%; PHT, 35.3%) were older and had more comorbid illness; the study also reported the use of EIAEDs resulted in higher healthcare costs compared with nEAAEDs.[25] Our findings also show that CBZ was most often prescribed for the elderly subgroup during era 1 (2003-2007). Given the higher susceptibility to risks associated with enzyme induction, as well as increased costs, a shift to nEAAEDs would appear a rational change that is reflected in era 3 prescribing trends.

In children, treatment patterns were more stable, which may reflect the situation that fewer new AEDs have become available for this population. Limited choices may be related to the more stringent criteria necessary for drug approval, with more complex trial designs and challenges in recruitment. The stability of VPA use in children may be related to its broad spectrum activity when diagnosis is uncertain.

In women, use of VPA greatly diminished across eras, lending support to a database study in the US that reported decreased VPA use among adult women.[26] These findings are perhaps not surprising given the teratogenic profile of VPA and increased warnings associated with VPA in girls and women of childbearing

potential. In 2018, the Medicines and Healthcare products Regulatory Agency advised against the use of VPA in girls and women of childbearing potential;[27] thus, one might anticipate further declines in its use going forward.

Our study shows that comorbidity burden increased across eras, indicating that patients newly diagnosed in era 3 were sicker than patients newly diagnosed in era 1 or 2. The reasons for this trend are not discerned, but may reflect a changing make-up of practices contributing CPRD data, societal changes in levels of physical inactivity and diet, improved diagnosis by healthcare providers, and increased treatment-seeking behaviour by patients. A similar observed increase in comorbidity burden from 2004 to 2014 has been reported in a UK population with cardiovascular disease.[28]

A longitudinal cohort study describing seizure freedom rates over 30 years reported a virtually unchanged seizure-freedom rate, and a decrease in the probability of achieving seizure freedom with each unsuccessful AED regimen prescribed.[11] The study reported 61% to 64% of patients achieved 1-year seizure freedom over time.[11] Study authors concluded that despite changing treatment patterns and greater use of newer AEDs, as observed in the present study, no meaningful improvements in long-term outcomes had occurred. In contrast, our study found an improvement in outcomes, with a higher proportion of patients entering remission, nearly half of whom subsequently relapsed. Across eras, an increasing proportion of patients achieved 1-year remission (eg, 71.9% to 81.4% for adult subgroup). There are a number of differences that may explain the discrepancy in results between these studies. First, the prior study assessed 1-year seizure freedom before study end (thus excluding those who were seizure-free for ≥12 months who relapsed before study end), whereas our study assessed 1-year remission from AED initiation. Because patients with longer follow-up also have more time and opportunity to relapse, in the prior study 1-year seizure freedom favours patients with shorter follow-up (ie, those diagnosed in later eras), which is not the case in the current study. By using Kaplan-Meier methods to adjust for this differential follow-up time between eras, we found increasing remission rates over time in adult and elderly subgroups. Other notable differences include time periods of the study cohorts (1982–2012 vs 2003–2012), available AEDs, reported study

population (overall vs age-specific subgroups), settings (single epilepsy centre in Glasgow vs general practitioner practices across England), and data source (medical records and notes vs structured electronic medical records). It is possible that reporting outcomes for an overall population may have masked trends in the adult population, as our study found treatment patterns and remission rates in children were relatively stable over time periods.

The proportion of patients who were refractory within 3 years of first starting AED treatment was similar across eras, although percentages varied somewhat according to age group. The trend for increasing remission rates and stable refractoriness rates would appear to be a contradiction. A possible explanation may be that patients progress through 3 AEDs treatments via more active management. Although these patients would meet the definition for refractory epilepsy, the AEDs may represent more specifically chosen, better tolerated treatments that lead to improved remission rates. Further, improved tolerability of newer AEDs may permit higher dosing, which may lead to improved efficacy outcomes. Thus, the increasing rates of remission over time may reflect the improved tolerability and efficacy of newer AEDs used in the later eras.

Study interpretation is limited by a number of factors. The conservative, stringent diagnostic criteria may have limited the generalisability of the data, as the study selection rate was approximately 25% to 30% of the expected incidence rate.[29] The accuracy of electronic medical records data is limiting, as instances whereby a seizure or epilepsy code was used after a non-seizure event could be present. The requirement for a neurologist visit as part of our epilepsy diagnosis criteria was intended to maximise the accuracy of the diagnosis. Additionally, the epilepsy type was not usually discernible from medical record recording practices in our study, with 70% to 80% of patients having been classified as having an unspecified epilepsy diagnosis. Because patient characteristics by AED were not assessed, the accuracy of selected AED(s) is not known (all prescriptions reflect data from general practitioners).

Outcome definitions may also contribute to limitations. Our definition of remission was based on healthcare consultations, and it could be argued that the 1-

year time period was insufficient to be considered as 'remission',[30] or that basing remission on healthcare encounters rather than information about seizure frequency may be unspecific. This proxy was designed to use as much information as is captured in the databases. No Read or *ICD-10* codes record seizure frequency. The QOF data, which is intended to record seizure frequency, was found to be very poorly populated. EMR free text is not available from CPRD. Further, the definition of seizure freedom has evolved, with the ILAE proposing a 'rule of three', including the absence of seizures for at least the previous 12 months OR for three times the longest pre-treatment interval between seizures, whichever is greater.[31] In our study, drug resistance (refractoriness) was based on switching AEDs and did not take into account the reasons for treatment changes, which are not explicitly recorded in CPRD (eg, adverse events/tolerability, pregnancy) but likely were predominantly driven by a combination of lack of efficacy and poor tolerability. This definition differs from that proposed by the ILAE in 2010: 'Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.'[31]

Our study is also limited by incomplete information regarding prescribing data from general practitioners, particularly lack of information regarding patient adherence and the appropriateness of AED selection based on patient characteristics. Indeed, database studies are subject to miscoding and missing or incomplete information. In our description of the data, we found that epilepsy is often coded with no more specificity than simply 'epilepsy', perhaps the result of the unwillingness or lack of necessity to code more specifically, on the part of physicians. Shifts in the make-up of practices supplying data to CPRD (eg, reflected by capture of higher rates of comorbidities and specified epilepsy diagnosis, and shifts in the regional make up of CPRD data, which may be associated with regional treatment practices) over time may have introduced unmeasured bias in patient baseline characteristics. Changes to data availability and accuracy over eras may have affected results, with a prior study noting the improved accuracy of administrative or registry data in later years.[32] A crucial limitation is that cohorts are unmatched and analyses unadjusted; thus, there is no statistical basis for

comparisons between outcomes. As such, our findings are exploratory in nature and should be interpreted with caution.

Despite these potential limitations, our study suggests an evolution of AED treatment patterns and AED effectiveness over a 15-year period in clinical practice in England. Major changes in treatment patterns, particularly a reduction in CBZ and PHT use in favour of earlier and increased use of LEV, were observed. Although our study did not assess the use of particular AEDs based on patient characteristics or appropriateness, we generally found a reduction in the use of EIAEDs in the elderly subgroup and VPA in women, in keeping with newer treatment recommendations. In contrast to other studies reporting no meaningful improvement in the overall epilepsy population,[10, 11] we found an increase in 1-year remission rates following AED initiation in adults, which, given the limitations of the current study, will need to be further studied. Overcoming the limitations of the current study would require a data source that captures relevant diagnosis and outcomes data, particularly reasons for treatment change and remission, in more depth; while also still being generalizable and with a sufficient sample size. The lack of availability of such data is currently a major hurdle to comparative effectiveness research and real world evidence in epilepsy.

Although some improvement in epilepsy treatment outcomes was observed, a sizable proportion of patients with epilepsy remain uncontrolled on first- and second-line treatment, indicating a continued need for innovations for patients living with poorly controlled epilepsy.

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Contributors GP and SB conceived of the study and had a role in study design. JL and VK conducted data collection, extraction, and analysis of the data. GP, SB, and JL contributed to data interpretation. All authors contributed to the review and revision of the manuscript and approved of the final manuscript for publication.

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Competing interests G Powell is a paid medical consultant for UCB Pharma. J Logan and V Kiri are paid consultants for UCB Pharma. S Borghs is an employee of UCB Pharma.

Patient consent for publication Not required.

Data sharing statement The CPRD and HES datasets used in this study are available from the National Institute for Health Research, the Medicines & Healthcare products Regulatory Agency, and NHS Digital, respectively.

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FIGURE LEGENDS

Figure 1 Time from first diagnosis to first AED prescription in A) adults (n=3861), B) children (n=527), and C) elderly subgroup (n=876).

AED, antiepileptic drug.

Figure 2 Treatment patterns by AED attempt in A) adults, B) children, and C) elderly subgroup.*

*AEDs accounting for ≥1% of attempts in any patient group in any era.

ACZ, acetazolamide; AED, antiepileptic drug CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; ESL, eslicarbazepine; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHB, phenobarbital; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

Figure 3. Treatment patterns in adult men and women for A) first-line, B) second-line, and C) third-line treatment.*

*AEDs accounting for ≥1% of attempts in any patient group in any era.

For first-line treatment, the proportions of women vs men receiving AEDs were, for era 1: VPA, 22.7% vs 35.2%; CBZ, 30.7% vs 39.2%, LTG, 31.4% vs 11.9%; and for era 3: VPA, 11.8% vs 26.1%; CBZ, 8.4% vs 12.8%; LTG, 42.6% vs 26.7%.

AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

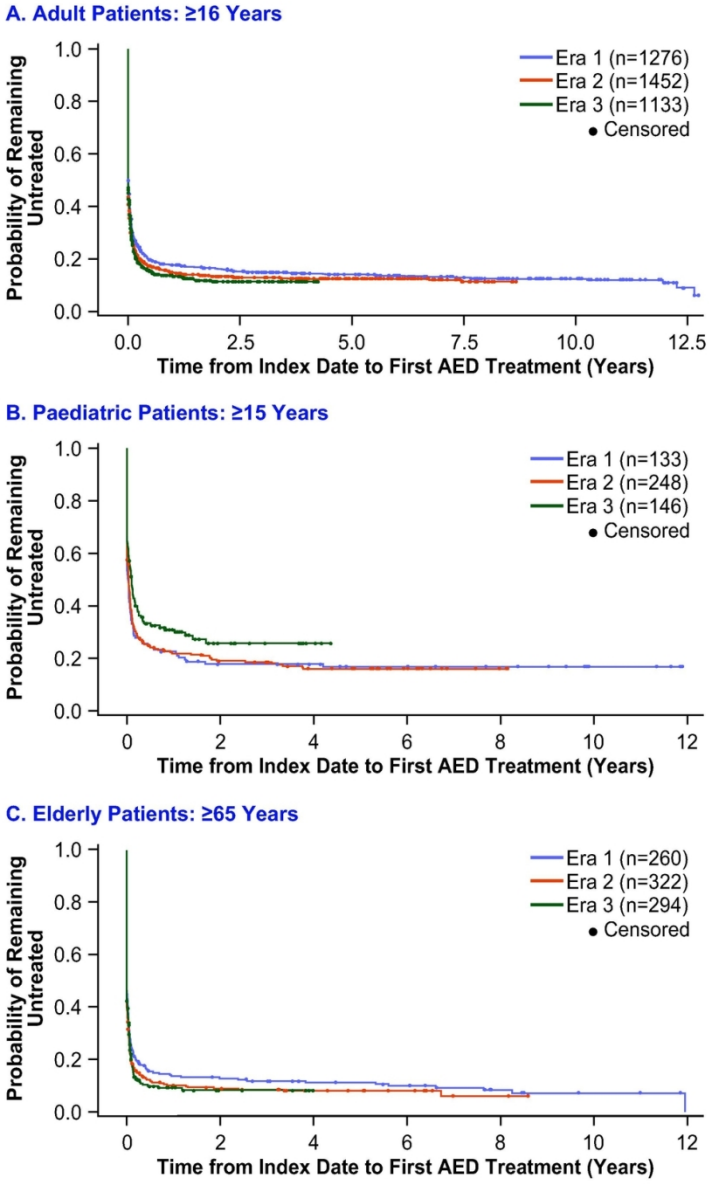

Figure 1. Time from first diagnosis to first AED prescription in A) adults (n=3861), B) children (n=527), and C) elderly (n=876).

84x142mm (300 x 300 DPI)

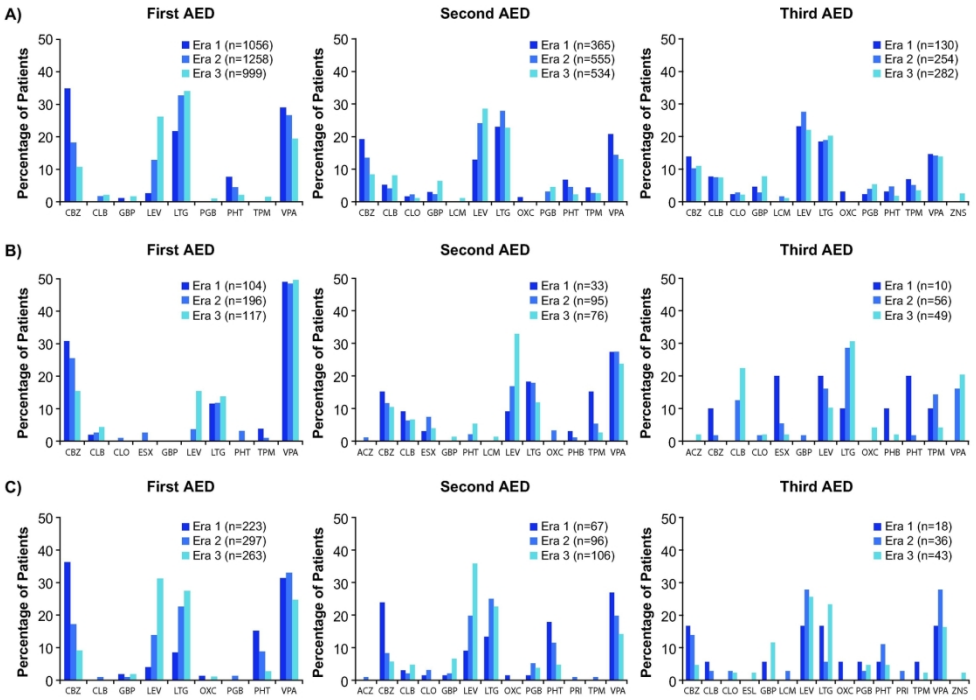

Figure 2. Treatment patterns by AED attempt in A) adults, B) children, and C) elderly.*

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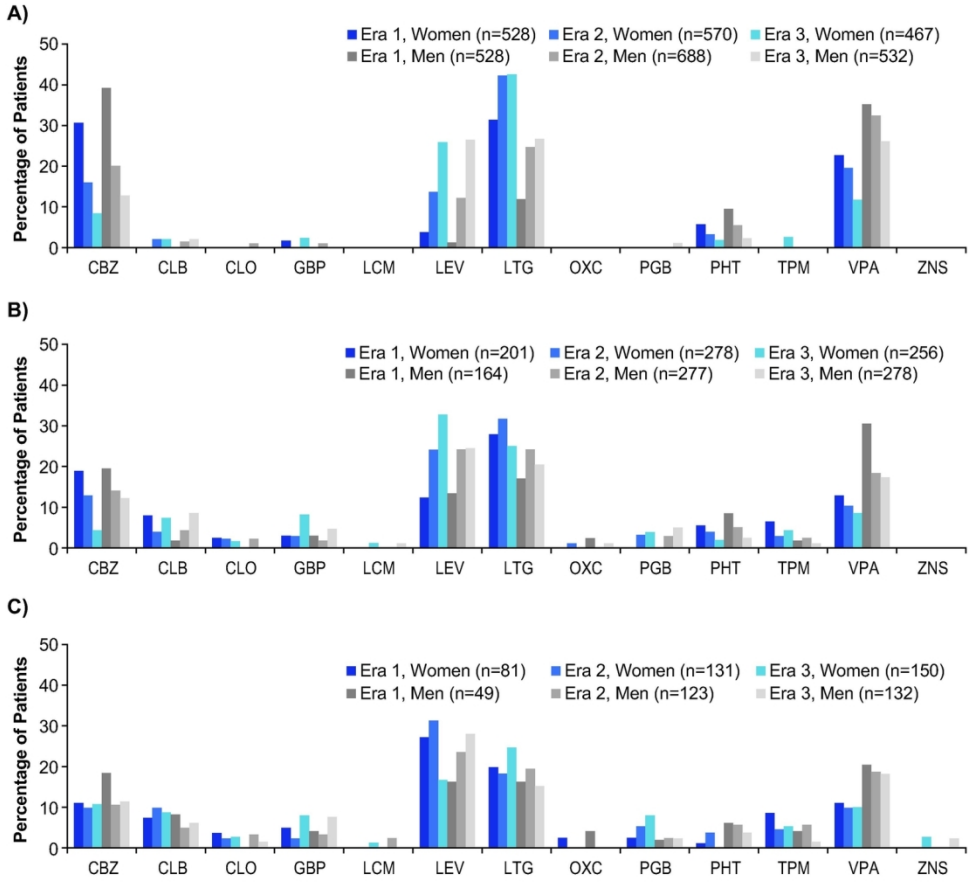


Figure 3. Treatment patterns in adult men and women for A) first-line, B) second-line, and C) third-line treatment.*

139x125mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016: a retrospective cohort study using electronic medical records

Graham Powell, John Logan, Victor Kiri, Simon Borghs

Supplemental Tables

Supplementary Table S1 Diagnostic codes for epilepsy

CODES	TERM	EPILEPSY TYPE
International Classification of Diseases, Tenth Revision (ICD-10)		
G40	Epilepsy	Unspecified
G40.0	Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset	Partial
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	Partial
G40.2	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures	Partial
G40.3	Generalized idiopathic epilepsy and epileptic syndromes	Generalised
G40.4	Other generalized epilepsy and epileptic syndromes	Generalised
G40.5	Special epileptic syndromes	Unspecified
G40.6	Grand mal seizures, unspecified (with or without petit mal)	Generalised
G40.7	Petit mal, unspecified, without grand mal seizures	Unspecified
G40.8	Other epilepsy	Unspecified
G40.9	Epilepsy, unspecified	Unspecified
READ codes		
1O30.00	Epilepsy confirmed	unspecified
667B.00	Nocturnal epilepsy	unspecified
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]	mixed
Eu84200	[X]Rett's syndrome	generalised
F035200	Rasmussen syndrome	partial
F130600	Aicardi Goutieres syndrome	mixed
F132100	Progressive myoclonic epilepsy	generalised
F132111	Unverricht - Lundborg disease	generalised
F25..00	Epilepsy	unspecified
F250.00	Generalised nonconvulsive epilepsy	generalised
F250000	Petit mal (minor) epilepsy	unspecified
F250100	Pykno-epilepsy	generalised
F250400	Juvenile absence epilepsy	generalised
F250500	Lennox-Gastaut syndrome	generalised
F250y00	Other specified generalised nonconvulsive epilepsy	generalised
F250z00	Generalised nonconvulsive epilepsy NOS	generalised
F251.00	Generalised convulsive epilepsy	generalised
F251000	Grand mal (major) epilepsy	generalised
F251011	Tonic-clonic epilepsy	generalised

CODES	TERM	EPILEPSY TYPE
F251100	Neonatal myoclonic epilepsy	generalised
F251111	Otohara syndrome	mixed
F251500	Tonic-clonic epilepsy	generalised
F251y00	Other specified generalised convulsive epilepsy	generalised
F251z00	Generalised convulsive epilepsy NOS	generalised
F254.00	Partial epilepsy with impairment of consciousness	partial
F254000	Temporal lobe epilepsy	partial
F254100	Psychomotor epilepsy	partial
F254200	Psychosensory epilepsy	unspecified
F254300	Limbic system epilepsy	partial
F254z00	Partial epilepsy with impairment of consciousness NOS	partial
F255.00	Partial epilepsy without impairment of consciousness	partial
F255000	Jacksonian, focal or motor epilepsy	partial
F255011	Focal epilepsy	partial
F255012	Motor epilepsy	partial
F255100	Sensory induced epilepsy	unspecified
F255200	Somatosensory epilepsy	partial
F255300	Visceral reflex epilepsy	unspecified
F255311	Partial epilepsy with autonomic symptoms	partial
F255400	Visual reflex epilepsy	unspecified
F255500	Unilateral epilepsy	partial
F255y00	Partial epilepsy without impairment of consciousness OS	partial
F255z00	Partial epilepsy without impairment of consciousness NOS	partial
F256.00	Infantile spasms	generalised
F256.11	Lightning spasms	generalised
F256.12	West syndrome	generalised
F256100	Salaam attacks	generalised
F256z00	Infantile spasms NOS	generalised
F259.00	Early infant epileptic encephalopathy wth suppression bursts	mixed
F259.11	Ohtahara syndrome	mixed
F25A.00	Juvenile myoclonic epilepsy	generalised
F25B.00	Alcohol-induced epilepsy	unspecified
F25C.00	Drug-induced epilepsy	unspecified
F25D.00	Menstrual epilepsy	unspecified
F25E.00	Stress-induced epilepsy	unspecified
F25F.00	Photosensitive epilepsy	mixed
F25G.00	Severe myoclonic epilepsy in infancy	generalised
F25G.11	Dravet syndrome	generalised

CODES	TERM	EPILEPSY TYPE
F25y.00	Other forms of epilepsy	unspecified
F25y000	Cursive (running) epilepsy	partial
F25y100	Gelastic epilepsy	partial
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset	partial
F25y400	Benign Rolandic epilepsy	partial
F25y500	Panayiotopoulos syndrome	partial
F25yz00	Other forms of epilepsy NOS	unspecified
F25z.00	Epilepsy NOS	unspecified
Fyu5000	[X]Other generalized epilepsy and epileptic syndromes	generalised
Fyu5100	[X]Other epilepsy	unspecified
P228300	Aicardi syndrome	mixed
PK61.00	Sturge-Weber syndrome	partial
PKyz511	Angelman syndrome	generalised
PKyz700	Angelman's syndrome	generalised
PKyz711	Angelman syndrome	generalised
SC20000	Traumatic epilepsy	partial
ZS82.11	Landau-Kleffner syndrome	mixed

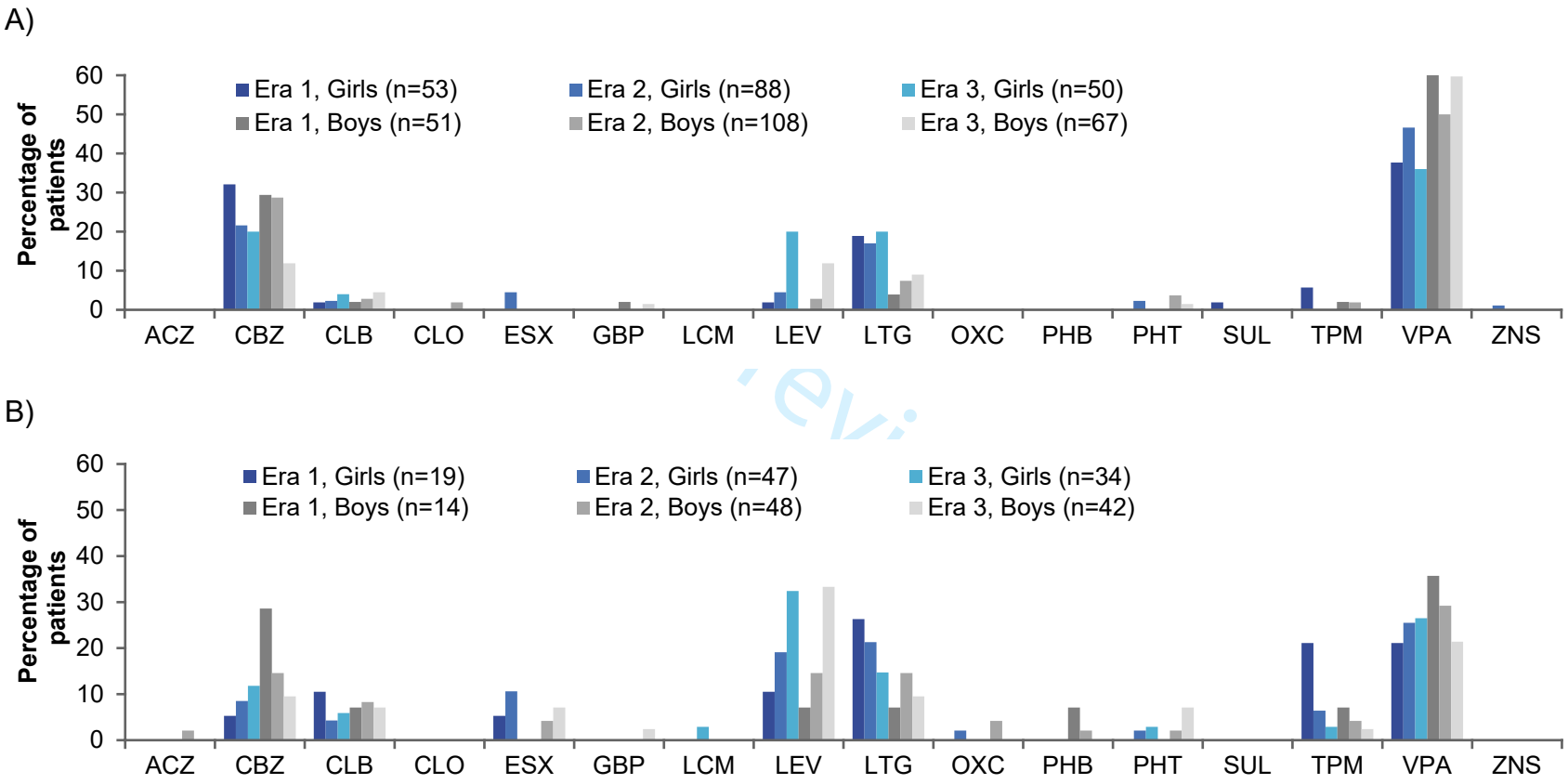
Supplementary Table S2 READ codes used to capture the primary outcome

CODE	TERM
Active epilepsy and seizures	
1B1W.00	Transient epileptic amnesia
1B27.00	Seizures in response to acute event
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
1B6B.00	Febrile convulsion
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..13	O/E - a seizure
2827	O/E - febrile convulsion
2828	Absence seizure
282Z.00	O/E - fit/convulsion NOS
667D.00	Epilepsy control poor
667Q.00	1 to 12 seizures a year
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	Daily seizures
667V.00	Many seizures a day
667W.00	Emergency epilepsy treatment since last appointment
F132z12	Myoclonic seizure
F250011	Epileptic absences
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251600	Grand mal seizure
F253.11	Status epilepticus
F254400	Epileptic automatism
F254500	Complex partial epileptic seizure
F255600	Simple partial epileptic seizure
F25H.00	Generalised seizure
F25X.00	Status epilepticus, unspecified
F25y300	Complex partial status epilepticus
F25z.11	Fit (in known epileptic) NOS
Fyu5200	[X]Other status epilepticus
Fyu5900	[X]Status epilepticus, unspecified

CODE	TERM
Q480.00	Convulsions in newborn
Q480.12	Seizures in newborn
R003.00	[D]Convulsions
R003000	[D]Convulsions, febrile
R003011	[D]Pyrexial convulsion
R003100	[D]Convulsions, infantile
R003400	[D]Nocturnal seizure
R003y00	[D]Other specified convulsion
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS
Ryu7100	[X]Other and unspecified convulsions
1B63.00	Had a fit
1B63.11	Fit - had one, symptom
282..12	O/E - a fit
2822	O/E - grand mal fit
2823	O/E - petit mal fit
2824	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2825	O/E - psychomotor fit
Q480.11	Fits in newborn
R003200	[D]Fit
F252.00	Petit mal status
F253.00	Grand mal status
F256.00	Infantile spasms
F256.11	Lightning spasms
F256z00	Infantile spasms NOS
F256100	Salaam attacks

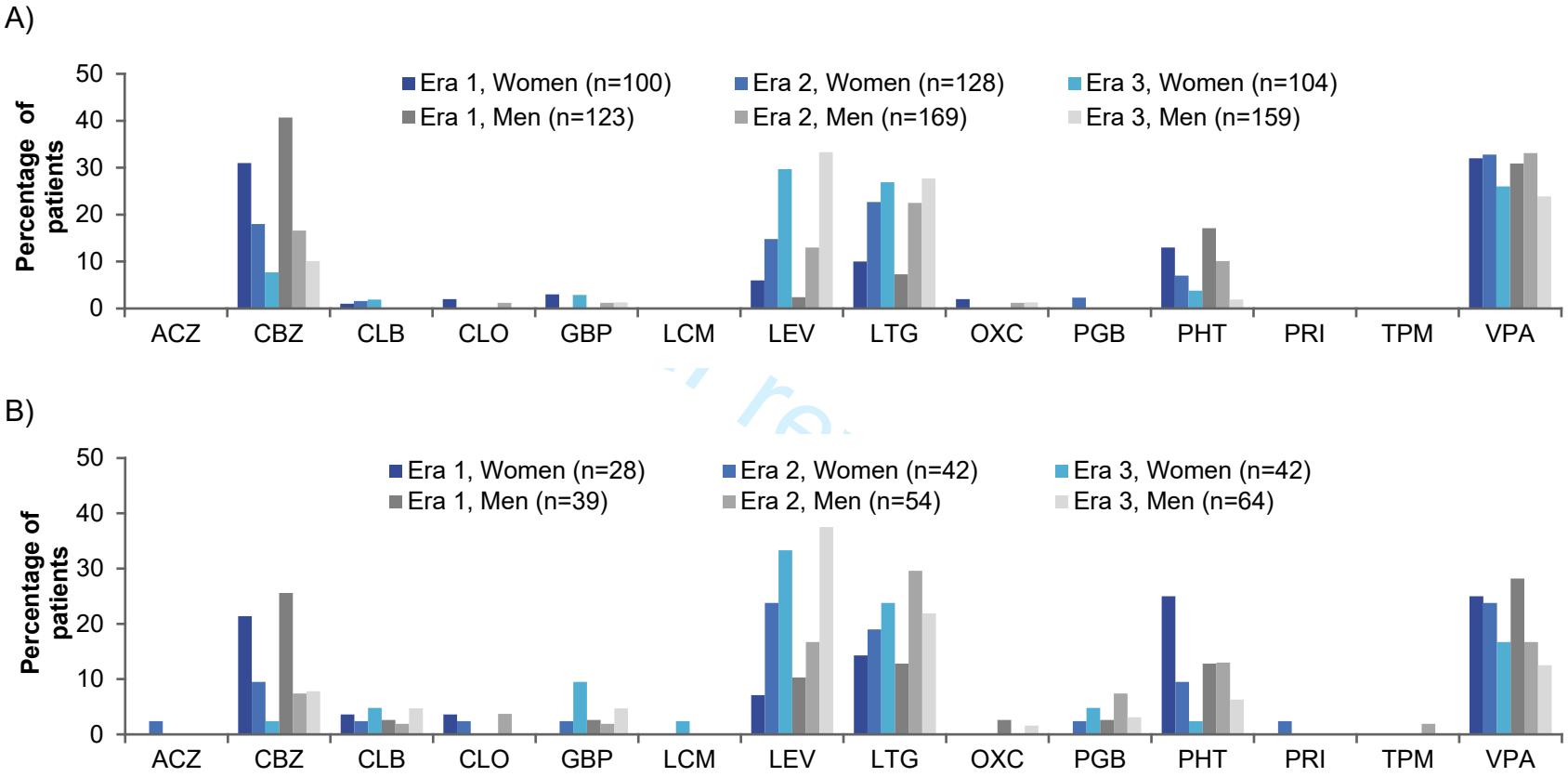
Supplementary Figures

Supplementary Figure S1 AED trends in boys and girls (<16 years of age) in A) first-line and B) second-line treatment.



ACZ, acetazolamide; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate.

Supplementary Figure S2 AED trends in elderly men and women (≥65 years of age) in A) first-line and B) second-line treatment.



ACZ, acetazolamide; CBZ, carbamazepine; CLB, clobazam; CLO, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PRI, primidone; TPM, topiramate; VPA, valproate.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.