Antiepileptic drugs discontinuation by people with epilepsy in the general population

Giorgia Giussani BiolD[1], Elisa Bianchi MSc[1], Valentina Canelli PharmD[1], Giuseppe Erba MD[2], Carlotta Franchi PharmD[1], Alessandro Nobili MD[1], J. W. Sander FRCP[3,4], Ettore Beghi MD[1], and the EPIRES Group[*]

[1] IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano, Italy.

[2] Department of Neurology, SEC, University of Rochester, Rochester, NY, United States.

[3] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, 2103 SW, The Netherlands.

[4] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, and Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0RJ, UK.

* EPIRES Group = Neurologists and child neurologists: Elio Agostoni, Larissa Airoldi, Francesco Basso, Marialuisa Carpanelli, Mariolina Di Stefano, Andrea Magnoni, Ottaviano Martinelli, Andrea Rigamonti, Andrea Salmaggi, Lorenzo Stanzani, Cristina Volpe, Nicoletta Zanotta, Claudio Zucca. General practitioners: Marco Agudio, Flavio Arienti, Graziano Rocco Arrigoni, Giancarlo Balestra, Piercarla Ballabio, Stefano Marco Balossi, Maria Rita Baratti, Fabrizia Enrica Barteselli, Fausto Bellani, Mauro Bellani, Gianpiero Bellini, Pier Aldo Beretta, Roberto Beretta, Massimo Bergamini, Annalisa Bertella, Francesco Bertolini, Rolando Bevilacqua, Marcellino Arturo Bianchi, Patrizia Bigiolli, Giuseppe Binda, Gigliola Biondelli, Libero Bodega, Edoardo Giovanni Bolis, Marco Vincenzo Carlo Bolla, Carlo Ambrogio Bonacina, Marco Bonfanti, Fausta Borghetti, Roberto Brambilla, Wilma Brancaleone, Francesco Brusadelli, Sabine Bub, Giovanna Caccia, Myriam Caglio, Carlo Calvi Rossi, Daniela Capra, Davide Carone, Giuseppe Carì, Silvio Carrera, Rosalia Cavenago, Maria Luisa Cecchetti, Bice Antonella Centonze, Fabio Cereghini, Ciro Cerrone, Maria

Pia Ciappetta, Bruno Cogliati, Ombretta Colombano, Alberto Colombo, Daniela Colombo, Maria Lia Corti, Nicla Cremonini, Marco Crippa, Rolando Antonio Crippa, Mario Crotta, Salvatore Curto, Patrizia Daielli, Domenico De Gilio, Giuseppe Pasquale De Pascalis, Elena Decet, Luigi Della Morte, Felice Duvia, Antonia Favorito, Roberto Ferrario, Luigi Fezzi, Angela Laura Finzi, Bruno Ugo Fiorentino, Agnese Fornaciari, Silvana Franceschetti, Fabio Fulconis, Giovanni Fumagalli, Maurizio Fumagalli, Giuseppe Galbiati, Carlo Andrea Galimberti, Donatella Gecchele, Barbara Ghiazza, Paolo Ghislanzoni, Laura Gioffredi, Taraneh Hassibi, Simone Julita, Giuseppe Leone, Claudio Levi, Giovanni Locatelli, Anna Alessandra Locati, Enrico Giovanni Longhi, Ingrid Lukacova, Mauro Giovanni Manfroi, Paola Manzoni, Claudio Marcolini, Fabio Minicucci, Mohammed Safwan Martini, Rita Masperi, Sussele Mayan, Valeria Mazzoleni, Antonio Menga, Fiorella Merlini, Enrico Messina, Marta Micheli, Rocco Micò, Andrea Millul, Barbara Montini, Alberto Palazzuolo, Silvano Primo Panzeri, Giovanni Passoni, Laura Pensotti, Maria Marcella Petrone, Roberto Pezzuto, Elisabetta Pigazzini, Nicoletta Pirovano, Margherita Pontiggia, Roberto Pozzi, Carlo Quadrelli, Filomena Rampello, Marco Realini, Giovanni Righetti, Cesare Ripa, Sonia Rivetta, Antonino Romeo, Carlo Rota, Tiziana Rusconi, Andrea Santarpia, Ivana Santi, Luigi Sciani, Gianni Scoccimarro, Eugenio Scopinaro, Angelo Giuseppe Semerano, Daniela Sferco, Anna Ersilia Sirtori, Angela Spandri, Bruno Spinelli, Fausto Stefanoni, Raffaele Taiana, Libero Tamagnini, Laura Tassi, Giorgio Tentori, Augusto Teodoro, Katerina Tinterova, Ampelio Tocchetti, Michela Todeschini, Lorenzo Trezza, Valter Valsecchi, Roberto Vanini, Claudio Felice Vercelloni, Anna Villella, Maria Viola, Pietro Vismara, Daniele Mario Zoboli.

Corresponding author: Ettore Beghi, MD
Laboratory of Neurological Disorders
IRCCS-Mario Negri Institute for Pharmacological Research
Via Giuseppe La Masa 19,
20156 Milan, Italy.
Tel. +39 02 39014542 fax +39 02 39001916

e-mail: ettore.beghi@marionegri.it

Running title: Antiepileptic drugs discontinuation

Keywords: Epilepsy, antiepileptic drugs, discontinuation

Number of text pages: 21

Number of words: 3368

Number of references: 41

Number of figures: 1

Number of tables: 4

Supporting information: Supporting Table S1 and Supporting Table S2

Abstract

Objective: Rate, reasons and predictors of antiepileptic drugs (AEDs) discontinuation were investigated in a well-defined cohort of people with epilepsy to verify efficacy and tolerability of treatment in up to twenty years from treatment initiation.

Methods: The history of AED usage in children and adults with epilepsy registered with 123 family physicians in an area of Northern Italy between 2000 and 2008 was recorded. Cumulative probabilities of AED withdrawal for specific reasons were estimated using cumulative incidence functions. The probabilities of withdrawing for terminal remission, or of achieving sustained remission while still on treatment, were also evaluated. The roles of sex, age at diagnosis, seizure types, duration at diagnosis and syndrome were assessed with hazard ratios (HR) and 95% confidence intervals (95% CI).

Results: 731/747 individuals were treated with one or more AEDs during the disease course. The three commonest drugs were valproate, carbamazepine and phenobarbital. Reported reasons for AED withdrawal were, in decreasing order, terminal remission, ineffectiveness and adverse events. The probability of withdrawing the first AED for terminal remission was 1.0% at one year and increased to 20.0% at twenty years. Corresponding rates for ineffectiveness were 2.9% and 12.6%; and for adverse events 0.5% and 3.3 %. Reasons for withdrawal varied with individuals' age, sex, disease characteristics, and drugs.

Significance: The initial AED given was retained in the majority of cases. Terminal remission, lack of efficacy and adverse effects were, in decreasing order, the commonest reasons for AED discontinuation. Withdrawal could be predicted by age at diagnosis, sex and clinical characteristics and varies among drugs.

Keywords: Epilepsy, antiepileptic drugs, discontinuation

Introduction

The response to antiepileptic drugs (AEDs) is an important indicator of the prognosis of epilepsy. AEDs are generally efficacious in controlling seizures. In randomized trials, but also in clinical practice, seizure freedom is seen in about 50% of people with previously untreatedepilepsy.[1-3] In people who do not respond to the first AED, the use of a second drug leads to complete seizure control in a lower proportion of cases and there is a further decrease with each subsequent treatment change.[4-7] If the first drug fails, however, seizure-free rates vary across studies and, although drug-resistant epilepsy has been defined as the failure of two appropriate AEDs,[8] there are reports of people achieving seizure freedom even after having failed several AEDs.[5, 9-11] While withdrawal of ineffective drugs, when given as first or subsequent treatments, is usually clearly documented, the information becomes fragmentary regarding the reasons for discontinuation. Additionally, with some exceptions,[12-14] AED retention has not been assessed in a population-based sample. Lastly, there are no data on the history of AED treatment in samples of children and adults with epilepsy from the same population and followed for a prolonged period of time.

We investigated rate, reasons and predictors of AED discontinuations in a well-defined population followed for up to twenty years from treatment start. We aimed: 1. To estimate the retention rate of AEDs according to the order of administration (first, second, or subsequent) in general and by drug; 2. To investigate the reasons for stopping AEDs with reference to the sequence of drug assignment; 3. To ascertain possible predictors of treatment discontinuation with reference to the commonest reasons for discontinuing the assigned drug.

Methods

The study sample (146,506; year 2008), representative of the general population, was based in the province of Lecco, Northern Italy.[15,16]

The details of the study design are given elsewhere[15,16] and are summarized here. In Italy, the diagnosis of epilepsy is confirmed by a neurologist who also takes the responsibility to start and, where needed, to change or stop the treatment. The individual is then followed by his/her general practitioner (GP) to obtain drugs free-of-charge. One hundred and twenty-three GPs (47% of those active in the province) were invited to identify people with epilepsy in their practice's list and who had lived in the area for at least one year between January 1st 2000 and December 31st 2008. The medical records of all these individuals in the practice and, if available, in other in- and out-patient facilities such as hospitals, nursing homes, out-patient clinics were reviewed. Epilepsy diagnosis was based on a history of two or more unprovoked seizures at least 24 hours apart[17] and confirmed by a neurologist. People with acute symptomatic seizures, neonatal seizures, single unprovoked seizures, and paroxysmal non-epileptic events were excluded. For each eligible case, data were collected on demographics (date of birth, sex), predominant seizure types,[18] date of diagnosis, epilepsy syndrome,[19] number and type of drugs used since the beginning of treatment. For each AED, details were collected on starting date, maximal maintenance daily dose, and withdrawal date or last follow-up date, whichever came earlier. If the drug was discontinued, reasons for discontinuation (ineffectiveness, adverse events, terminal remission or other) were recorded. As the study period preceded the new epilepsies classification scheme,[20] the 1989 classification[19] was used. As detailed information was not available in all cases, seizures and syndromes were classified using broad categories. Seizures were classified as focal, generalized, or unclassifiable. Syndromes were classified as partial (idiopathic, symptomatic, or cryptogenic), generalized (idiopathic or symptomatic/cryptogenic), undetermined, and special. All data from the GPs and, if needed, from the consulting neurologists (including those outside the study area) were de-identified and filed in a central database by two of us (GG and VC) who interacted with the GPs and, if required, with the neurologists. Two of us (EBe and GE) revised the information included in the database to confirm the appropriateness of the indications of all drugs assigned to each individual during the disease course.

Prevalence and incidence of epilepsy, of drug-resistant epilepsy and prognostic patterns in the same study population have been previously reported elsewhere.[15,16]

Statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc, Cary, NC, USA). Descriptive statistics are presented as counts and percentages. Administration frequencies and cause-specific withdrawal frequencies were calculated for each active principle and by prescription order. AEDs were also grouped in two different classes: old and newer (marketed before and after 1990). Old drugs included barbexaclone (BSC), carbamazepine (CBZ), clobazam (CLB), clonazepam (CNP), ethosuximide (ESM), phenobarbital (PB), phenytoin (PHT), primidone (PRM), valproate (VPA), valpromide (VPM); newer drugs included gabapentin (GBP), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), zonisamide (ZNS).

To account for competing risks, cumulative probabilities of AED withdrawal from specific causes over twenty years from treatment start were estimated using cumulative incidence functions. The cumulative probability of cause-specific AED withdrawal was calculated for the first, second, and third AED, for the most common AEDs (i.e. used by more than 100 people), and for new and old AEDs separately. Differences in the cumulative incidence functions between new and old AEDs were assessed using Gray's test.[21] For the first AED, the cumulative probability of withdrawing for terminal remission (ie, seizure freedom for at least two years at last follow-up) while still on treatment, was also evaluated.

The association between drug discontinuation and sex, age at diagnosis (<15, 15-64, 65+ years), seizure types (focal, generalized, unclassifiable), duration from first seizure to diagnosis, and epilepsy syndrome (idiopathic, cryptogenic/symptomatic, special/undetermined) was assessed using the Cox proportional hazards function. Models for the most commonly used AEDs were adjusted for the number of previous drugs taken. Results were presented as Hazard Ratios (HR) with 95% Confidence Intervals (95%CI). Missing data were handled using the listwise deletion method.

The study was approved by the Ethics Committee of the Provincial Hospital of Lecco (Protocol 2011-003428-11). Local Health Service authorization was obtained to collect de-identified data from the GPs. In less than 5% of cases, the GPs needed to collect additional information from individuals, after informed consent. All the data were managed according to the current Italian privacy rules.

Results

The study sample consist of 747 people with epilepsy aged 11 months through 94 years and followed for a total of 11,045.5 person-years (mean 14.8 years; interquartile range 4.5-22.5). Clinical characteristics are provided in Table 1; 731 people (98%) were treated with at least one AED.

The use of each compound as first, second, third, or fourth to ninth AED is shown in Table 2. The three AEDs most commonly used as first drug were valproate, carbamazepine and phenobarbital and the same drugs were also the commonest second option. The third option included, in decreasing order, carbamazepine, levetiracetam and topiramate.

The commonest reasons for drug withdrawal were, in decreasing order, terminal remission, ineffectiveness and adverse events. Table 3 shows the reasons for withdrawal with reference to the sequence of drug assignment. For the first AED, the main reasons for withdrawal were terminal remission followed by ineffectiveness; for the second AED the main reasons were ineffectiveness followed by terminal remission; for the third and the fourth AED the main reason was ineffectiveness, followed by adverse events. Withdrawal for ineffectiveness increased from the first to the seventh drug, while withdrawal for terminal remission decreased progressively after the first drug. Adverse events showed a moderate increase from the first to the last assigned drugs.

Reasons for drug withdrawal for each AED are provided in Table 4. The percentages of withdrawal of carbamazepine, phenobarbital and valproate due to ineffectiveness were in general lower than the percentages reported for other AEDs.

Cumulative probabilities and predictors of withdrawal of the first, second and third AED

1. First AED. The cumulative probability of withdrawal of the first AED for ineffectiveness increases from 2.9% at one year to 12.6% at twenty years (Supporting Table S1). The only predictor was age at diagnosis: compared to those aged less than 15 years, those in the 15-64 year group were less likely to withdraw due to ineffectiveness (HR 0.46, 95% CI 0.28-0.75), while those in the oldest group showed no significant differences (HR 1.26, 95% CI 0.61-2.59). The cumulative probability of withdrawing the first AED for terminal remission increased from 1.0% at one year to 20.0% at twenty years. The variables associated with first AED withdrawal due to seizure freedom were age at diagnosis, sex and epilepsy syndrome. Compared to those aged less than 15 years, those in the 15-64 year group were less likely to withdraw the drug (HR 0.58, 95% CI 0.40-0.86) while those in the oldest group had a similar HR although this was not statistically significant. . Females had a lower probability than males of withdrawing the drug (HR 0.56, 95% CI 0.39-0.82). Those with cryptogenic/symptomatic epilepsies (HR 0.43, 95% CI 0.29-0.63) had a lower probability of withdrawing the drug than those with idiopathic epilepsies. The cumulative probability of withdrawing the first drug for adverse events was 0.5% at one year and increased to 3.3% at twenty years. The probability of withdrawing the first drug for other reasons was 0.2% at one year and 6.6% at twenty years. Predictors for adverse events and other reasons were not assessed, due to the small numbers. No significant differences were observed between old and new AEDs given as first treatment (Supporting Table S2). Four hundred and sixty people never withdrew the first antiepileptic treatment and 224 of them (50.9%) started a period of remission lasting until the end of follow-up. The cumulative probability of either withdrawing the first AED for seizure freedom or of achieving sustained remission while still on treatment was 23.1% at one year and increased to 48.0% at twenty years.

2. Second AED. The cumulative probability of withdrawing the second drug at twenty years for ineffectiveness was 15.8%, for adverse events 4.3%, for terminal remission 13.3%, and for other reasons 7.7% (Supporting Table S1). The only variable associated with discontinuation of the

second AED for ineffectiveness was seizure type: compared to partial seizures, generalized seizures were more likely to lead to drug withdrawal (HR 2.05, 95% CI 1.10-3.83). Due to the small number of events, predictors for other reasons for the withdrawal of the second AED were not evaluated. No significant differences were found between old and new AEDs (Supporting Table S2).

3. Third AED. The cumulative probability of withdrawing the third AED at twenty years for ineffectiveness was 39.3%, for adverse events 8.0%, for seizure freedom 4.3%, and for other reasons 5.0% (Supporting Table S1). Due to the small numbers, predictors for the third AED withdrawal were not assessed. The comparison between old and new AEDs showed no significant differences (Supporting Table S2).

Cumulative probabilities and predictors of withdrawal of the most commonly used AEDs

At 20 years, the cumulative time-dependent probability of withdrawal of carbamazepine for ineffectiveness was 10.8%. The corresponding values were 13.5% for phenobarbital and 12.3% for valproate (Figure 1A). The 20-year probability of withdrawal for terminal remission was 12.9% for carbamazepine, 14.8% for phenobarbital and 27.4% for valproate (Figure 1B).

Predictors of withdrawal due to ineffectiveness were seizure type for carbamazepine and age for phenobarbital. No predictors were found for valproate. Generalized seizures were more likely than partial seizures to lead to withdrawal of carbamazepine for ineffectiveness (HR 3.07, 95% CI 1.35-6.98). Individuals in the 15-64 years group had a lower probability of withdrawing phenobarbital due to ineffectiveness than the youngest age group (HR 0.24, 95% CI 0.11-0.54), while those in the oldest group showed no significant differences (HR 0.21, 95% CI 0.03-1.57).

Variables associated with drug withdrawal due to seizure freedom were sex for carbamazepine and age, sex and syndrome for valproate. No predictors were found for phenobarbital. Females had a lower probability of withdrawing carbamazepine for seizure freedom than males (HR 0.47, 95% CI 0.22-0.99). Compared to people in the <15 year group, those aged 15-64 years were less likely to withdraw valproate due to ineffectiveness (HR 0.30, 95%CI 0.13- 0.70), while those in the oldest

group showed no significant differences (HR 0.36, 95%CI 0.05-2.58); females had a lower probability of withdrawing the drug than males (HR 0.52, 95% CI 0.30-0.91); compared with idiopathic epilepsies, those with cryptogenic/symptomatic epilepsies were less likely to have drug withdrawal (HR 0.35, 95% CI 0.19-0.65).

Due to the small number of events, cumulative probabilities and predictors of carbamazepine, valproate and phenobarbital withdrawal for adverse events and other reasons were not assessed.

Discussion

People in our cohort, a representative sample of people with epilepsy in a defined area of Northern Italy, have used a large number of AEDs over a 15-year period. However, during this time, the three most common drugs given at the start of treatment were valproate, carbamazepine and phenobarbital and only 10 percent of people started treatment with a new AED. Terminal remission was the commonest explanation for discontinuation of the first drug (20% at twenty years), followed by lack of efficacy (12.6%). Withdrawal of the first drug for adverse events was only 0.5% at one year and increased to 3.3% at twenty years. While the discontinuation of a drug for terminal remission tended to decrease with AED order, treatment stop for ineffectiveness and for adverse events tended to increase even though clear trends could not be detected because of the small samples at the highest rankings. The reasons for drug withdrawal varied with age, sex and disease characteristics.

The probability of retaining the first drug in the treatment schedule and starting a period of remission lasting until the end of follow-up, or of stopping the first treatment for terminal remission, was high, 48% at 20 years. Others found that the proportion of seizure-free individuals on the first AED ranged from 5.4% to 62%;[3,4,12,22-24] 60.5% never withdrew the first AED and 51% of them started a period of remission lasting until the end of follow-up. This finding supports the concept that in clinical practice the majority of people with epilepsy can be easily controlled with any of the available compounds even after long follow-up periods.

In our study, the cumulative probability of discontinuing the first drug at 12 months for lack of efficacy or adverse events was only 3.4%. Our findings are fairly similar to the results of a Lebanese study of people with newly diagnosed focal epilepsy, which found a 12-month retention rate of 93.6%.[25] Our data only partly agree, however, with other long-term follow-up studies. In the UK National General Practice Study of Epilepsy[12] the first assigned drug was discontinued for lack of efficacy in 21% of cases (compared to our 12.6%) but the discontinuation rate for adverse events was 11.5% (compared to 3.3% in our study). This difference may be explained by the use of carbamazepine, phenytoin, valproate or phenobarbital in 96% of the UK cases as compared to 87% in our cohort. The use of fairly low daily doses for some drugs in our study (see Supporting Table 3) could be another explanation. No differences were found in retention rates when comparing old and new AEDs. Our findings are in keeping with a study in children[26] but differ from a study in older adults[27] in which the 12-month retention rates ranged from 12.5% (oxcarbazepine) to 90% (valproate). In this latter study, however, the rates were calculated in people with refractory epilepsy.

When comparing drugs in our study, differences in retention were seen. Discontinuation for lack of efficacy was most common with GABAergic drugs while discontinuation for adverse events was mostly seen with topiramate, phenytoin, carbamazepine and levetiracetam in decreasing order. These findings are not unexpected even though the rates differ from those of other reports[28-33] on account of differing prescribing patterns and different populations at risk.

People in our cohort taking carbamazepine, valproate or phenobarbital discontinued the assigned treatment for adverse events in 5.6, 1.1 and 2.8% of cases respectively. Our rates are significantly lower than those reported by others (carbamazepine, valproate and lamotrigine stopped in 27, 13 and 10% of cases respectively).[3] Possible explanations for this difference are the source population, as the Scottish study was not population-based, and the use of different daily doses.

Children and elderly subjects tended to stop the first drug mostly for lack of efficacy and, less frequently, due to terminal remission. Childhood and adolescent syndromes less responsive to the

current treatments and the need to resort to complex therapeutic regimens in people with comorbidities are possible explanations.

The lower rates of treatment withdrawal due to terminal remission in women than in men likely reflects the higher proportion of females in the age class <15 years (59% versus 41% of male children) who continued the first treatment, perhaps because of the fear of withdrawal in a period of hormonal and emotional changes. As expected, people with idiopathic epilepsies and/or generalized seizures were most likely to respond to the assigned treatments.

The study has strengths and limitations. The major strengths are the population base, the fairly large sample size, and a long follow-up. In this regard, our findings apply to the general epilepsy population in which, by definition, severe epilepsies are less frequent than in secondary and tertiary referral centers. The major limitation is the uncontrolled setting. We do not know whether a drug was discontinued after having been given at the highest tolerated dose. Our aim, however, was to explore treatment changes as performed in clinical practice, where the selected daily dose generally represents a compromise between seizure control, adverse events, and individual preference. Another limitation is the time frame during which we started the follow-up. To include people with newly diagnosed epilepsy in the cohort with reasonable follow-up, we started the observation at a time in which mainly older AEDs were available. We are thus uncertain whether our findings apply to cohorts starting treatment with a new AED. In keeping with our findings, however, there is no evidence from more recent reports[34-41] that new AEDs have advantages over older compounds. Thus, we do not expect significant differences in other therapeutic contexts. Furthermore, the cumulative time-dependent probability of withdrawal of AEDs other than carbamazepine, phenobarbital and valproate was not assessed because of small numbers. The limited sample size can also explain some non-significant correlations between demographic and clinical variables and drug withdrawal. Lastly, we did our best to verify whether the indication for each drug was appropriate. However, we cannot entirely exclude that drug failure was due to incorrect use of a given drug in a given individual.

In conclusion, the majority of people with epilepsy living in a community and followed for a prolonged period of time remain treated with the first assigned drug. Seizure remission is the main reason for drug discontinuation, followed by lack of efficacy and adverse events. Withdrawal of the first drug for ineffectiveness and for adverse events tends to increase by AED order, while decreasing for terminal remission. Withdrawal of the first AED for ineffectiveness can be predicted by age at diagnosis while withdrawal of the second drug is predicted by seizure type, and reflects the predominance of more severe epilepsy syndromes in younger individuals. These findings can help the practicing physician to predict the response to the assigned treatment at diagnosis and when a treatment change is required.

KEY POINTS

1. The initial antiepileptic drug (AED) given was retained in the majority of cases and only 10 percent of people started treatment with a new AED.

2. Reported reasons for AEDs withdrawal were, in decreasing order, terminal remission, ineffectiveness and adverse events.

3. Discontinuation of a drug for terminal remission decreased with AED order; withdrawal for ineffectiveness and adverse events increased.

4. Reasons for withdrawal varied with individuals' age, sex, disease characteristics, and among drugs.

5. The majority of people with epilepsy can be easily controlled with any of the available compounds even after long follow-up periods.

ACKNOWLEDGEMENTS

The authors thank Gail Bell for technical editing. JWS is based at UCLH/UCL Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of

Health's National Institute for Health Research Biomedical Research Centres funding scheme. He receives support from the Dr Marvin Weil Epilepsy Research Fund and UK Epilepsy Society.
The study was supported by an unrestricted educational grant from UCB-Pharma.

ETHICAL PUBLICATION

We confirm that we have read the Journal position on issue involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURE OF CONFLICTS OF INTEREST

EBe serves on the editorial boards of *Amyotrophic Lateral Sclerosis, Clinical Neurology & Neurosurgery,* and *Neuroepidemiology*; has been an associate editor of *Epilepsia*; has received money for board membership from VIROPHARMA and EISAI; has received funding for travel and speaker honoraria from UCB-Pharma, Sanofi-Aventis, GSK; has received funding for educational presentations from GSK; reports grants from the Italian Drug Agency and from the Italian Ministry of Health. JWS has received research funding from Eisai, GSK and UCB, personal fees from Eisai, UCB Lundbeck and Teva, outside the submitted work.
The remaining authors have nothing to disclose.

References

1) Annegers JF, Hauser WA, Elverback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979;20:729-737.

2) Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006;129:617-624.

3) Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. Epilepsia 2001;42:1255-1260.

4) Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548-1554.

5) Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol 2009;65:510-519.

6) Berg AT, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 2006;60:73-79.

7) Schiller Y. Seizure relapse and development of drug resistance following long-term seizure remission. Arch Neurol 2009;66:1233-1239.

8) Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069-1077.

9) Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007;62:375-381.

10) Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62:382-389.

11) Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. J Neurol Neurosurg Psychiatry 2012;83:810-813.

12) Lhatoo SD, Sander JW, Shorvon SD. The dynamics of drug treatment in epilepsy: an observational study in an unselected population based cohort with newly diagnosed epilepsy followed up prospectively over 11-14 years. J Neurol Neurosurg Psychiatry 2001;71:632-637.

13) Wang WZ, Wu JZ, Ma GY, et al. Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. Lancet Neurol 2006;5:46-52.

14) Huang DH, Zheng JO, Chen J, Yu L. Treatment gaps of epilepsy and retention rates of sodium valproate in rural Guangxi, China. Genet Mol Res 2014;13:6202-6212.

15) Giussani G, Canelli V, Bianchi E, et al. A population-based study of active and drug-resistant epilepsies in Northern Italy. Epilepsy Behav 2016;55:30-37.

16) Giussani G, Canelli V, Bianchi E, et al. Long-term prognosis of epilepsy, prognostic patterns and drug resistance. A population-based study. Eur J Neurol 2016;23:1218-1227.

17) Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;34:592-596.

18) Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electrographic classification of epileptic seizures. Epilepsia 1981;22:489-501.

19) Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.

20) Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-685.

21) Gray R. A class of k-sample tests for comparing the cumulative incidence of a competing risk. The Ann Statistics 1988;16:1141–1154.

22) Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology 2001;57:2259-2264.

23) Wirrell E, Camfield C, Camfield P, Dooley J. Prognostic significance of failure of the initial antiepileptic drug in children with absence epilepsy. Epilepsia 2001;42:760-763.

24) Zhang Y, Yu N, Su L, Di Q. A prospective cohort study of prognosis for newly diagnoses epilepsy in east China. BMC Neurology 2013;13:116.

25) Beydoun A, Sawaya MT, Alam E, Hmaimess G, Ezzeddine K, Younes F. Treatment registry in focal epilepsy (TRIP): multicenter observational study in Lebanon. Seizure 2015;27:54-59.

26) Bourgeois FT, Olson KL, Poduri A, Mandl KD. Comparison of Drug Utilization Patterns in Observational Data: Antiepileptic Drugs in Pediatric Patients. Paediatr Drugs 2015;17(5):401-410.

27) Arif H, Buchsbaum R, Pierro J, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. Arch Neurol 2010; 67: 408-415.

28) Chung S, Wang N, Hank N. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure 2007;16:296-304.

29) Peltola J, Peltola M, Auvinen A, Raitanen J, Fallah M, Keränen T. Retention rates of new antiepileptic drugs in localization-related epilepsy: a single-center study. Acta Neurol Scand 2009;119:55-60.

30) Bootsma HP, Ricker L, Hekster YA, et al. The impact of side effects on long-term retention in three new antiepileptic drugs. Seizure 2009;18:327-331.

31) Kuba R, Novotná I, Brázdil M, et al. Long-term levetiracetam treatment in patients with epilepsy: 3-year follow up. Acta Neurol Scand 2010;121:83-88.

32) Lhatoo SD, Wong IC, Sander JW. Prognostic factors affecting long-term retention of topiramate in patients with chronic epilepsy. Epilepsia 2000;41:338-341.

33) Hufnagel A, Kowalik A, Rettig K, Schreiner A, Schäuble B; TOP-GER-11 Investigators. Long-term assessment of topiramate for epilepsy: an open-label, single-arm, multicentre, prospective study in a naturalistic setting. Clin Drug Investig 2011;31:779-790.

34) Wilby J, Kainth A, Hawkins N, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol Assess 2005;9:1-157, iii-iv.

35) Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016-1026.

36) Lee SK. Old versus New: Why Do We Need New Antiepileptic Drugs? J Epilepsy Res 2014;4:39-44.

37) Weijenberg A, Offringa M, Brouwer OF, Callenbach PM. RCTs with new antiepileptic drugs in children: a systematic review of monotherapy studies and their methodology. Epilepsy Res 2010;91:1-9.

38) Tomson T. Drug selection for the newly diagnosed patient: when is a new generation antiepileptic drug indicated? J Neurol. 2004;251:1043-1049.

39) Perucca E. Marketed new antiepileptic drugs: are they better than old-generation agents? Ther Drug Monit 2002;24:74-80.

40) Rowan AJ1, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 2005;64:1868-1873.

41) Steinhoff BJ, Hirsch E, Mutani R, Nakken KO. The ideal characteristics of antiepileptic therapy: an overview of old and new AEDs. Acta Neurol Scand 2003;107:87-95.

Table 1. General characteristics of the sample (n=747)

Variable	Category	N	%
Gender	W	366	49.0
	M	381	51.0
Family history of Seizures*	Yes	111	14.9
	No	584	78.2
	Unknown	52	6.9
Seizures	Partial	460	61.6
	Generalized	260	34.8
	Unclassifiable	27	3.6
Syndrome	GC/GS	74	9.9
	GI	154	20.6
	PC	167	22.4
	PI	54	7.2
	PS	265	35.5
	Undetermined	26	0.9
	Special	7	3.5
Age at diagnosis	<15y	318	42.7
	15-64y	353	47.4
	65+y	74	9.9
	Missing	2	
Disease duration at diagnosis	<1y	666	89.5
	≥1 y	78	10.5
	Missing	3	
Number of AEDs	0	16	2.1
	1	393	52.6
	2	199	26.6
	3	74	9.9
	4+	65	8.7

Legend: W women; M Men; GC/GS Generalized Cryptogenic/Generalized Symptomatic; GI Generalized Idiopathic; PC Partial Cryptogenic;
PI Partial Idiopathic; PS Partial Symptomatic; y Years; AED Antiepileptic drug.
*Any type of seizures in all known relatives.

Table 2. Administration frequency of first, second and third drug by active principle

	First drug		Second drug		Third drug		Fourth to ninth drug
	N	%	N	%	N	%	N
BSC	18	2.5	7	2.1	1	0.7	1
CBZ	203	27.8	60	17.8	18	12.9	4
CLB	2	0.3	22	6.5	12	8.6	7
CNP	2	0.3	31	9.2	8	5.8	16
ESM	9	1.2	4	1.2	4	2.9	2
GBP	2	0.3	6	1.8	4	2.9	6
LEV	13	1.8	32	9.5	18	12.9	29
LTG	4	0.5	32	9.5	13	9.4	15
OXC	31	4.2	16	4.7	5	3.6	10
PB	197	26.9	39	11.5	9	6.5	3
PHT	27	3.7	20	5.9	1	0.7	1
PGB	1	0.1	3	0.9	6	4.3	4
PRM	0	0.0	3	0.9	8	5.8	3
TGB	1	0.1	0	0.0	0	0.0	2
TPM	4	0.5	13	3.8	14	10.1	10
VGB	3	0.4	4	1.2	5	3.6	2
VPA	211	28.9	44	13.0	12	8.6	7
VPM	3	0.4	2	0.6	1	0.7	1
ZNS	0	0.0	0	0.0	0	0.0	3
Total N patients*	731		338		139		65
Old AEDs	672	91.9	232	68.6	74	53.2	45
New AEDs	59	8.1	106	31.4	65	46.8	81

AED Antiepileptic drugs, BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoin, PGB Pregabalin, PRM Primidone, TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate, VPM Valpromide, ZNS Zonisamide.

*16 did not start drugs.

Table 3. Reasons of drug withdrawal by order

Ranking	Patients treated	Ineffectiveness		Adverse events		Terminal remission		Other*		Never withdrawn	
	N	N	%	N	%	N	%	N	%	N	%
First	731**	83	11.3	20	2.7	117	16.0	45	6.2	460	62.9
Second	338**	45	13.3	11	3.2	24	7.1	20	5.9	232	68.6
Third	139	33	23.7	6	4.3	4	2.9	6	4.3	90	64.7
Fourth	65	22	33.8	3	4.6	0	0.0	2	3.1	38	58.5
Fifth	31	11	35.5	2	6.5	2	6.5	0	0.0	16	51.6
Sixth	18	6	33.3	0	0.0	1	5.6	0	0.0	11	61.1
Seventh	7	3	42.9	0	0.0	0	0.0	0	0.0	4	57.1
Eighth	3	0	0.0	2	66.7	0	0.0	0	0.0	1	33.3
Ninth	2	0	0.0	1	50.0	0	0.0	0	0.0	1	50.0

*Death, drug out of production, pregnancy, own volition.
** Missing information about AED withdrawal in six.

Table 4. Frequency of reasons of drug withdrawal by active principle

	Patients treated	Ineffectiveness		Adverse events		Terminal remission		Other*		Never withdrawn	
	N	N	%	N	%	N	%	N	%	N	%
BSC	27	6	22.2	1	3.7	4	14.8	9	33.3	7	25.9
CBZ	285	31	10.9	16	5.6	29	10.2	15	5.3	194	68.1
CLB	43	12	27.9	0	0.0	2	4.7	2	4.7	27	62.8
CNP	57	6	10.5	1	1.8	1	1.8	2	3.5	47	82.5
ESM	19	4	21.1	0	0.0	6	31.6	0	0.0	9	47.4
GBP	18	12	66.7	0	0.0	0	0.0	0	0.0	6	33.3
LEV	92	12	13.0	5	5.4	3	3.3	0	0.0	72	78.3
LTG	64	15	23.4	1	1.6	2	3.1	4	6.3	42	65.6
OXC	62	10	16.1	3	4.8	5	8.1	3	4.8	41	66.1
PB	248	34	13.7	7	2.8	34	13.7	23	9.3	150	60.5
PHT	49	16	32.7	3	6.1	2	4.1	4	8.2	24	49.0
PGB	14	1	7.1	0	0.0	0	0.0	2	14.3	11	78.6
PRM	14	2	14.3	0	0.0	1	7.1	1	7.1	10	71.4
TGB	3	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0
TPM	41	11	26.8	4	9.8	4	9.8	1	2.4	21	51.2
VGB	14	7	50.0	0	0.0	2	14.3	0	0.0	5	35.7
VPA	274	27	9.9	3	1.1	55	20.1	8	2.9	181	66.1
VPM	7	0	0.0	0	0.0	1	14.3	1	14.3	5	71.4
ZNS	3	0	0.0	0	0.0	0	0.0	0	0.0	3	100.0
Old AEDs	1023	138	13.5	31	3.0	135	13.2	66	6.5	654	63.9
New AEDs	311	70	22.2	14	4.5	16	5.1	10	3.2	201	64.6

AED Antiepileptic drug, BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoin, PRG Pregabalin, PRM Primidone, TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate, VPM Valpromide, ZNS Zonisamide. * Death, drug out of production, pregnancy, own volition withdrawal.

Figure 1. Cumulative incidence functions for withdrawal of carbamazepine, phenobarbital and valproate, for ineffectiveness (A) and terminal remission (B)