PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016: a retrospective cohort study using electronic medical records
AUTHORS	Powell, Graham; Logan, John; Kiri, Victor; Borghs, Simon

VERSION 1 – REVIEW

REVIEWER	Patricia Penovich Minnesota Epilepsy Group PA USA
REVIEW RETURNED	10-Jul-2019

GENERAL COMMENTS	This is a large retrospective analysis of AED treatment in newly diagnosed epilepsy patients from time of diagnosis until 2016, using large EMR databases in a limited section of England. There are some clear limitations to the methodology which you do address fairly well. You end with noting the limitations and further study needed; it may be helpful to suggest some ways you would address this e.g. how to extract data more thoroughly, perhaps address in fewer centers and over a wider geographical area (why were the centers primarily London, south and not eastern and northern etc?)The study would also be more valuable if the reasons for AED change were explored, such as patient dissatisfaction with side effects, or QOL factors. 1. It was not clear to this reader who is not familiar with the NHS and consultations system, if all patients had a neurological consultation. If not, does this explain the lack of specificity in the epilepsy diagnosis? 2. Do you have data that tells you if patients had EEG, video EEG monitoring, MRI/CT imaging? Does this explain the deficiency in specificity for the diagnosis. 3. Does the diagnosis of epilepsy type come from the primary care office or the neurology consultant's office? 4. I have some discomfort with the idea that "remission" may be defined solely as no relapses or epilepsy related hospital, ER, or other encounters; this was not clearly stated in the methods. Could you please clarify. 5. Was there no way that you could have evaluated seizure frequency with the EMR records? If not, then some further discussion of the limitation of this method would be important in the discussion. 6. In your tables, could you explain what the REED coding is and why both methods are used (if they were conjointly, or if some used ICD codes and others used the READ coding) 7. It seems that one of your discussion points might be that the guidelines are not keeping up with practice or else that practitioners do not follow guidelines.

	8. Are the comorbidity factors increasing over the time period because patients picked up in Era 1 are now aging in ERA 3? Or are the groups kept separate in the analysis - i.e. patient age 60 at entry in Era 1 retains the comorbidity index at entrance or is analyzed at the end of the 13 years of study with a new comorbidity index? Perhaps a clarification in the methods for this would help. 9. Not working in the NHS, it is not clear to the reader how specific the EMR is for evaluating epilepsy care. If you could explain this or have a reference that evaluates this, it would be helpful.

REVIEWER	Martin Holtkamp Epilepsy-Center Berlin-Brandenburg, Department of Neurology, Charité - Universitätsmedizin Berlin, Germany
REVIEW RETURNED	21-Jul-2019

GENERAL COMMENTS	The aim of this retrospective exploratory study was to assess AED treatment patterns and seizure outcomes in 4,388 patients from England in the periods 2003 to 2007 (after first NICE epilepsy guidelines which recommended carbamazepine for focal epilepsy and valproate for generalized epilepsy), 2007 to 2011 (after publication to the SANAD trials which favored lamotrigine for focal epilepsy and valproate for generalized epilepsy), and 2012 to 2016 (after second NICE epilepsy guidelines which recommended carbamazepine and lamotrigine for focal epilepsy and valproate for generalized epilepsy). The data were derived from electronic medical records. The main findings are slight improvement in efficacy over the three eras with more patients achieving 1-year remission and a decrease in the use of enzyme-inducing AEDs (carbamazepine and phenytoin) compensated by an increase in levetiracetam use. Some of the changes in treatment patterns are congruent with NICE guidelines and findings of the SANAD trials, while others are not, scrutinizing the impact of guidelines and large clinical trials on everyday clinical practice. The topic is of clinical interest, the methods are sound, the findings and the inherent limitations are critically discussed. I have some minor comments: The elderly are just a subgroup of the adult patients, but this is not clear every time the elderly are mentioned; so the authors may add each time „in the subgroup of“ elderly patients. This is also true in Table 1; despite the small asterix following „elderly“, the three groups are presented to be on the same hierarchical level. The subgroup of elderly may be separated more apparently from the two other groups. The epilepsy classification is based on ICD10 which uses different terminology than the current ILAE epilepsy classification (2017). This in particular is true for the term „unspecified“ epilepsy. The authors should make clear that this corresponds to the official term „unknown“ epilepsy, otherwise there may be some misunderstanding in the readership. May the authors define „seizure-related healthcare events“, and give examples to illustrate what is meant. Treatment patterns over time, page 10, paragraph 1: In adults, „use of first-line VPA remained relatively stable over eras 1 and 2, and decreased in era 3“. In the next sentence, it reads that VPA in adults in era 1 is 29.0% and in era 3 49.0%. Maybe one of the figures in not correct.

	Treatment patterns over time, page 10, paragraph 2: the listing of all figures on individual AEDs in men vs. women in two different eras is difficult to consume. The data are (roughly) presented in Fig. 3, details may be given in an additional table. One of the explanations for shorter times to 1-year remission is better tolerability (rather than better direct efficacy) of newer AEDs (such as lamotrigine and levetiracetam) compared to standard AEDs (such as carbamazepine and phenytoin). This is shortly mentioned at the beginning of the discussion but may be more elaborated. Better tolerability allows higher doses which may result in increased efficacy. Though this study cannot provide data on doses, this explanation is quite likely for better remission comparing the three eras.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Patricia Penovich
Institution and Country: Minnesota Epilepsy Group PA USA
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is a large retrospective analysis of AED treatment in newly diagnosed epilepsy patients from time of diagnosis until 2016, using large EMR databases in a limited section of England.
There are some clear limitations to the methodology which you do address fairly well. You end with noting the limitations and further study needed; it may be helpful to suggest some ways you would address this e.g. how to extract data more thoroughly, perhaps address in fewer centers and over a wider geographical area (why were the centers primarily London, south and not eastern and northern etc?)

Because participation in the CPRD (www.cprd.com) is voluntary, the data is subject to uneven regional representation. However, all regions are represented within the CPRD. Our statement only highlighted regions where changes had occurred in the proportion of general practitioner (GP) practices participating. Because London and the Southeast areas are the most populous regions of England, they might be expected to have the most participating practices. The text has been edited for clarity (page 8):
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 (eg, 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.

The study would also be more valuable if the reasons for AED change were explored, such as patient dissatisfaction with side effects, or QOL factors.

We agree that it would be of interest to explore reasons for AED change; unfortunately, such information is not consistently captured in EMRs, and restricting records to only those with such information might introduce bias. We have noted the lack of reasons for AED change on page 17, this text has been edited for clarity.

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.

And recommendations for further study are added in the discussion (page 18):
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.

1. It was not clear to this reader who is not familiar with the NHS and consultations system, if all patients had a neurological consultation. If not, does this explain the lack of specificity in the epilepsy diagnosis?

In brief, yes we required all patients to have seen a neurologist. The source data for this study consists of primary care EMR data, coded in Read, linked to hospital claims data (HES), coded in ICD-10. Neurologist consultations are captured in HES, but are usually also recorded in primary care EMRs, as GPs are the main record keeper and should receive information about any healthcare encounter for each patient. Per CPRD's documentation, diagnoses are poorly recorded in HES's outpatient specialist data. So the situation could occur where a patient sees a neurologist and that visit is logged in HES; the diagnosis from that consultation itself is not available in HES, but the GP is notified of the diagnosis by the neurologist, and the diagnosis is available once the GP logs it in the primary care EMR. To mitigate this, we decided to use all possible data to determine that all selected patients had evidence of both a neurological consultation and a diagnosis of epilepsy; and because HES data might be incomplete, we allowed the diagnosis to occur on or within 3 months after the date of the neurologist consultation, to allow the GP time to record it. With regards specificity, the diagnosis is probably made and relayed to the patient's GP with specificity but not recorded specifically in the data - perhaps a result of the unwillingness / lack of necessity to code more specifically, on the part of physicians. In addition, many codes (both Read and ICD-10) are unspecified in nature, and in cases where contradictory codes (eg, both focal and generalised epilepsy) were present, the patients were categorised as unspecified. The text has been edited for clarity (page 6):
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.

Added to the limitations discussion (page 17).
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.

2. Do you have data that tells you if patients had EEG, video EEG monitoring, MRI/CT imaging? Does this explain the deficiency in specificity for the diagnosis.

We assume that the neurologist would have performed any necessary testing at their consultation and used this information when making their diagnosis. The diagnosis is probably made and relayed to the patient's GP with specificity but not recorded specifically in the data - perhaps a result of the unwillingness / lack of necessity to code more specifically, on the part of physicians.

Added to the limitations discussion (page 17).

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.

3. Does the diagnosis of epilepsy type come from the primary care office or the neurology consultant's office?

As above, all selected patients had evidence of both a neurological consultation, and a diagnosis of epilepsy, however the actual diagnosis code could have been recorded either at the neurological consultation or in primary care referral data.

4. I have some discomfort with the idea that "remission" may be defined solely as no relapses or epilepsy related hospital, ER, or other encounters; this was not clearly stated in the methods. Could you please clarify.

We agree that defining remission in this way is less ideal than what is commonly used for clinical trial assessments, however the nature of CPRD's EMR/HES data does not permit such rigor in definition. The proxy used for remission, the absence of AED changes or seizure-related events, which could reflect seizure occurrence, is designed to use as much information as is captured in the databases.

Remission has been further defined under Outcomes Measures in the Methods (page 6):
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'), and QOF data and Read codes (online supplementary table S2) indicating a seizure at any time for at least 1 year.

Additionally, text has been added to the Discussion (page 17):
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',[29] 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 epilepsy QOF data, which is intended to record seizure frequency, was found to be very poorly populated. In addition, EMR free text is not available from CPRD.

5. Was there no way that you could have evaluated seizure frequency with the EMR records? If not, then some further discussion of the limitation of this method would be important in the discussion.

As noted above, no Read or ICD-10 codes record seizure frequency. The NHS employs an improvement scheme called 'Quality Outcomes Framework' by which GPs are rewarded to capture information; in the case of epilepsy this is seizure frequency. This information is available in the CPRD primary care data set. In our description of the data we have found that despite intentions, this quality outcomes framework data is very sparsely recorded and would not allow a generalizable analysis of seizure frequency for the entire cohort. We have used this data, where present, in our definition of remission as described above. The CPRD does not make EMR free text available and as such this information was not available for study.

6. In your tables, could you explain what the REED coding is and why both methods are used (if they were conjointly, or if some used ICD codes and others used the READ coding)

Read codes are a set of standard clinical terms used in UK general practice to complete EMRs, and document patient findings and procedures (epilepsy-specific codes are listed in supplementary table S2). In contrast, hospital-based/secondary care providers use ICD-10 codes to document diagnoses in HES claims data.
New text has been added to the Study Design for clarity (page 5):
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 (eg, 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.

7. It seems that one of your discussion points might be that the guidelines are not keeping up with practice or else that practitioners do not follow guidelines.

We have added a statement to precede the discussion on variances in guidelines vs practice (page 14):
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.

Ideally, guidelines reflect best evidence to date, whereas clinical practice relies on a range of factors, where physician preference and prior experience may outweigh evidence-based guidance. As such, guidelines should lead prescribing practice rather than vice versa. However in epilepsy, guidelines have evolved more slowly than prescribing practices. The nature of evidence that contributes to guidelines might play a role. In epilepsy, the reliance of guidelines primarily on randomized controlled trials, which are scarce, may have led to relevant information being ignored.

8. Are the comorbidity factors increasing over the time period because patients picked up in Era 1 are now aging in ERA 3? Or are the groups kept separate in the analysis - i.e. patient age 60 at entry in Era 1 retains the comorbidity index at entrance or is analyzed at the end of the 13 years of study with a new comorbidity index? Perhaps a clarification in the methods for this would help.

The study captured patients who were newly diagnosed in each era separately, thus each cohort represents a separate set of patients. The comorbidity index as presented in Table 1 reflects the baseline values for each cohort.
Text has been added for clarification (page 6):
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).

Text interpreting the change in comorbidity index has been added to the Discussion (page 15):
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]

9. Not working in the NHS, it is not clear to the reader how specific the EMR is for evaluating epilepsy care. If you could explain this or have a reference that evaluates this, it would be helpful.

CPRD's primary care EMR data is taken exclusively from GP practices that use the Vision EMR software (https://www.visionhealth.co.uk/). This EMR is not specific to epilepsy.
Read codes have been used in the UK since the 1980s to capture EMRs on patients in general practice. They reflect a patient's interactions with GPs, who record diagnoses, treatments, and other notable findings. Thus, while not epilepsy-specific per se, the EMRs would contain records of epilepsy diagnosis, treatment, and management. Because many readers of BMJ Open would have familiarity with these codes, references for further reading have been added to the text (page 5; refs 17-19).

In addition, a more complete description of items captured in the CPRD has been added to the Methods (page 5):
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 that are commonly 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.

Lack of detailed coding with respect to epilepsy care is reflected by the lack of seizure frequency records, and has been added to the Discussion (page 17):
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.

Finally, text that recommends areas of further study also focuses on data availability (page 18):
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.

Reviewer: 2
Reviewer Name: Martin Holtkamp
Institution and Country: Epilepsy-Center Berlin-Brandenburg, Department of Neurology, Charité - Universitätsmedizin Berlin, Germany
Please state any competing interests or state 'None declared': None.

Please leave your comments for the authors below
The aim of this retrospective exploratory study was to assess AED treatment patterns and seizure outcomes in 4,388 patients from England in the periods 2003 to 2007 (after first NICE epilepsy guidelines which recommended carbamazepine for focal epilepsy and valproate for generalized epilepsy), 2007 to 2011 (after publication to the SANAD trials which favored lamotrigine for focal epilepsy and valproate for generalized epilepsy), and 2012 to 2016 (after second NICE epilepsy

guidelines which recommended carbamazepine and lamotrigine for focal epilepsy and valproate for generalized epilepsy). The data were derived from electronic medical records. The main findings are slight improvement in efficacy over the three eras with more patients achieving 1-year remission and a decrease in the use of enzyme-inducing AEDs (carbamazepine and phenytoin) compensated by an increase in levetiracetam use. Some of the changes in treatment patterns are congruent with NICE guidelines and findings of the SANAD trials, while others are not, scrutinizing the impact of guidelines and large clinical trials on everyday clinical practice.
The topic is of clinical interest, the methods are sound, the findings and the inherent limitations are critically discussed.

I have some minor comments:

1. The elderly are just a subgroup of the adult patients, but this is not clear every time the elderly are mentioned; so the authors may add each time „in the subgroup of" elderly patients. This is also true in Table 1; despite the small asterix following „elderly", the three groups are presented to be on the same hierarchical level. The subgroup of elderly may be separated more apparently from the two other groups.

The Table 1 header has been edited to 'Elderly subgroup*', with asterisk intact to provide more explicit definition. Similar revisions have been made to Table 2. In addition, the text has been revised throughout the manuscript to refer to the 'elderly subgroup'.

2. The epilepsy classification is based on ICD10 which uses different terminology than the current ILAE epilepsy classification (2017). This in particular is true for the term „unspecified" epilepsy. The authors should make clear that this corresponds to the official term „unknown" epilepsy, otherwise there may be some misunderstanding in the readership.

The term 'unspecified' in the study is used to indicate that the epilepsy type is not specified in the data available. This does not necessarily mean that the patient's epilepsy is unknown as defined by the ILAE (ie, 'where it is understood that the patient has Epilepsy but the clinician is unable to determine if the Epilepsy Type is focal or generalized because there is insufficient information available'). It is much more likely that the epilepsy type is known but not recorded in the data, rather than the epilepsy type itself being truly unknown. Therefore, it's more conservative to call it 'unspecified'.

May the authors define „seizure-related healthcare events", and give examples to illustrate what is meant.

Seizure-related healthcare events have been further defined (page 6):
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') and…

Treatment patterns over time, page 10, paragraph 1: In adults, „use of first-line VPA remained relatively stable over eras 1 and 2, and decreased in era 3". In the next sentence, it reads that VPA in adults in era 1 is 29.0% and in era 3 49.0%. Maybe one of the figures in not correct.

The figure demonstrates the correct trend; the text has been corrected to 19.4%.

3. Treatment patterns over time, page 10, paragraph 2: the listing of all figures on individual AEDs in men vs. women in two different eras is difficult to consume. The data are (roughly) presented in Fig. 3, details may be given in an additional table.

We agree that this is a lot of data to digest, and prefer not to add additional tables to an already table- and figure-heavy manuscript. We have instead transferred this data from the text to a footnote to Figure 3:
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%.
We hope this approach is acceptable.

4. One of the explanations for shorter times to 1-year remission is better tolerability (rather than better direct efficacy) of newer AEDs (such as lamotrigine and levetiracetam) compared to standard AEDs (such as carbamazepine and phenytoin). This is shortly mentioned at the beginning of the discussion but may be more elaborated. Better tolerability allows higher doses which may result in increased efficacy. Though this study cannot provide data on doses, this explanation is quite likely for better remission comparing the three eras.

We agree that this situation is likely, and have added text to the discussion (page 16):
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.

VERSION 2 – REVIEW

REVIEWER	Patricia Penovich Minnesota Epilepsy Group, PA United States Speakers Bureaus: Aquestive, Eisai, GW Pharmaceuticals, UCB Pharma Consulting/Advisory: Neurelis, SK Biosciences
REVIEW RETURNED	02-Sep-2019

GENERAL COMMENTS	The revision has addressed my concerns. I feel it is complete and acceptable at this time.

REVIEWER	Martin Holtkamp Epilepsy-Center Berlin-Brandenburg, Berlin, Germany
REVIEW RETURNED	20-Sep-2019

GENERAL COMMENTS	All minor concerns have now be addresed.