Protocol for a prospective observational study of adverse drug reactions of anti-epileptic drugs in children in the UK

Oluwaseun Egunsola,¹ Helen M Sammons,^{1,2} Shalini Ojha,¹ William Whitehouse,³ Mark Anderson,⁴ Dan Hawcutt,⁵ Imti Choonara¹

To cite: Egunsola O, Sammons HM, Ojha S, *et al.* Protocol for a prospective observational study of adverse drug reactions of anti-epileptic drugs in children in the UK. *BMJ Paediatrics Open* 2017;1:e000116. doi:10.1136/bmjpo-2017-000116

Received 29 May 2017
Revised 13 July 2017
Accepted 13 July 2017

ABSTRACT

Background Epilepsy is a common chronic disease of children that can be treated with anti-epileptic drugs (AEDs). AEDs, however, have significant side effects. Newer AEDs are thought to have fewer side effects. There have, however, been few comparative studies of AED toxicity. The aim is to compare the safety profile of the most frequently used AEDs by performing a multicentre prospective cohort study. This protocol describes the planned study.

Design A multicentre prospective cohort study of children on AED treatment in hospitals across the UK. Ethical approval will be obtained.

Sample size Three thousand children on treatment for epilepsy will be recruited from paediatric clinics. It is expected that this sample size will have the potential to compare toxicity between the most frequently used AEDs.

Duration of study 24 months.

Outcome measure Adverse drug reactions (ADRs) to AEDs. These will be identified by the use of a validated questionnaire, the Paediatric Epilepsy Side Effect Questionnaire. They will be evaluated using the Naranjo algorithm. Preventability will be assessed using the Schumock and Thornton scale.

Discussion Toxicity of individual AEDs when given as monotherapy and polytherapy will be determined. Additionally, discontinuation rates due to ADRs will be determined. The data will assist clinicians in choosing AEDs with the least toxicity.

What is already known on this topic?

- ▶ Anti-epileptic drugs (AEDs) have significant drug toxicity.
- ▶ New AEDs are being more widely used.

What this study hopes to add?

- ▶ Comparative data regarding the safety profile of individual AEDs.
- ▶ Discontinuation rates for individual AEDs.

AED prescriptions.³ This increase in the utilisation of new AEDs in children presents a fresh challenge of identifying new toxicities and new drug interactions.

AEDs are the most common cause of drug-induced fatalities in children in the UK.⁴ A 10-year retrospective review of adverse drug reactions (ADRs) in children in the USA also identified AEDs as the third most common cause of ADRs.⁵ A report of ADRs in Swedish children over a 15-year period (1987–2001) showed that lamotrigine was the seventh most common cause of ADRs.⁶ According to a 2012 UK clinical audit for children with epilepsy, lack of sufficient information on side effects was identified as one of the most common areas for improvement in epilepsy care in children.⁷ Large pharmacovigilance studies of ADRs of AEDs in children are lacking. Most studies of toxicity of AEDs have focused on a single AED.^{8–10}

There have been few prospective cohort studies of children with epilepsy on AEDs focusing on toxicity.^{11–13} These studies identified ADRs in 31%–63% children receiving AEDs. The number of children in the studies ranged from 102 to 277, which is too small to compare the toxicity of the AEDs statistically. With the increasing use of new AEDs, there is a greater need to determine and compare the

CrossMark

¹Department of Child Health, School of Medicine, University of Nottingham, Derby, UK

²Department of Paediatrics, North Devon District Hospital, Nottingham, UK

³Department of Child Health, School of Medicine, University of Nottingham, Nottingham, UK

⁴Newcastle Childrens Hospital, Newcastle, UK

⁵University of Liverpool, Alder Hey Children's Hospital, Liverpool, UK

Correspondence to

Professor Imti Choonara; Imti.Choonara@nottingham.ac.uk

INTRODUCTION

Epilepsy is a widespread disorder affecting 0.5% children under 16 years old in the UK.¹ Conventional (old) anti-epileptic drugs (AEDs), which are AEDs in use before the early 1990s, are still generally preferred to the second generation AEDs in children in the UK.² Lamotrigine is the most commonly prescribed new generation AED (0.55 subjects per 1000 person-years).² A study of the UK General Practice Research Database showed a fivefold increase in the prevalence of newer AED prescription for children in 2005.³ Over the 13-year period, there was a 17% decrease in conventional AED prescriptions with a corresponding increase in new

safety of these drugs, especially with the more established old generation drugs.

Randomised controlled trials (RCTs) are useful to compare effectiveness of AEDs. They are however, rarely, powered to look at toxicity,¹⁴ and toxicity is poorly described in RCTs.¹⁵ Additionally, RCTs of AEDs in children are uncommon. Most RCTs of AEDs involve adults and children, and the paediatric data are not usually reported separately.¹⁵ Discontinuation of an AED is due to either lack of effectiveness or toxicity. The discontinuation rate to toxicity has ranged from 2% to 30% for most AEDs.^{10 12 16–18}

When comparative efficacies are similar, clinicians select AEDs based on their safety profile. Studies have shown that many of the newer AEDs do not have superior efficacy to the older drugs, and their relative safety, based on the available knowledge, is their only comparative advantage.¹⁹ Therefore, large pharmacovigilance studies are required to identify ADRs in children and adolescents.

Only two validated questionnaires have been developed for AED ADRs in children. These are the Hague Side Effect Scale (HASES)²⁰ and the Paediatric Epilepsy Side Effect Questionnaire (PESQ).²¹ PESQ is the more recent of the two, and it was designed to address the shortcomings of the HASES that include: validation in a small sample size, validation only in patients with chronic epilepsy and not being representative of patients receiving new generation AEDs. For this study, PESQ will be used to elicit ADRs. There have been no prospective national multicentre studies of AED toxicity in children. Additionally, many of the single-centre studies have not used either HASES or PESQ. This study will provide an excellent opportunity to use and evaluate the value of PESQ in determining the extent of AED toxicity in children.

The aim is to perform a prospective cohort study of children on AEDs to determine the nature and rate of ADRs in this population.

Primary objectives

This study aims to:

- ▶ describe the incidence of ADRs in children receiving each AED
- ▶ compare the safety profile of the most frequently used AEDs
- ▶ determine discontinuation rates for the most frequently used AEDs.

Secondary objectives

The secondary objectives are:

- ▶ to compare toxicity of individual AEDs when given as monotherapy and polytherapy
- ▶ to evaluate the preventability of ADRs in these children
- ▶ to determine the current prescription rates of AEDs in children

- ▶ to describe the effect of factors such as age, dose, polypharmacy and duration of treatment on toxicity of AEDs.

STUDY DESIGN

Study configuration and population

This protocol is for the first multicentre prospective cohort study of the safety of AEDs in children in the UK. The aim is to prospectively study 3000 children with epilepsy for ADRs. We aim to enrol a minimum of 500 children receiving valproic acid, carbamazepine, lamotrigine and levetiracetam, respectively, so as to compare the adverse effect profile of these drugs effectively. It is expected that this sample size will allow one to compare toxicity between the most frequently used AEDs. There will be no other intervention other than that obtained in routine practice in the respective hospitals. Information on ADRs will be extracted and recorded onto a case record form.

Paediatric patients receiving AED treatment will be recruited from hospital outpatient clinics over a period of 12 months. Enrolment shall start as soon as the research ethics committee (REC) and research & development (R&D) approvals are obtained. The study will close at 24 months, after the last recruited patients have been followed up for the requisite minimum of 12 months.

Participants will be recruited from outpatient clinics and inpatients attending participating centres (Nottingham Children's Hospital, Derbyshire Children's Hospital, Alder Hey Children's Hospital Liverpool, Newcastle Children's Hospital, Coventry Hospital and Kings Mill Hospital, Mansfield, have all agreed to participate so far. It is hoped other centres will also join the study). All recruited children will be seen for follow-up in the hospitals where treatment was initiated. In order to avoid selection bias, all eligible patients will be approached for inclusion into the study from general paediatric and epilepsy clinics. A member of the potential participant's usual care team will inform the potential participant and their parents or guardian about the details of the study; this may be directly at their usual clinic visit or by a letter from the team about the study, which includes the patient information sheet. This information will be appropriate for age and maturity of the participants, and if required, the usual hospital interpreter and translator services will be used. The participant information sheets, and consent forms, will only be available in English. Patients and their parents/guardian shall be informed that participation is voluntary and that they are free to withdraw from the study at any time. They shall also be informed that refusal to participate or withdrawal from the study will not affect the quality of care received. In the event of their withdrawal, it will be explained that their data collected so far can be withdrawn, and we will seek consent to use the data in the final analyses where appropriate.

Inclusion criteria

- ▶ Paediatric patients with epilepsy aged 18 years or less.
- ▶ Paediatric patients receiving one or more AEDs for epilepsy.
- ▶ Patients whose parents/guardian have provided written informed consent or who have themselves (if 16 years old or over) signed a written informed consent to participate in the study.

Exclusion criteria

- ▶ Unable or unwilling to give informed consent or withdrawal of consent.
- ▶ Plans to relocate to an area not covered by the study. Study participants will be followed up for 12–18 months.

Data collection

All relevant data will be recorded, by nominated member(s) of the research team, on a case report form (CRF). Each participant will have a CRF and be assigned a unique identification number.

Baseline data

At entry into the study, the following baseline information will be recorded in the CRF:

- ▶ unique patient identification number
- ▶ contact telephone number and/or email address
- ▶ date of entry into the study
- ▶ eligibility for study entry based on inclusion/exclusion criteria
- ▶ age at study entry, in years and months
- ▶ gender
- ▶ weight and height
- ▶ seizure type (eg, generalised tonic clonic, absence, myoclonic and partial)
- ▶ epilepsy syndrome (if identified); epilepsy category
- ▶ cause of the epilepsy (if identified)
- ▶ concomitant neurological disorder(s)
- ▶ the age at diagnosis and duration of epilepsy
- ▶ seizure frequency recorded as average number of seizures per month in the preceding 3 months (for patients already on AEDs) or average number of seizures per month since presentation in newly diagnosed epileptics
- ▶ current anticonvulsant(s) with doses and formulation
- ▶ date of commencement of current AEDs
- ▶ other medications
- ▶ concurrent medical disorders
- ▶ prior or current reported behavioural problems
- ▶ first recognised seizure date
- ▶ girls aged 10 years and over will also be asked whether they have received advice about contraception and possible effects of AEDs on pregnancy.

Follow-up data

Follow-up data will be collected during regularly scheduled clinic visits (3–6 monthly). Relevant data will also be obtained after any unscheduled clinic visit. This information will be obtained from the participants' hospital

notes. Important information to be collected at follow-up will include:

- ▶ date of the visit
- ▶ weight
- ▶ AEDs, their doses and formulation
- ▶ plasma concentrations of AEDs (if clinician has requested these and reason for requesting them)
- ▶ type of seizures since the last visit
- ▶ emergence of any new seizure types
- ▶ frequency of seizures, recorded as average number of seizures per month since last visit
- ▶ suspected ADRs since last visit
- ▶ a detailed record of any change to the drug regime
- ▶ reason for change in drug regime.

All data on ADRs will be forwarded on to the chief investigator.

Outcome evaluation

The main outcomes are ADRs. The methods used to detect the ADRs and their evaluation and classification are described below.

ADR surveillance

Surveillance for ADRs will be carried out prospectively on all patients in the cohort by the clinician, researcher, parents/guardian and the patient. Patients will be followed up 3–6 monthly for 12–18 months. If a patient experiences an ADR to one AED that results in a change in therapy, then the monitoring will continue for up to a maximum of 18 months.

ADRs will be detected by administering a validated questionnaire for ADRs (PESQ) to patients or their parents.²² Only ADRs occurring within the preceding 3 months of enrolment will be recorded. During each of the follow-up visits, attending physicians will also ask parents/patients generally about the occurrence of any adverse reaction. ADR information from this general enquiry will be documented on a specifically designed form that will be kept in the patient's case notes. Patients will have a total of at least three follow-up visits. The follow-up visits will ensure that transient self-correcting ADRs are distinguished from more clinically significant ADRs.

At enrolment, participants will be asked if they wish to be contacted by email or by telephone. For participants who wish to be contacted by email, a 3 monthly email will be sent to parents/guardian or directly to the participant (if 16 years old or more). This will be sent by a nominated member of the research team. The email will include a link to the PESQ, which the patients/parents will be required to fill anonymously (table 1). For participants or their parents/guardian who wish to be contacted by telephone, they will be contacted and questions regarding ADRs from the structured questionnaire (PESQ) will be asked. The attending physicians will be notified of any severe ADR indicated by the patients or parents on the PESQ.

Information from general ADR enquiry will be documented on a follow-up visit form by the attending

Table 1 The Paediatric Epilepsy Side Effect Questionnaire (PESQ)

	Side effect related to seizure medicine	Not present (1)	Low severity (2)	Low--moderate severity(3)	Moderate severity (4)	Moderate--high severity(5)	High severity (6)
1	Slow thinking						
2	Memory problems						
3	Confusion						
4	Poor school results						
5	Decreased concentration						
6	Attention difficulties						
7	Unstable walking						
8	Poor coordination, clumsiness						
9	Falling (not seizure)						
10	Speech difficulties						
11	Aggression						
12	Hyperactivity						
13	Personality change						
14	Drowsiness, sleepiness						
15	Fatigue, tiredness						
16	Dizziness, lightheadedness						
17	Headaches						
18	Increase in appetite						
19	Weight gain						
20	Others						

physician during each follow-up visit. This will supplement all ADR information elicited specifically with the questionnaire. The clinical course of each suspected ADR will be followed until resolution or stabilisation. All prescription changes, interventions, laboratory findings and the time course relationship of the reaction to the medication will be documented. The progress of the ADR will be monitored in subsequent clinic visits to determine if it is unchanged, has resolved or worsened.

If AEDs are changed, a member of the research team will determine from the participant's notes the reason for the prescription change. If the reason for the change is not satisfactorily stated in the notes, a member of the research team may enquire from the attending physician. In the event of a child experiencing an ADR, any relevant clinical blood tests will be performed if deemed necessary by the treating clinician, and this may include determination of a drug level where applicable. In the event of a child experiencing an ADR, any relevant clinical blood tests will be performed if deemed necessary by the treating clinician, and this will include determination of a drug level where applicable. The attending physician shall take all necessary steps to mitigate the ADR. This may include: discontinuation of the drug or any other concomitant drug or reduction in drug dosages. The

participants and their parents/guardians will be fully informed of all the measures towards ameliorating the effect of the ADR.

Evaluation and classification of suspected ADRs

All suspected ADRs will be assessed by a member of the research team, by using the Naranjo algorithm, which is a standardised causality assessment tool for suspected ADRs.⁹ This method has previously been used in paediatric ADR surveillance studies.^{11 12}

All suspected ADRs will be evaluated and classified¹³ as:

Definite

A clinical event or abnormal laboratory test finding that has a plausible time relationship to the drug and cannot be explained by disease or concomitant drug. There is usually a favourable response to drug withdrawal and recurrence on rechallenge. This ADR will have a Naranjo score of 9 or more.

Probable

A clinical event or abnormal laboratory test with a reasonable time course relationship to the administered drug and not due to other drugs or concurrent disease. There

is a reasonable favourable response on withdrawal. This will have a Naranjo score of 5–8.

Possible

A clinical event or abnormal laboratory finding with a reasonable time course relationship to the drug but could also be explained by a concomitant drug or a concurrent illness. This will have a Naranjo score of 1–4.

Not related

No possible relationship (ie, the temporal relationship between treatment exposure and the adverse event onset/course is unreasonable or incompatible; or a causal relationship to study treatment is implausible). This will have a Naranjo score of <1.

ADRs considered to be unrelated to treatment will not be included in the analysis of incidence rates and will not be included when comparing toxicity. All other ADRs (definite, probable and possible) will be combined together when comparing toxicity.

The severity of ADRs will be classified in accordance with previously used method^{22 23}

1. Severe: fatal or potentially life threatening.
2. Moderate: requiring treatment or prolonging the length of stay in hospital.
3. Mild: no treatment required and no effect on length of stay in hospital.

Severe ADRs will be reported to the Committee on Safety of Medicines.

Calculation of incidence of ADRs and discontinuation rates

The most valuable comparative data will be from patients who are receiving monotherapy. The incidence rate for specific ADRs in relation to a specific AED will be calculated by dividing the number of cases of the ADR occurring while on treatment with the number of children receiving the AED. The duration of treatment with the AED will be used to calculate the incidence of the ADR in relation to time. An incidence rate per child per year will be calculated. Discontinuation rates will be calculated by dividing the number of children who terminated treatment with an AED due to toxicity, divided by the number of children who received the drug.

Preventability of ADRs

The preventability of ADRs will be assessed using the Schumock and Thornton scale.²⁴ This scale, which has been used previously in another AED pharmacovigilance study,¹² evaluates the preventability of ADRs based on a set of seven questions. These questions cover the appropriateness of the medicine; the dose, route and frequency of administration; therapeutic drug monitoring and serum concentrations (if appropriate); allergy; drug interactions and adherence.

Statistics

The primary outcome will be the incidence of ADRs for each of the prescribed AED. Using χ^2 analysis, and

Fischer's exact test when appropriate, ADRs and discontinuation rates of individual AEDs will be compared.

Secondary outcomes will be the effects of polytherapy and monotherapy on ADRs and discontinuation rates. χ^2 analysis, and Fischer's exact test when appropriate, will be used. Other secondary outcomes such as the association between age and type of epilepsy with ADR will be analysed using one-way analysis of variance. Multivariate logistic regression will be used to determine the predictors of ADRs in children receiving AEDs. Excel and SPSS will be used for statistical analyses.

Ethics and dissemination

The study will only be initiated after the protocol, consent form and the participants' information sheet are approved by the REC, and the respective National Health Service (NHS) R&D departments. If an amendment to the protocol requiring REC approval is necessary, such amendments will not be effected until revised informed consent forms and participant information sheets are reviewed and approved by the R&D departments and the REC. Should the amendment be intended to prevent a clear immediate hazard to participants, such amendment may be effected, provided that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately, and the REC will be informed.

The study will be conducted in compliance with the principles of: Good Clinical Practice, the Department of Health Research Governance Framework for Health and Social Care, 2005, and in accordance with the 1996 Declaration of Helsinki.

Informed consent

Written informed consent will be obtained from parents/guardian of potential participants less than 16 years old, at the time of clinic appointment. Written consent will be sought directly from patients 16 years old or over. If a participant turns 16 years old during the course of the study, consent will be sought from the participant in order to continue participation in the study. The investigator will explain the details of the study and provide age-appropriate participant information sheet to the participants and their parents/guardian. All questions about the study, by either the patient and or the parent/guardian, will be answered by the investigator. Participants will be allowed sufficient time to decide whether to participate in the study or not. Before enrolment into the study, the consent form will be signed by parents/guardian, or by the participant if aged 16 years or more. If either the potential participant or their parent/guardian decline to consent, or if under 16 years of age the child or young person declines to be included, they will not enter the study.

The participant or their parent/guardian will keep a copy of the consent form, while the original copy will be kept by the chief investigator in the recruitment file, a third copy will be kept in the patient's hospital record. In the event of a significant protocol change, a fresh signed

written consent will be sought from participants, parents or guardians, and the revised document will be submitted to the REC and the sites' R&D for approval. Assent will be sought from any patient considered mature enough to comprehend the importance of the study.

Discontinuation of study participation

Participants may choose to withdraw from the study, on their own or on the request of their parents/guardian, at any time during the course of the study. Subjects may withdraw for any reason without prejudice to his/her future medical care by the physician or at the institution. On withdrawal of consent, the date and reason for consent withdrawal will be documented. Participants' data collected up to the date of the withdrawal of consent may be included in the final analysis. The investigator may also choose to withdraw a participant from the study if such person is lost to follow-up, has moved out of the study area, does not comply with treatment or for any other practical reason that may affect the integrity of the study. Withdrawn participants will not be replaced.

Study records and data management

Case report forms

Each participant will be assigned a unique study patient identification number, for use on CRFs, other study documents and the electronic database. CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number and patient identification number to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the chief investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The chief investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Record retention and archiving

The chief investigator will retain all records and documents pertaining to the study for 7 years in compliance with the International Conference on Harmonisation/Good Clinical Practice guidelines and the University of Nottingham Code of Research Conduct and Research Ethics. If the responsible investigator can no longer retain these records, another person will be nominated for this purpose.

The final archiving of the study documents and databases (and associated meta-encryption codes) held by the chief investigator shall be at the secure archive facility at the University of Nottingham.

Publication and dissemination policy

Participants will not be paid to participate in the study. There will be no hospital visits in excess of usual care. Findings will be published in peer-reviewed journals.

Competing interests

Obtained

Provenance and peer review

Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics. 2011 [http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_\(3\).pdf](http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf) (accessed 20 Jan 2014).
2. Hsia Y, Neubert A, Sturkenboom MC, et al. TEDDY Network of Excellence. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia* 2010;51:789–96.
3. Ackers R, Murray ML, Besag FM, et al. Prioritizing children's medicines for research: a pharmaco-epidemiological study of antiepileptic drugs. *Br J Clin Pharmacol* 2007;63:689–97.
4. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 2002;87:462–6.
5. Le J, Nguyen T, Law AV, et al. Adverse drug reactions among children over a 10-year period. *Pediatrics* 2006;118:555–62.
6. Kimland E, Rane A, Ufer M, et al. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Saf* 2005;14:493–9.
7. Royal College of Paediatrics and Child Health. United Kingdom collaborative clinical audit of health care for children and young people with suspected epileptic seizures, 2012:1–118. http://www.rcpch.ac.uk/system/files/protected/page/Epilepsy_web.pdf.
8. Aurich-Barrera B, Wilton L, Brown D, et al. Paediatric Postmarketing Pharmacovigilance using Prescription-Event monitoring. *Drug Saf* 2010;33:751–63.
9. Aurich-Barrera B, Wilton L, Brown D, et al. Paediatric post-marketing pharmacovigilance: comparison of the adverse event profile of vigabatrin prescribed to children and adults. *Pharmacoepidemiol Drug Saf* 2011;20:608–18.
10. Egunsola O, Choonara I, Sammons HM, et al. Safety of lamotrigine in paediatrics: a systematic review. *BMJ Open* 2015;5:e007711.
11. Anderson M, Egunsola O, Cherrill J, et al. A prospective study of adverse drug reactions to antiepileptic drugs in children. *BMJ Open* 2015;5:e008298.
12. Bansal D, Azad C, Kaur M, et al. Adverse effects of antiepileptic drugs in North Indian paediatric outpatients. *Clin Neuropharmacol* 2013;36:107–13.
13. Choonara IA. Anticonvulsant toxicity in paediatric out-patients. *Br J Clin Pract* 1988;42:21.
14. Makuch RW. Detecting rare adverse events in postmarketing studies: sample size considerations. *Drug Information Journal* 2006;40:89–98.
15. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. *Arch Dis Child* 2010;95:731–8.
16. Egunsola O, Choonara I, Sammons HM. Safety of Levetiracetam in Paediatrics: a systematic review. *PLoS One* 2016;11:e0149686.
17. Dudley RW, Penney SJ, Buckley DJ. First-drug treatment failures in children newly diagnosed with epilepsy. *Pediatr Neurol* 2009;40:71–7.
18. de Silva M, MacArdle B, McGowan M, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 1996;347:709–13.
19. Guerrini R, Zaccara G, la Marca G, et al. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. *Drug Saf* 2012;35:519–33.

20. Carpay HA, Arts WF, Vermeulen J, *et al.* Parent-completed scales for measuring seizure severity and severity of side-effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res* 1996;24:173–81.
21. Morita DA, Glauser TA, Modi AC, *et al.* Development and validation of the Pediatric Epilepsy Side Effects Questionnaire. *Neurology* 2012;79:1252–8.
22. Marson AG, Appleton R, Baker G, *et al.* *A Randomised Controlled Trial examining the Longer-term outcomes of Standard Versus New antiepileptic drugs: the SANAD Trial: national Co-ordinating Centre for Health Technology Assessment*, 2007.
23. Biton V, Edwards KR, Montouris GD, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001;35:173–9.
24. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992;27:538.