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

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Complete List of Authors:	Lamberink, Herm; University Medical Center Utrecht, Department of (Child) Neurology and Neurosurgery, Brain Center Rudolf Magnus Geleijns, Karin; University Medical Center Utrecht, Department of (Child) Neurology and Neurosurgery, Brain Center Rudolf Magnus Otte, Willem; University Medical Center Utrecht, Pediatric Neurology Arzimanoglou, Alexis; University Hospitals of Lyon, Clinical Epileptology, Sleep Disorders and Functional Neurology in Children; INSERM U1028, CNRS UMR5292, DYCOG Team, Lyon Neuroscience Research Centre (CRNL) Cross, J.; Great Ormond Street Hospital, University College London, Department of Clinical & Experimental Epilepsy Korff, Christian; University Hospitals, Child and Adolescent Ramantani, Georgia; University Childrens Hospital, Neuropediatrics Braun, Kees; University Medical Center Utrecht, Brain Center Rudolf Magnus, Child Neurology
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Why the TimeToStop trial failed to recruit: a survey on antiepileptic drug withdrawal after paediatric epilepsy surgery.

Herm J Lamberink[a], Karin Geleijns[a], Willem M Otte[a,b], Alexis Arzimanoglou[c,d], J Helen Cross[e], Christian M Korff[f], Georgia Ramantani[g], Kees PJ Braun[a], on behalf of the TimeToStop trial group

Affiliations:

[a] Department of Child Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht and Utrecht University, Utrecht, the Netherlands.

[b] Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Utrecht, the Netherlands

[c] Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology Department, University Hospitals of Lyon (HCL), Member of the European Reference Network EpiCARE, Lyon Neurosciences Research Centre, Lyon, France.

[d] Universitat de Barcelona, Hospital San Juan de Deu Epilepsy Unit, Member of the European Reference Network EpiCARE, Barcelona, Spain

[e] Clinical Neurosciences, UCL-Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London & Young Epilepsy Lingfield, UK.

[f] Unité de Neuropédiatrie, Hôpitaux Universitaries de Genève, Genève, Switzerland

[g] Neuropediatrics, University Children's Hospital Zürich, Zürich, Switzerland

Corresponding author:

Prof Kees P J Braun, Department of Child Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, 3508 AB, Utrecht, Netherlands.

k.braun@umcutrecht.nl

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ABSTRACT:

Following the results of the multicentre European retrospective "TimeToStop" cohort study we initiated a randomized trial to determine cognitive benefits of early postoperative antiepileptic drug withdrawal. Unfortunately the trial failed to recruit and was terminated; parents preferred early drug withdrawal. The objectives of the current survey were to obtain insight in current practices regarding drug withdrawal after paediatric epilepsy surgery among epileptologists and better understand the reasons for difficulties in recruitment. A survey was sent to three international epilepsy surgery networks, questioning drug withdrawal policies. Forty-seven (19%) were returned. In polytherapy, withdrawal was started at a median of 3 and 6 months, by the TimeToStop collaborators, and other paediatric epileptologists, respectively. Withdrawal was completed at a median of 12 and 20 months, respectively. In monotherapy, tapering was initiated at 5 and 11 months in these two groups, and ended at a median of 7 and 12months, respectively. Most TimeToStop collaborators thought it was not justified to wait for AED reduction until 12 months after surgery.

In conclusion, current AED policies in Europe have changed as a consequence of the retrospective TimeToStop results, explaining why recruitment for a randomized trial was not feasible.

INTRODUCTION

On the achievement of 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 [1–3]. A multicentre European retrospective cohort study strongly suggested that the timing of postoperative AED withdrawal does not influence eventual seizure outcomes[4]; although the seizure recurrence risk was increased with earlier AED withdrawal, there was no relation with long-term freedom of seizures or medication status at final follow-up. 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" randomized controlled trial (EudraCT number 2011-005971-18)[5]. We aimed to compare cognitive functioning, intelligence, and seizure outcome at 12 and 24 months after epilepsy surgery between children who were randomized to start withdrawal after 4 months, and those who started withdrawal at 12 months after surgery. Eight centres in five countries agreed to participate, and recruitment was started in Utrecht, the Netherlands in November 2015 whilst the other centres were in preparation. Until February 2017, 47 children were screened of whom 35 were not eligible (Supplementary Table 1). Twelve children were eligible, but 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 and children wanted randomization 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 in current practices and to better understand the reasons for difficult recruitment in the TimeToStop trial, with this survey we aimed to describe AED withdrawal policies among paediatric epileptologists by using a short survey. The hypotheses were that 1) current beliefs about safety and benefits of early postoperative AED withdrawal among treating physicians justify

premature discontinuation of the TTS trial for feasibility issues, 2) that partners of the original TTS study group and European paediatric epileptologists tend to withdraw medication sooner than others, and 3) that 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 adult neurologists or physicians who treat both children and adults to respond. The full survey can be found in appendix 1; it contained several items on the timing of postoperative AED withdrawal in children who underwent anticipated curative epilepsy surgery, factors influencing timing, and on personal preferences and those of parents/children with epilepsy. The survey was widely distributed among epilepsy surgery specialists collaborating in three broad networks: 1) U-Task (the 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, a EU-funded pilot reference network of epilepsy surgery centres, aiming to improve access to, and outcome of, epilepsy surgery and harmonize (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.
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 statistic 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 and non-European respondents.

RESULTS

The survey was sent out to 251 addresses, 47 (19%) surveys were returned by 32 paediatric epileptologists and 15 specialists who treated both children and adults. Nine respondents had been partners of the previous retrospective TimeToStop study [4] or the prospective TimeToStop trial [5] 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 the TTS collaborators and those who did not participate is given in Figure 1 and Table 1. Both for initiating and completely discontinuing AEDs, TTS collaborators were earlier than the other respondents. In children on polytherapy, the median start of withdrawal was at 3 months for the TTS collaborators compared to 6 months for other respondents ($U = 258.5$, $p = 0.02$). AEDs were completely tapered off at 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 5 months compared to 11 months ($U = 222.5$, $p = 0.08$), and completely discontinued at 7 months compared to 12 months ($U = 243$, $p = 0.01$). European respondents started and discontinued AEDs earlier compared to non-Europeans in case of monotherapy (start at median 6 vs. 12 months, and discontinuation at 9 vs. 17 months); for polytherapy the groups started AED withdrawal at a similar time but there were differences in complete discontinuation (start at median 5 vs. 6 months, discontinuation at 16 vs. 24 months).

Three questions were posed regarding the safety and justification of starting withdrawal at either four or 12 months after surgery. Figure 2 summarizes the responses; all TTS collaborators deemed it safe to start withdrawal of polytherapy at four months, compared to 71% of other respondents. Sixty-seven percent of TTS collaborators deemed AED withdrawal safe at four months in case of monotherapy, compared to 47% of other respondents. Only 33% of TTS collaborators

thought it was justified to wait until 12 months after paediatric epilepsy surgery, compared to 54% of others.

Figure 3 illustrates how respondents judged different clinical factors to 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 visualized 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).

Comparing taper duration between the TTS collaborators and other paediatric epileptologists gives the following medians (IQR), respectively: 2.5 months per drug (2.5-2.6) and 5.3 months (3.0-9.8). 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). In open comments, side effects were mentioned 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 with early withdrawal for their adult patients, by starting withdrawal later for polytherapy (median time difference 2 months, IQR 0-5) and for monotherapy (median time difference 2 months, IQR 0-9). Complete discontinuation was also later in cases of adult care, with a median time difference of 6 months (IQR 0-24) and 12 months (IQR 0-12), in case of poly- and monotherapy respectively. In adult care, 50% deemed it safe to start AED withdrawal at 4 months in the case of polytherapy and 14% in the case of monotherapy,

compared to 53% and 46% for children. Sixty percent stated it was justified to wait for 12 months after adult epilepsy surgery, compared to 47% in paediatric care.

Of all respondents, 32 (68%) indicated to advise mainly in favour of withdrawal, 4 (9%) counsel toward 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, 5/45 (11%) late. In 7/45 (16%) it 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.

The last question was: did results from the previous retrospective TimeToStop study [4] influence clinical practice? Thirty-two (from 46, 70%) indicated it did, 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 that they consider AED withdrawal earlier than before because of this study. As one respondent put it: "no more waiting for the magic 2 years".

DISCUSSION

This study shows that European paediatric epileptologists who participated in the TTS study start tapering off AEDs between on average three and five months (in case of poly- or monotherapy respectively) after successful epilepsy surgery, which is earlier than the median 6-11 months for the other respondents. In addition, the vast majority of the TTS respondents deemed waiting for 12 months not justified and half of the other respondents shared this opinion. In addition, the majority of respondents indicated that the retrospective TTS study has influenced their clinical decision making towards earlier postoperative AED withdrawal. These results, together with the experiences in the coordinating centre of the planned TTS trial (UMC Utrecht) – where all parents of eligible patients refused randomization – was the rationale for prematurely stopping the trial without having included a single patient.

Comparison of our data with previous surveys on postoperative medication policy is problematic for several reasons. The three surveys that have been performed in 2007 [6], 2012 [7] and 2013 [8] were all performed in the US and Canada. Furthermore, one only questioned adult neurologists [6], and the other two mixed answers from paediatric and adult neurologists [7,8]. We have shown that when an epileptologist treats both children and adults, the timing of AED withdrawal is later for adults, especially regarding the timing of complete discontinuation. This may be related to the potential consequences regarding, for example, employment and driver's license. The median time to first reduction was 12.5 months in the European TimeToStop study [4], including 766 children who were operated on between 2000 and 2008 (poly- and monotherapy combined). Comparing with those numbers, 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 but has 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 is not possible to provide an informative response-rate in this study: the email lists that were used as basis for the survey also contained neurosurgeons and other experts who may not be 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 case of polytherapy 3-12 months after surgery. Undoubtedly, the most ideal candidate would be tapered off at 3 months in that case. In this study however, the above example would have been analysed as the mean of the range, i.e. 7.5 months, possibly biasing the average statistic. Nevertheless, we can conclude that the median start of 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 high heterogeneity of countries. We can only speculate on the reasons for a more conservative AED policy outside Europe. If the fear for poor seizure outcome after early withdrawal persists among paediatric epileptologists, future comparative studies could address the safety of early withdrawal in specific populations, particularly children with higher-risk profiles.

"Test Yourself"

1. Should one wait for 12 months after paediatric epilepsy surgery before starting AED withdrawal?
    a. No, most respondents to this survey start earlier. About half of them even think it is not justified to postpone withdrawal to 12 months.
2. Is it safe to start postoperative antiepileptic drug withdrawal at 4 months, for children?
    a. The majority of (mostly European) paediatric epileptologists are of the opinion that this is safe, both for mono-, and polytherapy.
3. What are current practices regarding postoperative timing of antiepileptic drug withdrawal?
    a. In the case of polytherapy, AED withdrawal is usually initiated between 3 and 6 months (IQR); for TTS collaborators this was even earlier, between 1 and 4 months (IQR). In case of monotherapy, the IQR ranged from 6 to 13 months, and for TTS collaborators from 4 to 6 months.

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Disclosures

AA received institutional research grants from the European Commission, UCB and the La Caixa Foundation. He occasionally serves as an advisory board member, consultant, or lecturer for Eisai, GW, the John Libbey Eurotext editions, Shire, Takeda, UCB and Zogenix and has received royalties. *JHC* has received remuneration to her department as clinical investigator for Vitaflo, GW Pharma and Zogenix. She 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. She holds grants from the European Union, National Institute for Health and Research (NIHR), Action Medical Research, Great Ormond Street Hospital Charity and SPARKS.

HJL, KG, WMO, CMK, GR and *KPJB* have no conflicts of interest. 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.

TimeToStop trial group

JH Cross (Great Ormond Street Hospital for Children, London, UK); C Korff, M Seeck (Hôpitaux Universitaires de Genève, Genève, Switzerland); T Polster (Krankenhaus Mara, Epilepsiezentrum Bethel, Bielefeld, Germany); G Ramantani (University Children's Hospital Zürich, Zürich, Switzerland); A de Saint-Martin (University Hospital Strassbourg, Strassbourg, France); A Arzimanoglou (University Hospitals of Lyon, Lyon, France); HJ Lamberink, K Geleijns, WM Otte, K Boshuisen, E Bloemen-Carlier, CS Uiterwaal, MMJ van Schooneveld, KPJ Braun (University Medical Center Utrecht, Utrecht, the Netherlands); RFM Chin (Western General Hospital Edinburgh, Edinburgh, UK)

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FIGURES AND TABLES

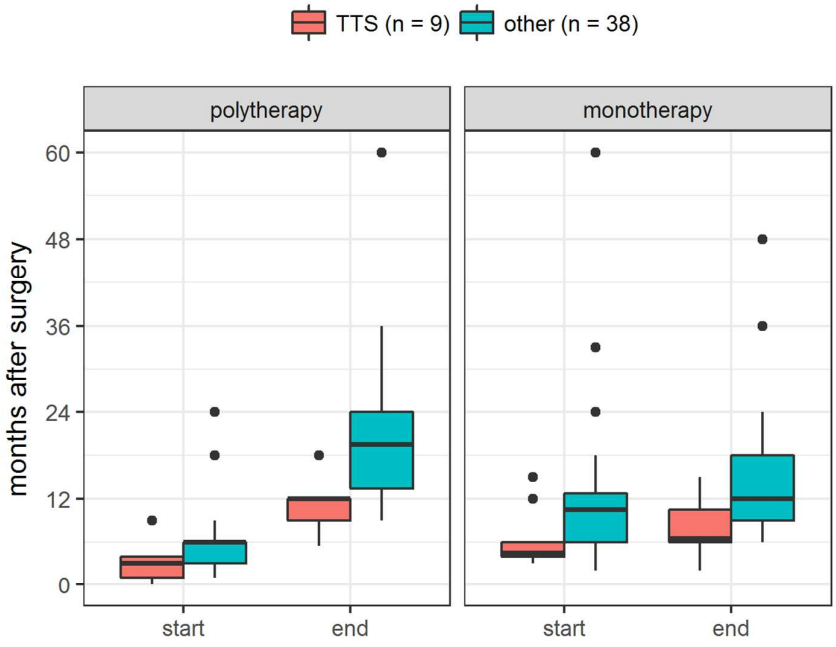


Figure 1 | The timing of antiepileptic drug (AED) withdrawal after paediatric epilepsy surgery in case of polytherapy and monotherapy, compared between the two cohorts of TTS collaborators and other respondents. The boxes show the median and interquartile range (IQR), the whiskers extend to 1.5*IQR. 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. The summary statistics are given in Table 1.

Table 1 | Median time to start 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	*222.5, p=0.08*	*243, p=0.01*

All given values are median (IQR) in months after paediatric epilepsy surgery, rounded to full months. Visual representation of group differences is shown in Figure 1.

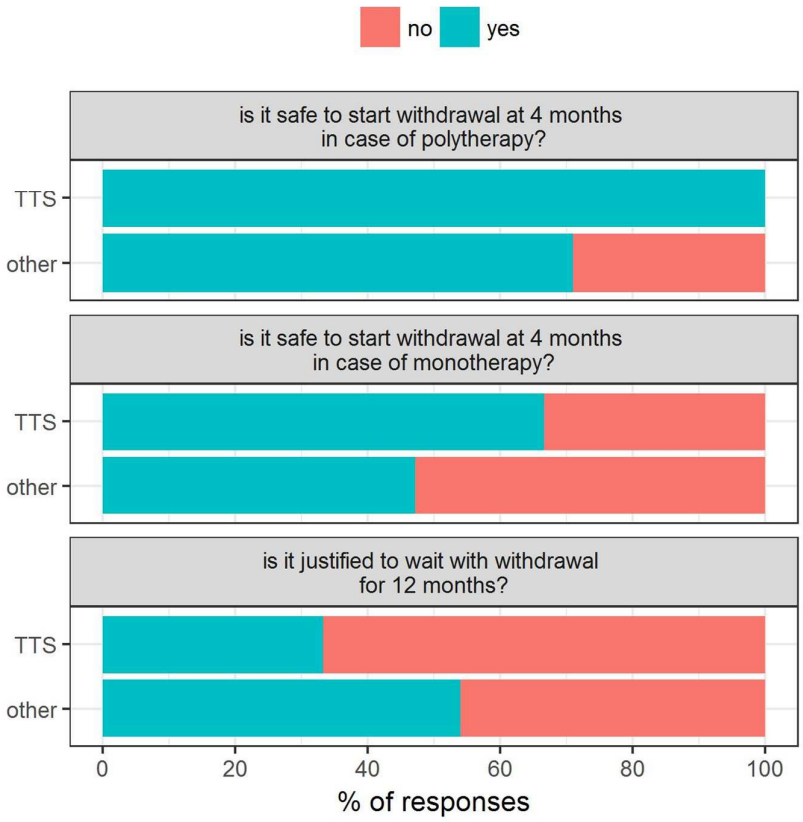


Figure 2 | Responses to three questions, compared between TimeToStop (TTS) collaborators and all other respondents.

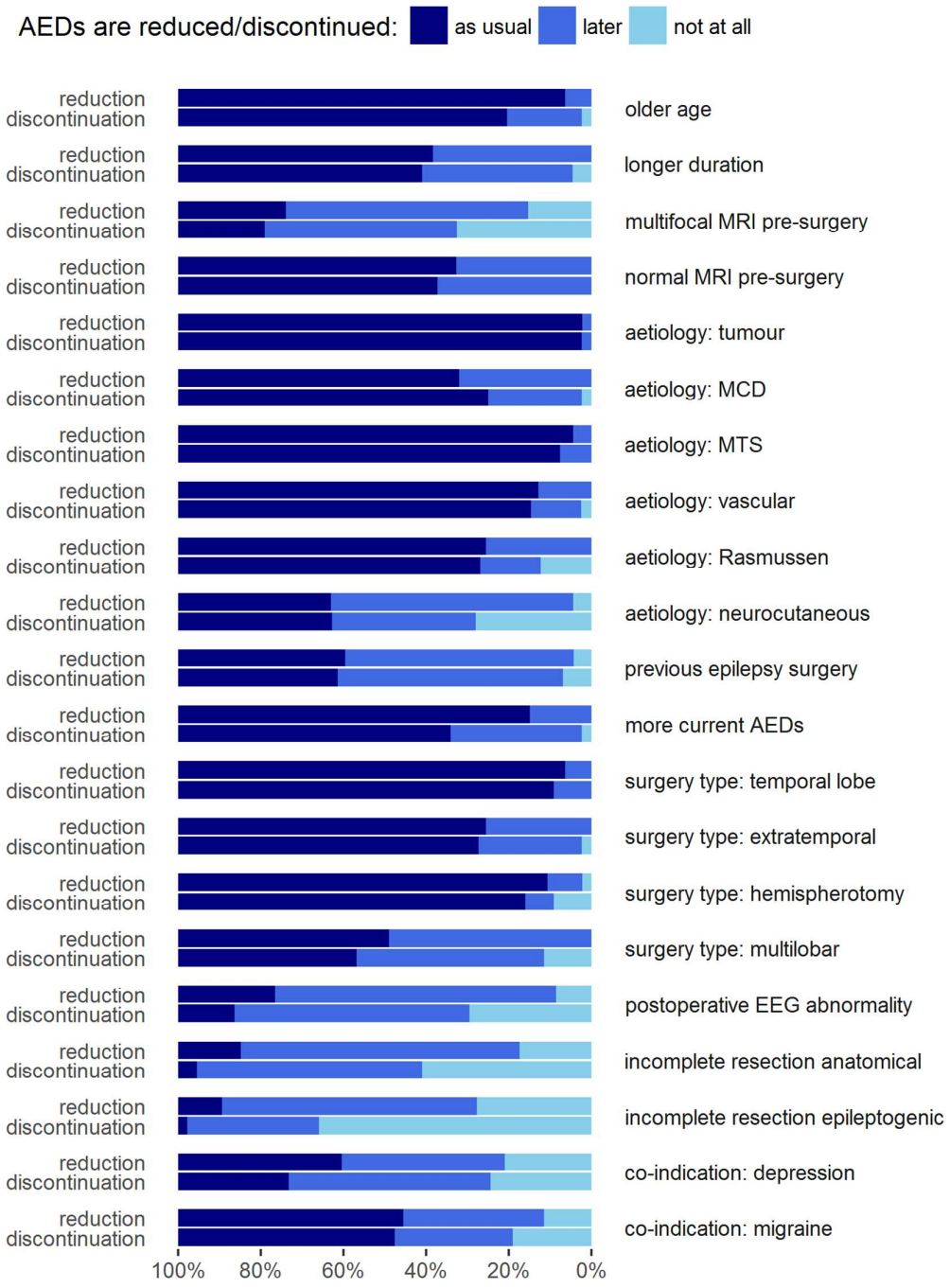


Figure 3 | Factors influencing the decision to start reduction of AEDs and complete discontinuation of AEDs. The question was answered: "In the presence of this factor, would you [*reduce or discontinue*] AEDs (a) as usual, (b) later, or (c) not at all?"

Supplementary Table 1 | Eligibility for the TimeToStop trial and reasons for non-eligibility

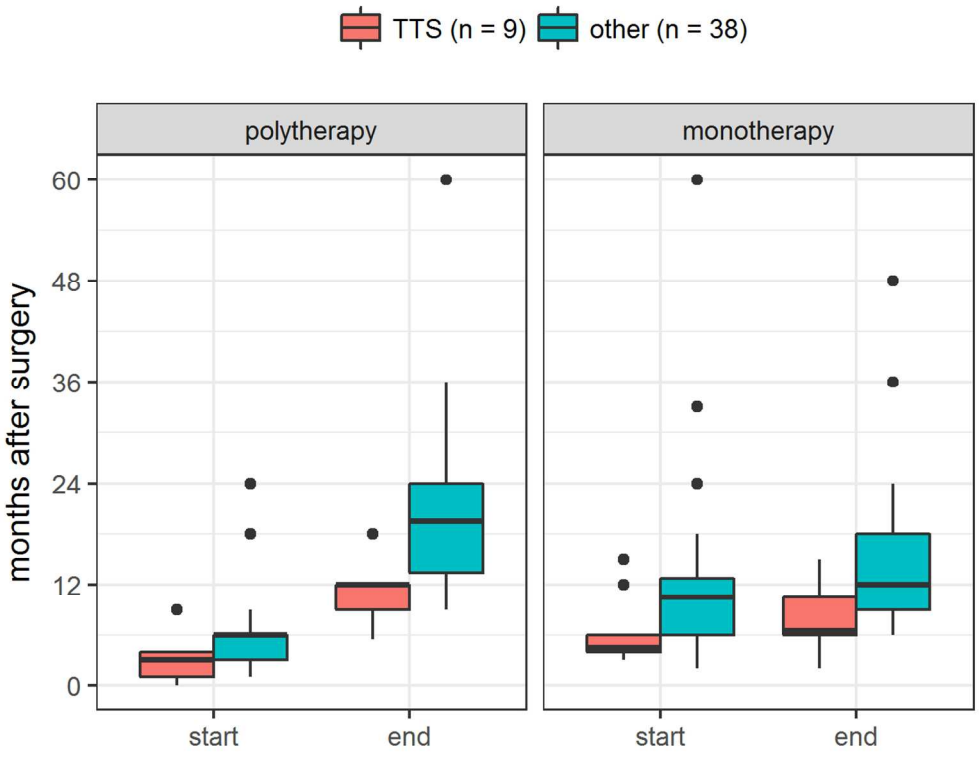
Eligibility	Number of children
Eligible for inclusion	12
Objection against late withdrawal	11
Objection against early withdrawal	1
Willing to participate	0
Not eligible	35
Age at surgery > 15 years	8
Age at surgery < 6 years (too young to perform Epitrack Junior)	10
No Epitrack Junior performed (not able to take it or not performed)	8
Postoperative epileptiform discharges on EEG or ECoG	3
No postoperative seizure-freedom	1
Vagus nerve stimulator	1
Not using AEDs before surgery	2
Only surgery in our centre, follow-up elsewhere	1
Already started AED withdrawal <4 m because of side-effects	1

Total number of patients who were screened and approached for participation in the TimeToStop trial, between 1-11-2015 until 28-2-2017.

Supplementary Table 2 | Does the type of drug influence timing of AED withdrawal?

Drug name	Longer taper period	Later start withdrawal	No complete discontinuation
phenobarbital	17	1	0
benzodiazepines	14	3	0
carbamazepine	7	5	0
phenytoin	4	0	0
vigabatrin	2	2	0
valproic acid	2	1	0
primidone	2	1	0
oxcarbazepine	2	1	0
topiramate	2	0	0
lamotrigine	1	2	0
bromide	1	0	0
zonisamide	1	0	0
levetiracetam	0	3	0
lacosemide	0	1	0
cannabidiol	0	0	1

37/47 answered the question. Six respondents specifically mentioned that no drug influenced the decision.
No drug was indicated to be related to not starting AED withdrawal.



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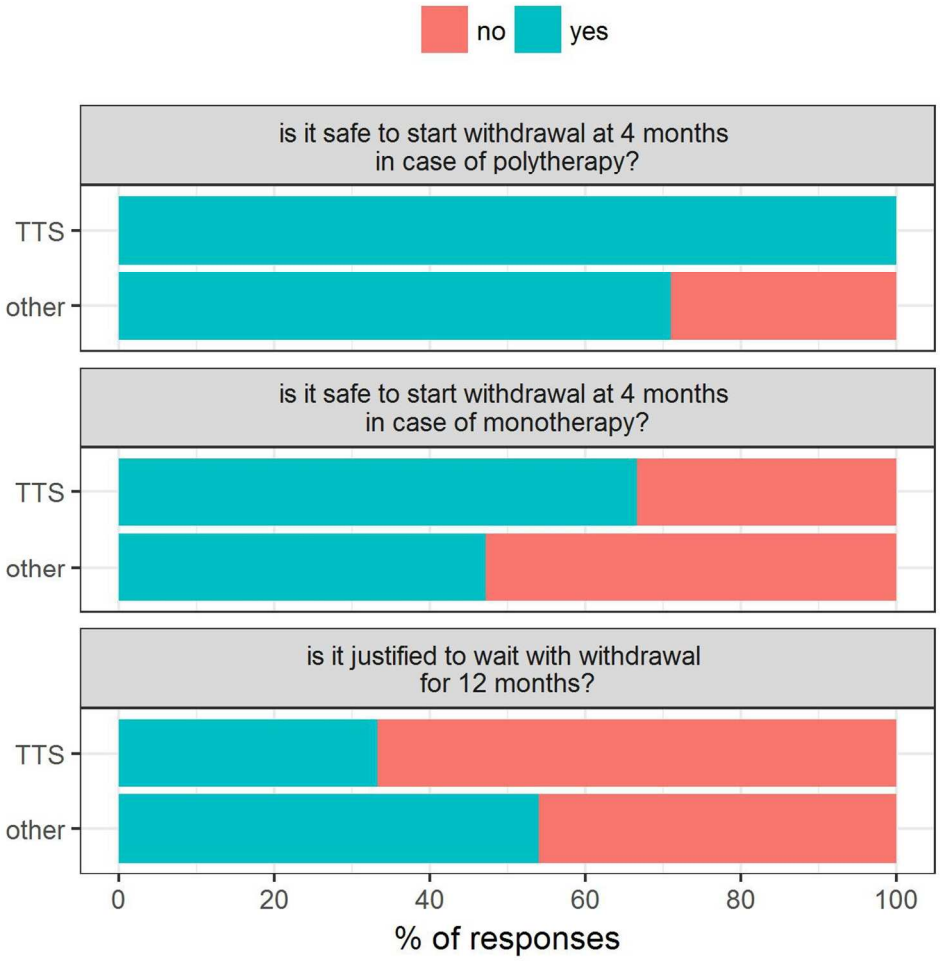

Responses to three questions, compared between TimeToStop (TTS) collaborators and all other respondents.

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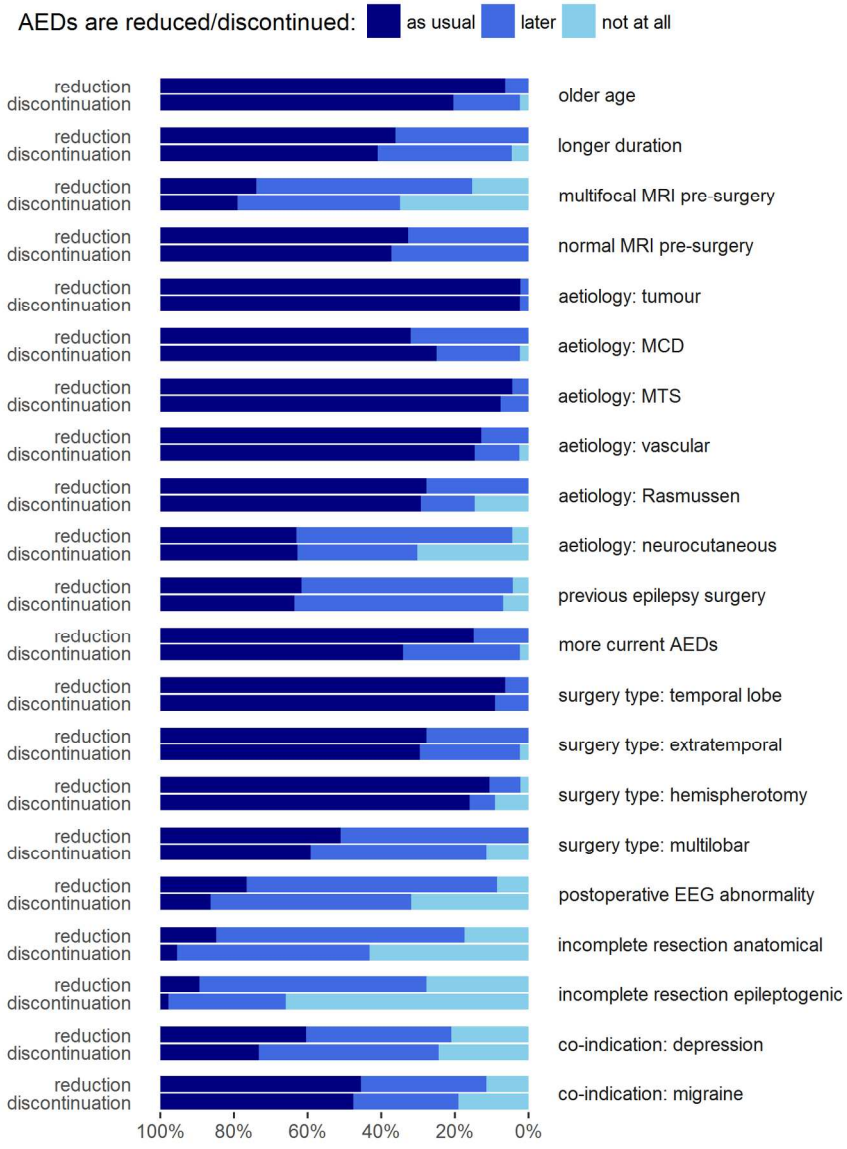
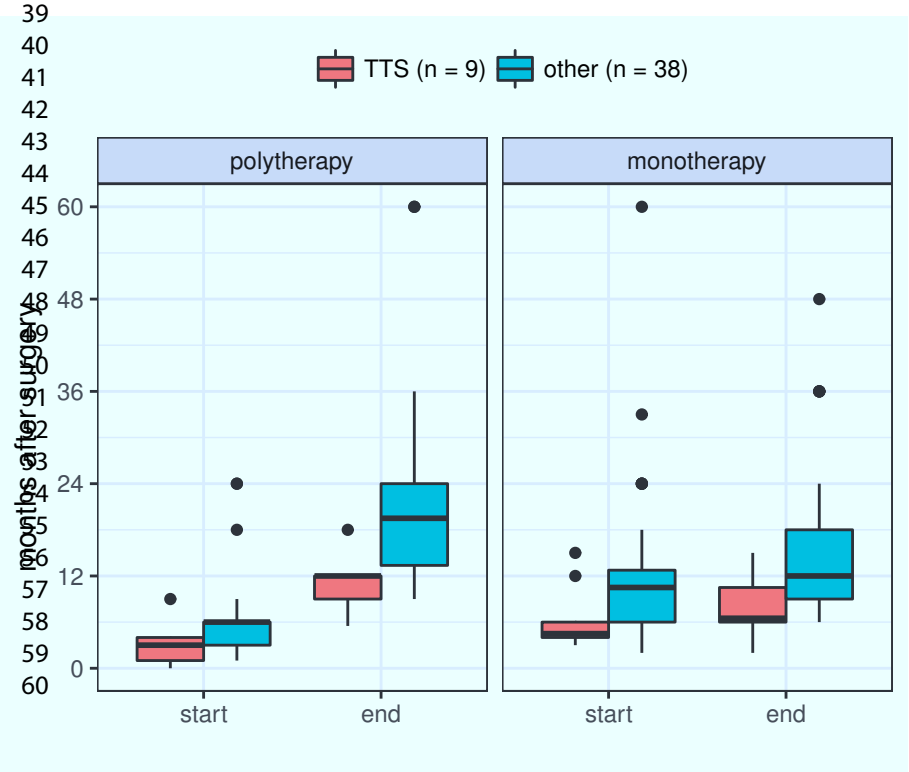
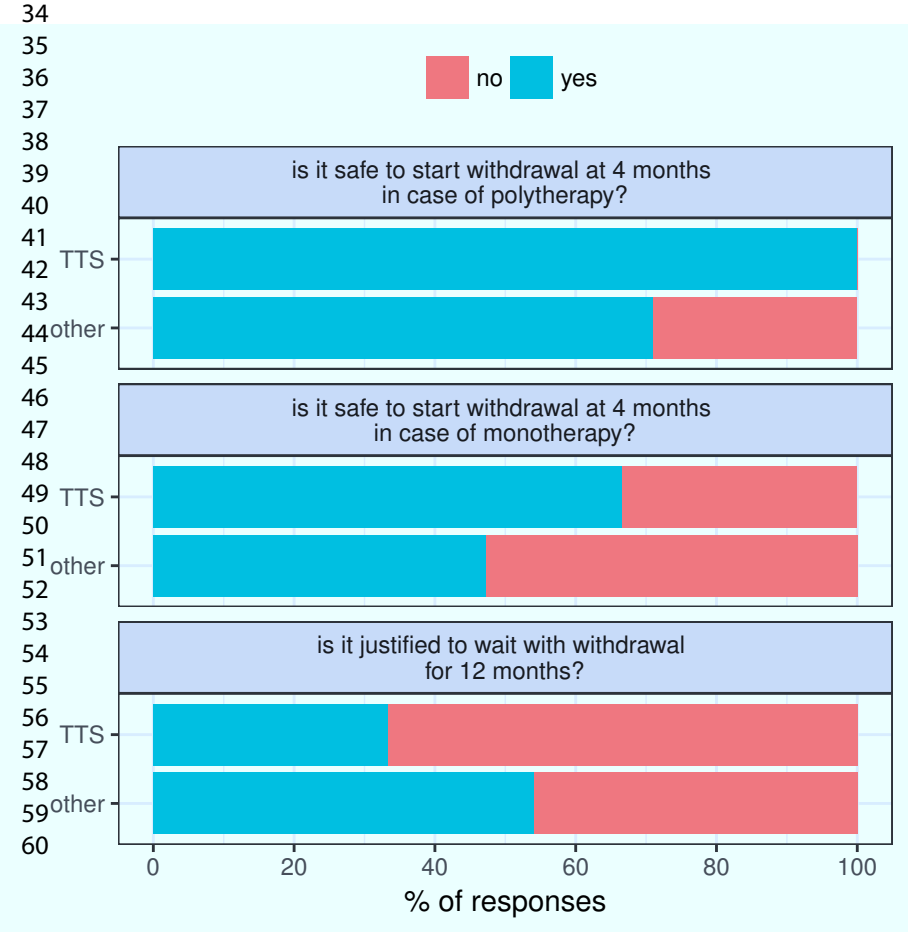
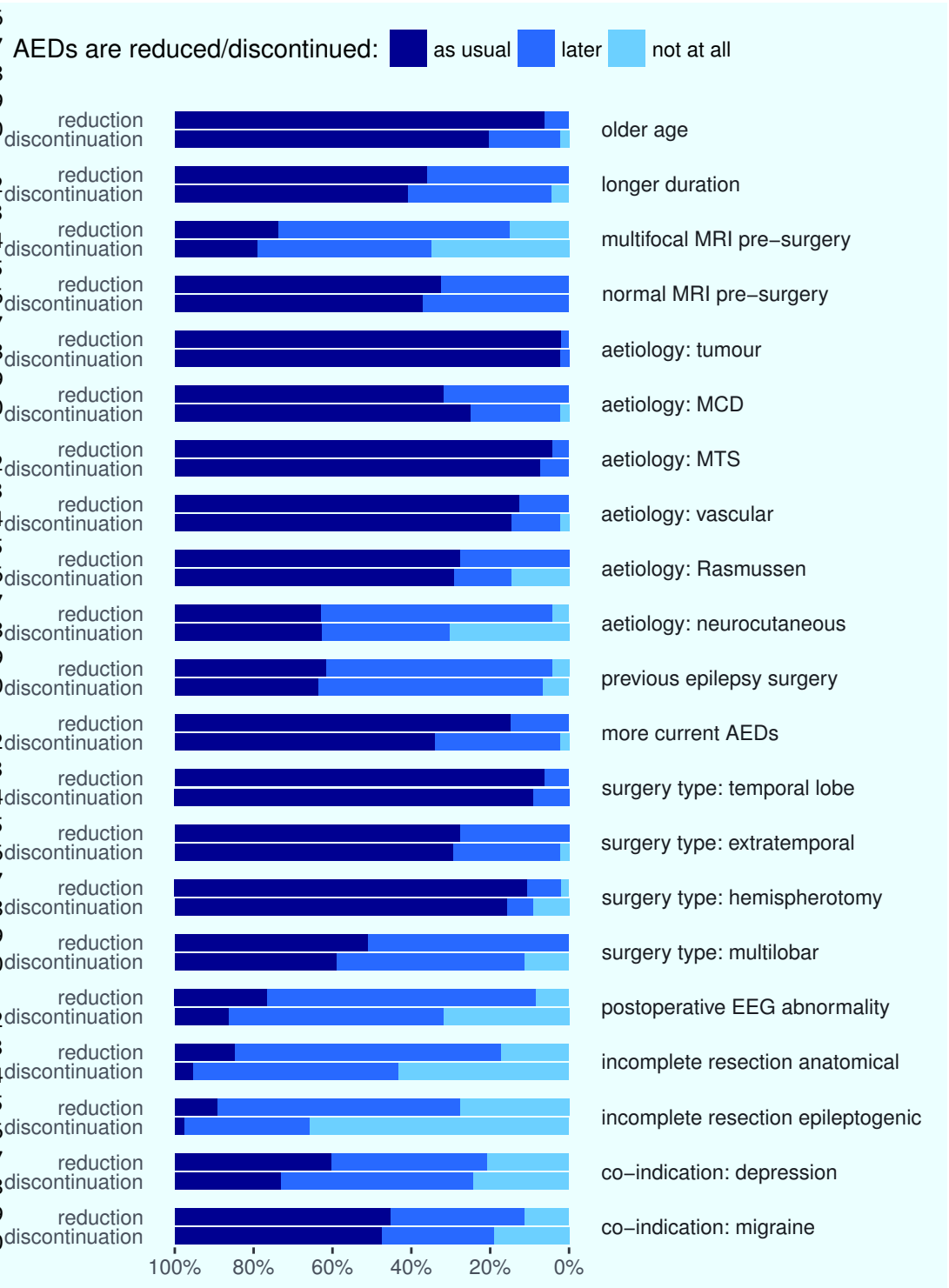


Factors influencing the decision to start reduction of AEDs and complete discontinuation of AEDs. The question was answered: "In the presence of this factor, would you [reduce or discontinue] AEDs (a) as usual, (b) later, or (c) not at all?"






AEDs are reduced/discontinued:
as usual
later
not at all
reduction
discontinuation
older age
longer duration
multifocal MRI pre−surgery
normal MRI pre−surgery
aetiology: tumour
aetiology: MCD
aetiology: MTS
aetiology: vascular
aetiology: Rasmussen
aetiology: neurocutaneous
previous epilepsy surgery
more current AEDs
surgery type: temporal lobe
surgery type: extratemporal
surgery type: hemispherotomy
surgery type: multilobar
postoperative EEG abnormality
incomplete resection anatomical
incomplete resection epileptogenic
co−indication: depression
co−indication: migraine
100%
80%
60%
40%
20%
0%