Original article

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Why the TimeToStop trial failed to recruit: a survey on antiepileptic drug withdrawal after paediatric epilepsy surgery

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on behalf of the TimeToStop trial group

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ABSTRACT – *Aims*. Following the results of the multicentre European retrospective "TimeToStop" cohort study, we initiated a randomised trial to determine cognitive benefits of early postoperative antiepileptic drug withdrawal. Unfortunately, the trial failed to recruit and was terminated, as almost all parents preferred early drug withdrawal. The objectives of the current survey were to obtain insight into current practices regarding drug withdrawal after paediatric epilepsy surgery among epileptologists, and better understand the reasons for difficulties in recruitment.
Methods. A survey was sent to three international epilepsy surgery networks, questioning drug withdrawal policies. Forty-seven (19%) surveys were returned.

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Results. For polytherapy, withdrawal was started at a median of three and six months by the TimeToStop collaborators and other paediatric epileptologists, respectively. Withdrawal was completed at a median of 12 and 20 months, respectively. For monotherapy, tapering was initiated at five and 11 months in these two groups, and ended at a median of seven and 12 months, respectively. Most TimeToStop collaborators believed that it was not justified to wait 12 months after surgery before reducing AEDs, regardless of the number of AEDs taken.
Conclusion. Current AED policies in Europe have changed as a consequence of the retrospective TimeToStop results, and this accounts for why recruitment in a randomised trial was not feasible.

Key words: anticonvulsive medication, discontinuation, epileptologist, children, epilepsy surgery

On achieving seizure freedom following epilepsy surgery, the ultimate proof of surgical success and thus of "cure" is the complete discontinuation of antiepileptic drugs (AEDs). In children, AED withdrawal favours, on average, improved psychomotor speed and intelligence (Skirrow *et al*., 2011; Van Schooneveld *et al*., 2013; Boshuisen *et al*., 2015a). A multicentre European retrospective cohort study strongly suggested that the timing of postoperative AED withdrawal does not influence eventual seizure outcomes (Boshuisen *et al*., 2012); although the risk of seizure recurrence was increased with earlier AED withdrawal, there was no association with long-term freedom of seizures or medication status at final follow-up visits. Early withdrawal therefore uncovers incomplete surgical success sooner, while preventing overtreatment for the large majority of children in whom surgery has successfully removed the epileptogenic zone. To assess the potential cognitive benefits of early versus late withdrawal, we initiated the "TimeToStop" randomised controlled trial (EudraCT number 2011-005971-18) (Boshuisen *et al*., 2015b). We aimed to compare cognitive functioning, intelligence, and seizure outcome at 12 and 24 months after epilepsy surgery between children who were randomised to start withdrawal at four months and those who started withdrawal at 12 months after surgery. Eight centres in five countries agreed to participate. In November 2015, recruitment was started in Utrecht, the Netherlands, and was in preparation in the other centres. Up to February 2017, 47 children were screened, of whom 35 were not eligible (*supplementary table 1*). Of the 12 children who were eligible, their parents declined participation; 11 did not want to wait until 12 months after surgery before withdrawing medication, and the parents of one child considered withdrawal at four months too early. None of the parents or children agreed with participation based on randomisation to determine the timing of postoperative AED withdrawal. After deliberation with the trial collaborators, it was decided to terminate recruitment for reasons of non-feasibility.

To gain insight into current practices and better understand the reasons for difficult recruitment in the TimeToStop trial, we aimed to describe AED withdrawal policies among paediatric epileptologists using a short survey. The survey was based on the following hypotheses:
– current beliefs about safety and benefits of early postoperative AED withdrawal among treating physicians justify premature discontinuation of the TTS trial for feasibility issues;
– partners of the original TTS study group and European paediatric epileptologists tend to withdraw medication sooner than others;
– the previous retrospective TTS cohort study has changed decision-making regarding AED withdrawal.

Methods

A survey was created focusing on paediatric neurologists, but also enabling neurologists or physicians who treat both children and adults, to respond. The full survey can be found in *Appendix 1* and contains several items on the timing of postoperative AED withdrawal in children who underwent anticipated curative epilepsy surgery, factors influencing timing, and personal preferences of participants and parents/children with epilepsy. The survey was widely distributed among epilepsy surgery specialists collaborating in three broad networks: (1) the U-Task (European Task Force for Epilepsy Surgery in Children), which meets twice a year to discuss surgical cases and collaborative research projects; (2) the E-PILEPSY consortium, an EU-funded pilot reference network of epilepsy surgery centres, aiming to improve access to, and outcome of, epilepsy surgery and harmonise (pre-) surgical approaches across Europe; and (3) the mailing list of the International League Against Epilepsy (ILAE) Pediatric Epilepsy Surgery Task Force. The mailing lists contained paediatric and adult neurologists, neurosurgeons, and other staff involved, with considerable overlap between the three lists.

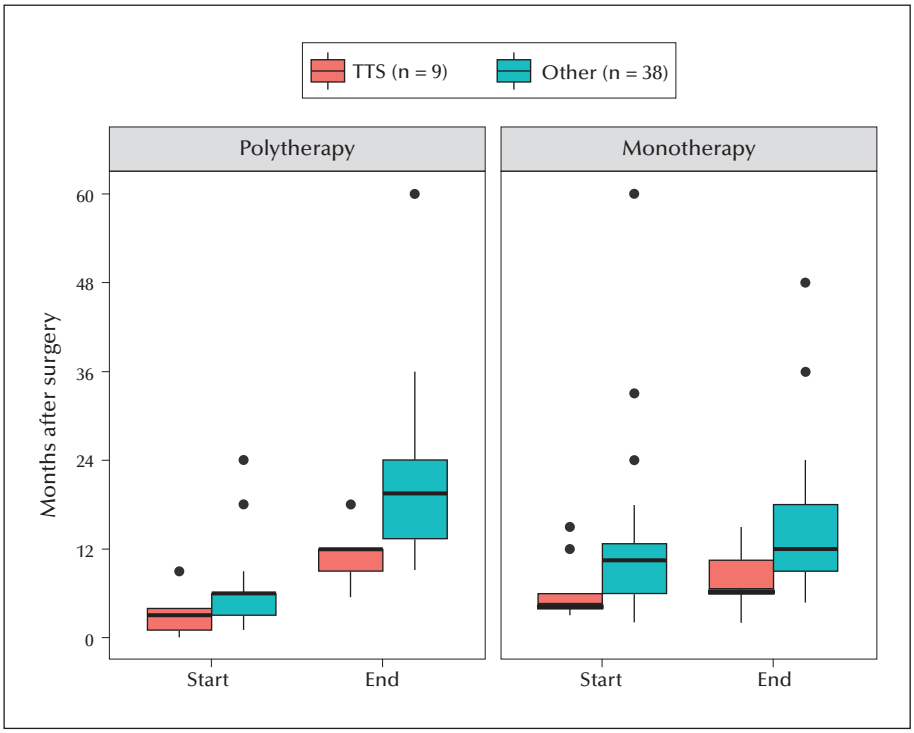

Figure 1. The timing of antiepileptic drug (AED) withdrawal after paediatric epilepsy surgery in the case of polytherapy and monotherapy, compared between the two cohorts of TTS collaborators and other respondents. The boxes show the median and interquartile range (IQR), and the whiskers extend to 1.5*IQR. End: complete discontinuation of last AED; start: start of AED withdrawal; TTS: collaborators of the TimeToStop study on safety of early drug tapering and/or the TimeToStop trial on the cognitive benefits of early drug tapering. A summary of the statistics is provided in *table 1*.

When information on the timing of AED withdrawal was given as a range, the average was used as input for the analysis. The values were non-normally distributed, hence summary statistics are given as medians and interquartile ranges (IQR), and a Mann-Whitney U test was used to test group differences. Results were compared between respondents who collaborated in the retrospective TTS study or prospective TTS trial and all other participants, and between European (TTS collaborators and non-collaborators) and non-European respondents.

Results

The survey was sent to 251 addresses; 47 (19%) surveys were returned by 32 paediatric epileptologists and 15 specialists who treated both children and adults. Nine respondents had participated in the previous retrospective TimeToStop study (Boshuisen *et al.*, 2012) or the prospective TimeToStop trial (Boshuisen *et al.*, 2015b) described in the introduction. There were 38 additional respondents, from Europe (22), Brazil (2), India (2), Japan (5), Mexico (1), South Africa (1), Thailand (1), and the United States of America (4). The number of unique centres was 39 from 21 countries.

A comparison of the postoperative timing of AED withdrawal between TTS collaborators and other respondents is given in *figure 1* and *table 1*. With regards to both initiating and completely discontinuing AEDs, this was earlier for TTS collaborators than the other respondents. For children on polytherapy, the median start of withdrawal was three months following surgery for the TTS collaborators compared to six months for other respondents (U=258.5; p=0.02). AEDs were completely tapered off after a median of 12 months compared to 20 months, respectively (U=246; p=0.002). For children on monotherapy at the time of surgery, AEDs were reduced at a median of five months following surgery for the TTS collaborators compared to 11 months for other respondents (U=222.5; p=0.08), and completely discontinued at seven months compared to 12 months, respectively (U=243; p=0.01). European respondents started and discontinued AEDs earlier compared to non-Europeans in the case of monotherapy (starting at a median of six vs. 12 months, and discontinuation at nine vs. 17 months, respectively); for polytherapy, the two groups started AED withdrawal at a similar time (a median of five vs. six months, respectively), but there were differences in the timing of complete discontinuation (16 vs. 24 months, respectively).

Table 1. Median time corresponding to initiation of AED withdrawal and complete discontinuation compared between the three groups.

		Start of AED withdrawal	Complete discontinuation of last AED
Polytherapy	TTS	3 (1-4)	12 (9-12)
	Other	6 (3-6)	20 (13-24)
	Mann-Whitney U	258.5; p=0.02	246; p=0.002
Monotherapy	TTS	5 (4-6)	7 (6-11)
	Other	11 (6-13)	12 (9-18)
	Mann-Whitney U	p=0.08	243; p=0.01

All given values are medians (IQR) corresponding to months after paediatric epilepsy surgery (rounded to full months). Data are presented graphically in *figure 1*.

Three questions were asked regarding the safety and justification of starting withdrawal at either four or 12 months after surgery; the responses are summarised in *figure 2*. For polytherapy, all TTS collaborators deemed initiation of AED withdrawal safe at four months, compared to 71% of other respondents. For monotherapy, 67% of TTS collaborators deemed AED withdrawal safe at four months, compared to 47% of other respondents. Only 33% of TTS collaborators believed it was justified to wait until 12 months after paediatric epilepsy surgery, compared to 54% of others.

Figure 3 illustrates how respondents judged the different clinical factors that may influence AED withdrawal timing. Overall, the decision to completely wean off medication is taken more cautiously than the decision to start reduction of AEDs. The strongest reasons for not completely discontinuing medication were (as outlined in *figure 3*): incomplete resection of the epileptogenic zone (66% of respondents), incomplete resection of the anatomical lesion (43%), preoperative multifocal MRI abnormalities (33%), and postoperative epileptic EEG abnormalities (30%).

The combined strongest reasons to start AED withdrawal later or not at all were: incomplete resection of the epileptogenic zone (89%) or anatomical lesion (85%), postoperative EEG abnormalities (77%), multifocal MRI abnormalities (74%), neurocutaneous aetiology (63%), previous epilepsy surgery (60%), and depression as co-indication for AED treatment (60%). Taper duration ranged from 0.5 to 18 months per drug, with a median of 3.0 months (IQR: 2.5-9).

The median (IQR) taper duration for TTS collaborators and other paediatric epileptologists was 2.5 months/drug (2.5-2.6) and 5.3 months/drug (3.0-9.8), respectively. Drugs with a longer taper period for some of the respondents were phenobarbital (17/37 responses), benzodiazepines (14/37), and carbamazepine (7/37) (*supplementary table 2*). Some respondents reported side effects experienced by patients as a reason for initiating withdrawal earlier, especially when these were more prominent after successful epilepsy surgery.

Fifteen physicians were treating both children and adults, which allowed for a comparison of withdrawal practices. On average, physicians were more careful regarding early withdrawal for their adult patients, and started withdrawal later for both polytherapy (median time difference: two months; IQR: 0-5) and monotherapy (median time difference: two months; IQR: 0-9). Complete discontinuation was also later in adult cases, with a median time difference of six months (IQR: 0-24) and 12 months (IQR: 0-12) in the case of polytherapy and monotherapy, respectively. For adults, 50% deemed initiation of AED withdrawal safe at four months in the case of polytherapy and 14% in the case of monotherapy, compared to 53% and 46% for children, respectively. Sixty percent stated that it was justified to wait for 12 months after adult epilepsy surgery, compared to 47% in paediatric care.

Of all the respondents, 32 (68%) indicated that they would advise mainly in favour of withdrawal, four (9%) were in favour of counselling towards continuation of medication, and 11 (23%) indicated that counselling depends on case-specific factors. This is reflected by the impression of parental preferences in the respondents' centres: 30/45 (67%) indicated that parents would prefer early withdrawal and 5/45 (11%) late withdrawal. For 7/45 (16%), this depended on the situation, and for 3/45 (7%) of respondents, most children and parents would prefer to reduce the dose but not completely discontinue all AEDs.

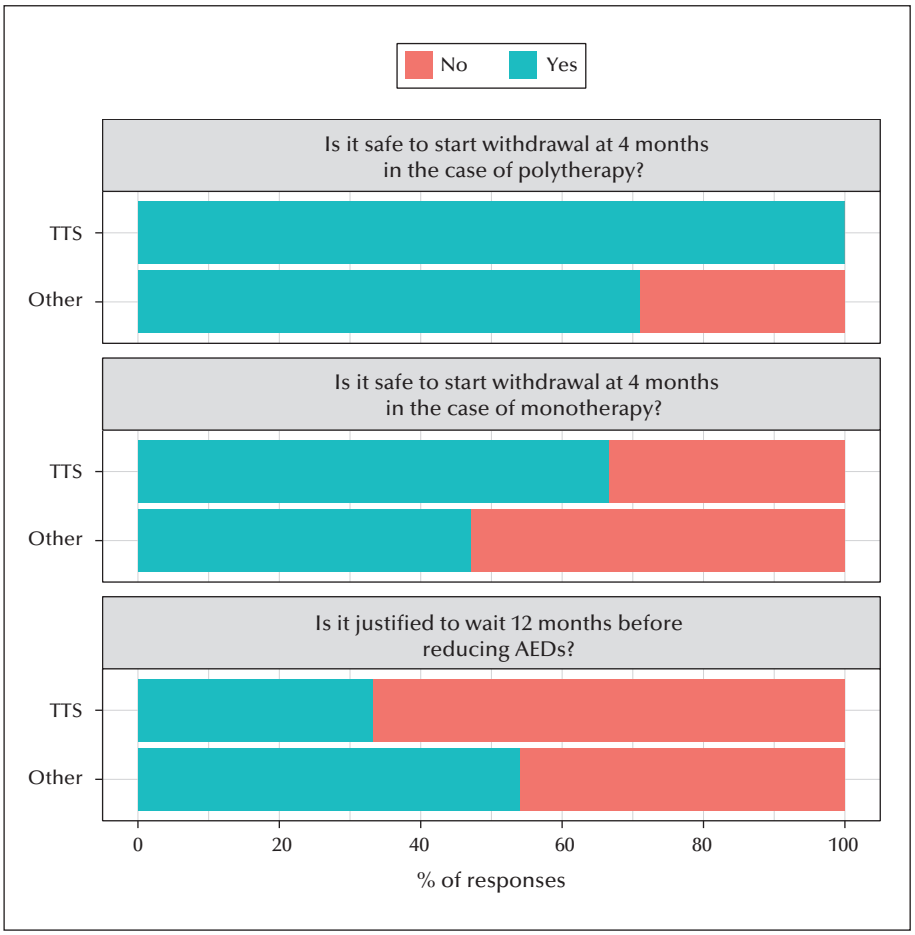

Figure 2. Responses to the three questions, compared between TimeToStop (TTS) collaborators and all other respondents.

The last question addressed whether results from the previous retrospective TimeToStop study (Boshuisen *et al.*, 2012) influenced clinical practice. A total of 32/46 (70%) indicated that this was the case; 88% of all TTS epileptologists (one indicated that the results did not influence his/her clinical practice), compared to 66% of the other paediatric epileptologists. Most responded stating that they now consider AED withdrawal earlier as a result of this study. As one respondent put it: "no more waiting for the magic two years".

Discussion

This study shows that European paediatric epileptologists who participated in the TTS study started tapering off AEDs, on average, between three and five months (in the case of polytherapy or monotherapy, respectively) after successful epilepsy surgery, which is earlier than the median of 6-11 months for the other respondents. In addition, the vast majority of the TTS respondents were unable to justify waiting for 12 months at this moment, and half of the other respondents shared this opinion. In addition, the majority of respondents indicated that the retrospective TTS study influenced their clinical decision-making towards earlier postoperative AED withdrawal. These results, together with the experiences of the coordinating centre of the planned TTS trial (UMC Utrecht), where all parents of eligible patients refused randomisation, was the rationale for prematurely stopping the trial without having included a single patient.

A comparison of our data with previous surveys on postoperative medication policy is problematic for several reasons. The three surveys that were performed in 2007 (Berg *et al.*, 2007), 2012 (Téllez-Zenteno *et al.*, 2012), and 2013 (Swisher and Sinha, 2013) were all performed in the US and Canada. Furthermore, adult neurologists were only questioned in one survey (Berg *et al.*, 2007), and the other two involved mixed answers from paediatric and adult neurologists (Téllez-Zenteno *et al.*, 2012; Swisher and Sinha, 2013). We have shown that when an epileptologist treats both children and adults, the timing of AED withdrawal is later

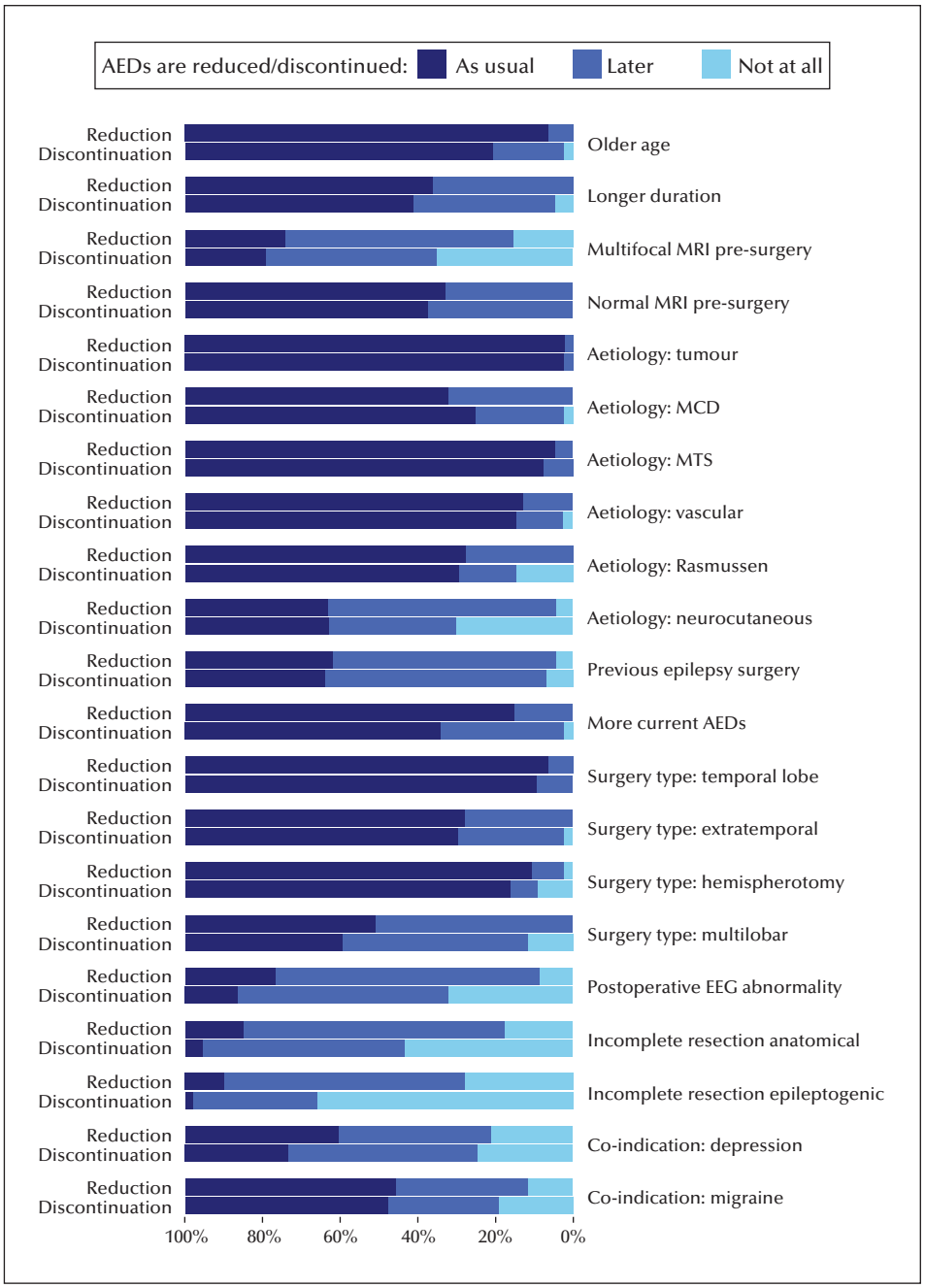

Figure 3. Factors influencing the decision to start reduction of AEDs and complete discontinuation of AEDs. The data are based on answers to the question: "In the presence of this factor, would you (*reduce or discontinue*) AEDs (a) as usual, (b) later, or (c) not at all?".

for adults, especially regarding the timing of complete discontinuation. This may be related to the potential consequences regarding, for example, employment and driving. The median time to first reduction was 12.5 months in the European TimeToStop study (Boshuisen *et al*., 2012), which included 766 children who were operated on between 2000 and 2008 (polytherapy and monotherapy combined). Relative to this study, and in line with our own experience, the current results show a marked shift to earlier AED withdrawal after paediatric epilepsy surgery.

This survey illustrates current practices, however, there are several limitations. First, the total number of responses is low making strong generalizations invalid. However, the response rate of 19% is misleadingly low because it was not possible to provide

an informative response rate in this study; the email lists that were used as a basis for the survey also contained those of neurosurgeons and other experts who may not have been directly involved in decisions regarding medication. Also, several adult neurologists received the survey and may have ignored it because it focused on a paediatric population. Since the survey was directed at the caring physician and not at the patient, we have no direct information on the preferences of the patient. As for the average timing of postoperative AED withdrawal, the indicated numbers are only averages across both low- and high-risk cases. Many respondents indicated a range for the timing, for example, starting AED withdrawal in the case of polytherapy 3-12 months after surgery. In this case, for the ideal candidate, AEDs would undoubtedly be tapered off at three months. However, in this study, the mean of the range, *i.e*. 7.5 months, would have been considered for analysis, which might influence the average. Nevertheless, we can conclude that the median time for starting AED withdrawal is well below 12 months after anticipated successful epilepsy surgery for the majority of European paediatric epileptologists. Conclusions regarding specialists outside Europe cannot be made because of the significant heterogeneity between countries. We can only speculate on the reasons for a more conservative AED policy outside Europe. If the fear of poor seizure outcome after early withdrawal persists among paediatric epileptologists, future comparative studies might be designed to address the safety of early withdrawal in specific populations, particularly children with higher-risk profiles. □

Supplementary data.
Summary didactic slides and supplementary tables are available on the www.epilepticdisorders.com website.

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JHC has received remuneration to her department as clinical investigator for Vitaflo, GW Pharma and Zogenix, and has participated in advisory boards for GSK, UCB, Zogenix, GW Pharma, Nuticia and Eisai, and as speaker for Shire, Nutricia, Zogenix, GW Pharma and Biomarin, again for which remuneration was made to her department. JHC also holds grants from the European Union, National Institute for Health and Research (NIHR), Action Medical Research, Great Ormond Street Hospital Charity, and SPARKS.
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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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TEST YOURSELF

(1) Should one wait for 12 months after paediatric epilepsy surgery before starting AED withdrawal (for both mono- and polytherapy)?

(2) Is it safe to start postoperative antiepileptic drug withdrawal at four months for children?

(3) What are the current practices regarding postoperative timing of antiepileptic drug withdrawal?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Appendix 1

Utrecht, May 29, 2017

Dear colleague,

You have received this survey because you are a specialist in epilepsy surgery. Within different international epilepsy surgery networks we would like to gather information on **current practices regarding postoperative antiepileptic drug withdrawal, particularly in children**.

We conduct this survey because we have the impression that medication policies have changed over the past years. We noticed that parental attitudes more often urge us to start drug withdrawal in children early after surgery, and wondered how professionals' attitudes have changed.

We value your insights and hope you will take the time to complete this **four page questionnaire**. Either fill it in digitally, or print it and return a scanned version with your response. Personal details such as name and centre will be dealt with confidentially, information on the country will be used in publication of the results.

The survey can be returned to our PhD candidate Herm Lamberink, h.j.lamberink@umcutrecht.nl

Thanks for your efforts,

With warm regards,

Kees Braun

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Survey on antiepileptic drug withdrawal policy after paediatric epilepsy surgery

Name ...
Centre ...
Country ...

1. For children seizure-free after anticipated curative epilepsy surgery, at what time interval would you start AED withdrawal, in case of
   a) Polytherapy? ..... months after surgery
   b) Monotherapy? ..... months after surgery

   If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
   At what time interval would you start AED withdrawal, in case of
   c) Polytherapy? ..... months after surgery
   d) Monotherapy? ..... months after surgery

2. For children seizure-free after anticipated curative epilepsy surgery, at what time interval would you completely discontinue the last AED, in case of
   a) Polytherapy? ..... months after surgery
   b) Monotherapy? ..... months after surgery

   If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
   At what time interval would you completely discontinue the last AED, in case of
   c) Polytherapy? ..... months after surgery
   d) Monotherapy? ..... months after surgery

3. Do you think starting AED withdrawal 4 months after epilepsy surgery is safe, in case of
   a) Polytherapy? Yes/no
   b) Monotherapy? Yes/no

   If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
   Do you think starting AED withdrawal 4 months after epilepsy surgery is safe, in case of
   a) Polytherapy? Yes/no
   b) Monotherapy? Yes/no

Survey on antiepileptic drug withdrawal policy after paediatric epilepsy surgery

4. What is the average duration of tapering of AED withdrawal per individual drug (from start of reduction to complete discontinuation):
..... months

If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
..... months

5. Do you think waiting with AED withdrawal for 12 months or more after surgery is justified in children?
Yes/no

If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
Yes/no

6. Are there specific drugs with which you are more careful to start withdrawal? Would you start reduction of these drugs later, taper over a longer period, or not withdraw them at all? Please list them in the table below.

	Check the box which most reflects your action with the drug. Multiple answers are possible.			
Drug name	**No reduction at all**	**Later start reduction**	**Longer taper period**	**No complete discontinuation**

Please turn to the next page.

Survey on antiepileptic drug withdrawal policy after paediatric epilepsy surgery

7. Is your decision to reduce or completely discontinue AEDs in children influenced by the following items?
For every item, check one of the boxes in the 'Reduction' section, and one of the boxes in the 'Discontinuation' section. Indicate whether you would reduce AEDs as usual, later or not at all, and whether you would discontinue AEDs as usual, later or not at all.

Example (reduction is advised as usual, but drugs are never completely discontinued):

Factor	**Reduction**			**Discontinuation**		
	As usual	Later	No	As usual	Later	No
Example factor influencing drug policy	x	□	□	□	□	x

Actual question (in children):

Factor	**Reduction**			**Discontinuation**		
	As usual	Later	No	As usual	Later	No
Higher age at withdrawal	□	□	□	□	□	□
Longer duration of epilepsy before surgery	□	□	□	□	□	□
Multifocal MRI	□	□	□	□	□	□
Normal MRI	□	□	□	□	□	□
Postoperative epileptic EEG abnormalities	□	□	□	□	□	□
Temporal lobe surgery	□	□	□	□	□	□
Extratemporal lobe surgery	□	□	□	□	□	□
Hemispherectomy	□	□	□	□	□	□
Multilobar surgery	□	□	□	□	□	□
Aetiology	□	□	□	□	□	□
Tumour	□	□	□	□	□	□
Malformation of cortical development	□	□	□	□	□	□
Mesiotemporal sclerosis	□	□	□	□	□	□
Vascular lesion	□	□	□	□	□	□
Rasmussen encephalitis	□	□	□	□	□	□
Neurocutaneous syndrome	□	□	□	□	□	□
Other	□	□	□	□	□	□
Incomplete resection of anatomic lesion	□	□	□	□	□	□
Incomplete resection of epileptogenic lesion	□	□	□	□	□	□
Previous epilepsy surgery	□	□	□	□	□	□
Higher number of AEDs before surgery	□	□	□	□	□	□
AEDs are also used as antidepressant/psychotropic	□	□	□	□	□	□
AEDs are also used in treatment of migraine	□	□	□	□	□	□

Please turn to the next page.

Survey on antiepileptic drug withdrawal policy after paediatric epilepsy surgery

8. Do you tend to counsel parents/children in favour of AED withdrawal (cognitive advantages) or against AED withdrawal (risk of relapse and not regaining seizure-freedom)?
   .....
   .....

   If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
   Do you tend to counsel patients in favour of AED withdrawal (cognitive advantages) or against AED withdrawal (risk of relapse and not regaining seizure-freedom)?

9. In your clinic, what is your general experience on patient/parents' preferences?
   .....
   .....

   If you are also involved in adult epilepsy surgery; please answer the same question for adult patients:
   In your clinic, what is your general experience on patient/parents' preferences?
   .....
   .....

10. Have your AED withdrawal policies been influenced by the retrospective TimeToStop study results (Lancet Neurol 2012; 11: 784-91)?
    Yes/ No
    If so, how? ....

Do you have any additional comments?

Thank you for filling out this survey. You can return a digital version to our PhD candidate Herm Lamberink, h.j.lamberink@umcutrecht.nl