Epilepsy & Behavior 47 (2015) 120–126

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

What do epileptologists recommend about discontinuing antiepileptic drugs for a second time in children?

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ARTICLE INFO

Article history:
Received 19 March 2015
Revised 6 April 2015
Accepted 7 April 2015
Available online 9 May 2015

Keywords:
AEDs
Pediatric
Epilepsy
Treatment
Discontinuation
Survey

ABSTRACT

Objective: There is a broad consensus that antiepileptic drugs (AEDs) may be withdrawn after two years of seizure freedom for most children with epilepsy. If seizures recur and are, again, completely controlled with AEDs, little is known about discontinuing a second time. We surveyed American and Canadian pediatric epileptologists to understand their current practice.

Methods: In 2014, a survey was sent via e-mail to 193 pediatric epileptologists to learn about AED discontinuation practices in children. The survey asked direct questions about practice and posed five "real-life" cases where the decision to discontinue might be difficult. Participants were identified through membership lists of several US and Canadian epilepsy organizations.

Results: There were 94 (49%) completed surveys. Sixty-three participants had ≥10 years in practice ("more experienced": mean 23 ± 9 years), and 31 had <10 years ("less experienced": mean 6 ± 2). Overall, 62% recommended AED discontinuation for the first time after 2–3 years of seizure freedom, and 61% recommended discontinuation for the second time after 2–3 years. Fifty-six percent of "more experienced" clinicians required a longer seizure-free period prior to a second discontinuation ($p < 0.001$) compared with 26% of "less experienced" clinicians ($p = ns$). Overall, most participants suggested an AED taper duration of 2–6 months for the first and second attempts, 52% and 68%, respectively. Both groups wean AEDs more slowly during the second attempt ($p < 0.001$). There was only 40–60% agreement among participants to discontinue AEDs in four of the cases.

Conclusion: Nearly half (46%) of pediatric epileptologists require a longer seizure-free period the second time they attempt to discontinue AEDs compared with the first attempt and wean down AEDs somewhat more slowly. Although a variety of factors influence decision-making, there was a high level of disagreement to discontinue AEDs a second time in "real-life" cases.

1. Introduction

Discontinuing antiepileptic drugs (AEDs) in pediatric patients with epilepsy who have been seizure-free for one to two years is a generally accepted practice [1–3]. Approximately 30% will be unable to discontinue treatment because of a recurrence of their seizures [4–6]. Medication is often restarted and nearly half of the children will become seizure-free a second time, prompting clinicians to consider a second attempt to withdraw AEDs [7]. However, few studies have addressed this issue. It is unknown if the factors that predict seizure recurrence after the first seizure-free period apply to discontinuation a second time [8–10]. Our study was designed to compare the current practices and factors that influence recommendations from pediatric epileptologists for discontinuing AEDs for the first and the second time.

2. Methods

2.1. Participants

The study was approved by the Institutional Review Board at Drexel University College of Medicine. A group of 193 pediatric epileptologists currently practicing in North America were identified through various sources including American Epilepsy Society, Child Neurology Society, Canadian Pediatric Epilepsy Network, and the American Board of Psychiatry and Neurology (ABPN) Certification and Status Verification System [11].

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http://dx.doi.org/10.1016/j.yebeh.2015.04.014
1525-5050/

2.2. Survey

The survey (Supplemental data) was adapted from the questionnaire used by Berg et al. [12] and Téllez-Zenteno et al. [13] Participants were instructed to respond to questions as they would typically manage seizure-free patients in their clinical practice. Seizure freedom was defined as the absence of any generalized or focal seizures with the exception of subjective auras. The survey contained 17 questions. Seven questions asked participants to compare timing, clinical tests (magnetic resonance imaging (MRI), electroencephalography (EEG), and AED blood levels), and patient factors (age at onset less than two years, presence of intellectual disability, abnormal neurologic exam, patient request, the reaching of driving age, epilepsy syndrome, polytherapy, and etiologies) that influence their decision to discontinue AEDs for the first and the second time. Questions about timing of discontinuation offered multiple choice answers with specific time periods. Using a five-point scale (nearly always, most of the time, often, sometimes, and almost never), patients answered questions about how often tests were used as a guide in their decision to discontinue AEDs. Each patient-related factor was scored from 1 to 6 (1 = unfavorable through 6 = very favorable) for the first and second attempts to withdraw AEDs. Two questions asked participants to provide additional comments regarding special considerations for AED discontinuation after the first seizure-free period and then the second seizure-free period.

Five cases were included to provide a "real-life" scenario that may be more predictive of actual behavior than specific questions (Table 1). These questions evaluated the influence for a second discontinuation of focal cortical dysplasia, congenital hemiparesis, Doose syndrome, myoclonus in juvenile myoclonic epilepsy (JME), and unknown cause with and without persistent EEG discharges. The three remaining questions assessed the demographics and experience of the participant.

2.3. Data collection

Between February and March 2014, the selected group of 193 pediatric epileptologists was invited to take part in the study by following a SurveyMonkey [14] link provided in an e-mail. An e-mail reminder to complete the survey was sent to nonresponders two weeks later. Participation was voluntary without an honorarium. The epileptologists who chose to be recognized are listed in the Acknowledgment section.

2.4. Data analysis

Data were transferred to Microsoft Excel 2011, version 14.3.4, and then analyzed with Stata software, version 10 (StataCorp, College Station, TX), and statistical significance was assessed at the 0.05 level.

Surveys that were less than 80% complete were removed from the analysis. Many of the questions had multiple parts; if any part of the question was missed or skipped by a participant, the entire question was considered missed. Demographic data were analyzed with descriptive statistics, chi-squared test, and unpaired Student's t-test. For the seven questions where each participant answered the same question for the first and second attempts to discontinue, matched responses were evaluated with the Wilcoxon matched-pairs signed-rank test. This test is a nonparametric method that compares before and after of matched subjects. It does this by calculating the difference between sets of matched pairs and then compares the median of those changes against a hypothetical median of zero using the Wilcoxon signed-rank

Table 1
"Real-life" case questions presented in the survey.

Topic	"Real-life" case scenarios	Question
Cortical dysplasia	An otherwise normal 10-year-old boy has dyscognitive (complex partial) seizures with a small area of cortical dysplasia in his right amygdala on MRI. His current EEG shows a few spikes from the same area. The onset of his epilepsy was at the age of 4 years, and he was first treated with carbamazepine. He became immediately seizure-free for 2 years, discontinued carbamazepine, had 2 seizures, restarted carbamazepine, and now has been seizure-free again for 4 years.	Would you discontinue his AED medication?
Congenital hemiparesis	A 15-year-old girl has a congenital hemiplegia. She is able to walk but has little use of her left hand and has mild global intellectual disability. Seizures started at the age of two years — long, left-sided clonic attacks with 2 episodes of status epilepticus. She became seizure-free on a combination of levetiracetam and phenobarbital and, at the age of eight years, had been seizure-free for 2 years. Phenobarbital was discontinued successfully. At the age of 9 years, levetiracetam was discontinued, but, 2 months later, she had an episode of status epilepticus. Levetiracetam was restarted, and she has now been 6 years seizure-free.	(1) Would you ever discontinue her AED medication? (2) If yes, would you discontinue her AED now? (3) If she remains seizure-free for 10 years, would you discontinue her AED?
Doose syndrome	A normal 6-year-old boy had the onset of several generalized tonic–clonic seizures and many "drop seizures" at the age of 2 years. He was thought to have Doose syndrome (myoclonic astatic epilepsy). His seizures stopped promptly with valproic acid which was discontinued at the age of 4 years. He then had a single generalized tonic–clonic seizure, valproic acid was restarted, and he has had no further seizures and has been seizure-free for 2 years. His current EEG is normal, and his neurological and developmental examinations are normal.	Would you discontinue his AED at this point?
Juvenile myoclonic epilepsy	A 16-year-old girl has juvenile myoclonic epilepsy (JME) with onset at the age of 11, with 2 generalized tonic–clonic seizures, some myoclonus, and a typical EEG. She has been treated with lamotrigine and became completely seizure-free. Lamotrigine was tapered off at the age of 13. Occasional myoclonus returned, and she chose to restart lamotrigine but continues to have occasional very minor myoclonic jerks. Her EEG shows a few fragments of spike–wave during photic stimulation only. She wants to stop lamotrigine.	What do you think?
Unknown case with normal EEG	A normal 12-year-old boy had the onset of multiple complex partial seizures at the age of 3. Seizures consisted of loss of awareness with some lip smacking. Initial and current EEG and 3-T MRI are normal. His seizures were diurnal which exclude Panayiotopoulos syndrome. He was treated initially with phenobarbital, but his behavior was bad. It was discontinued after 4 months, and he remained seizure-free off AED treatment for 2 years when the same seizures recurred. They stopped with modest doses of carbamazepine, and he has remained seizure-free for the past 7–8 years.	(1) Would you discontinue his AED treatment? (2) If the same boy showed left parietal spikes on his initial EEG and they still are present, would it change your approach?

Magnetic resonance imaging (MRI), electroencephalography (EEG), antiepileptic drug (AED).