Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study

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Summary

Background Postoperative antiepileptic drug (AED) withdrawal practices remain debatable and little is known about the optimum timing. We hypothesised that early AED withdrawal does not affect long-term seizure outcome but allows identification of incomplete surgical success earlier than late withdrawal. We aimed to assess the relation between timing of AED withdrawal and subsequent seizure recurrence and long-term seizure outcome.

Methods TimeToStop included patients aged under 18 years from 15 centres in Europe who underwent surgery between Jan 1, 2000, and Oct 1, 2008, had at least 1 year of postoperative follow-up, and who started AED reduction after having reached postoperative seizure freedom. Time intervals from surgery to start of AED reduction (TTR) and complete discontinuation (TTD) were studied in relation to seizure recurrence during or after AED withdrawal, seizure freedom for at least 1 year, and cure (defined as being seizure free and off AEDs for at least 1 year) at latest follow-up. Cox proportional hazards regression models were adjusted for identified predictors of timing intervals.

Findings TimeToStop included 766 children. Median TTR and TTD were 12·5 months (95% CI 11·9–13·2) and 28·8 months (27·4–30·2), respectively. 95 children had seizure recurrence during or after AED withdrawal. Shorter time intervals predicted seizure recurrence (hazard ratio [HR] 0·94, 95% CI 0·89–1·00, p=0·05 for TTR; and 0·90, 0·83–0·98, p=0·02 for TTD). After a mean postoperative follow-up of 61·6 months (SD 29·7), 728 patients were seizure free for at least 1 year. TTR and TTD were not related to regain of seizure freedom after restart of drug treatment (HR 0·98, 95% CI 0·92–1·05, p=0·62; and 0·93, 0·83–1·05, p=0·26, respectively), or to seizure freedom (0·97, 0·89–1·07, p=0·55; and 1·03, 0·93–1·14, p=0·55, respectively) or cure (0·97, 0·97–1·03, p=0·84; and 0·98, 0·94–1·02, p=0·31, respectively) at final follow-up.

Interpretation Early AED withdrawal does not affect long-term seizure outcome or cure. It might unmask incomplete surgical success sooner, identifying children who need continuous drug treatment and preventing unnecessary continuation of AEDs in others. A prospective randomised trial is needed to study the possible cognitive effects and confirm the safety of early AED withdrawal after epilepsy surgery in children.

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Introduction

Epilepsy surgery is an effective treatment for children with intractable epilepsy. Seizure freedom rates vary from 50% to over 80%[1] and are generally reported without reference to antiepileptic drug (AED) use. Since AEDs have cognitive side-effects, drug withdrawal after successful surgery will optimise the child's cognitive abilities. Ultimately, surgery should be undertaken with the aim of curing the epilepsy, which can be defined as reaching both seizure freedom and drug freedom.[2]

In our experience, many parents report improved alertness, attention, and behaviour once AEDs are discontinued after surgery. Findings from withdrawal studies show that AED withdrawal improves several neurocognitive outcome measures.[3,4] Nevertheless, AEDs are usually continued for at least 2 years after epilepsy surgery,[5] often because of fear of seizure recurrence after withdrawal and the anticipated risk of not regaining seizure freedom after restart of drugs. Although findings from some studies have suggested a worse seizure outcome after early compared with late postoperative AED withdrawal, results are conflicting,[5–9] and there is no consensus among centres about the optimum timing of drug withdrawal. We hypothesised that timing of drug withdrawal itself does not affect seizure outcome in the long term, but that early AED withdrawal merely identifies the need for continuation of postoperative AEDs sooner in patients who were not cured by surgery. We undertook a collaborative European multicentre study, the TimeToStop study, to assess AED withdrawal practices after epilepsy surgery in children and to study the relation between timing of AED withdrawal and seizure outcome.

Methods

Patients

The TimeToStop study is a retrospective European multicentre cohort study that was started within the

European Taskforce for Epilepsy Surgery in Children (appendix). 15 paediatric epilepsy surgery centres in Europe agreed to collaborate and shared their data on clinical characteristics, drug policy, and seizure outcome of children in whom AED withdrawal was started postoperatively. The decision to start withdrawal was generally made by the treating physician. The parents of some patients started withdrawing AEDs, but in these cases the date of drug withdrawal was known and noted in the medical files.

Patients were included if they were operated on between Jan 1, 2000, and Oct 1, 2008, were younger than 18 years at surgery, had at least 1 year of postoperative follow-up, and if AED withdrawal was started postoperatively. Patients were excluded if their treating physician or parents decided to taper their drug treatment despite continuing postoperative seizures, including auras.

The TimeToStop study was approved by the institutional ethical committee of the University Medical Center Utrecht, which concluded that the Dutch Medical Research Involving Human Subjects Act did not apply and written informed consent was not needed. The local ethical committees of all participating centres subsequently gave permission to undertake the study.

Procedures

Between April 13, and Dec 19, 2009, one of the study investigators (KB) visited all centres and collected data in collaboration with local investigators and treating epileptologists. To ascertain accuracy of data extraction from the medical files, at least one collaborator per centre reviewed the data of his or her patients. Missing data were collected by means of telephone interviews with the patients or their parents, if possible.

We collected data on general patient characteristics, MRI findings, pathological diagnosis, functional imaging findings, surgical strategies, first postoperative electroencephalogram (EEG), AEDs that were ever tried during the course of the epilepsy, AEDs used at time of surgery, the first AED to be withdrawn, and the timing of AED withdrawal. The data included all variables that were previously reported to be independently associated with seizure outcome after epilepsy surgery (appendix).[1,6–21] Preoperative cognitive functioning was classified as developmental delay if intelligence or developmental quotients were below 70 or if mental retardation was noted but not further specified in the patient files. Invasive EEG recordings included grid or strip implantation, stereo-EEG, or other depth electrodes. Type of surgery was classified as lobar (including tailored) resection, multilobar resection, or hemispherectomy. Lobar resections were subclassified as frontal, temporal, parietal, and occipital. The resection of MRI-confirmed lesions was classified as anatomically complete if the region of the structural abnormality was completely resected according to postoperative MRI scans or histology and incomplete if these examinations suggested residual abnormal tissue. In all other patients, completeness of resection of the anatomical lesion was classified as not determined. Resection of the epileptogenic focus was classified as complete if post-resection intraoperative electrocorticography did not show persistent active spiking with consistent focality, rhythmic features such as trains of fast focal activity, or spiking associated with focal attenuation of background activity,[13] and as incomplete if it showed persistent epileptic activity or if the resection did not include the whole epileptogenic zone, as assessed by preoperative intracranial recordings. In all other patients, completeness of resection of the epileptogenic focus was classified as not determined. Immediate seizure freedom was defined as not having had any seizures since surgery. Delayed seizure freedom was defined as either having had running down seizures (defined as ongoing seizures in the immediate postoperative period that disappear within 2 weeks) or having had seizures over a period of more than 2 weeks after surgery and reaching seizure freedom at least 2 months before the start of AED withdrawal. Subjective determinants of withdrawal, such as AED side-effects, parents insisting on withdrawal, and the treating physician's estimates of surgical success (the chance of reaching seizure freedom) were not consistently documented and could therefore not be analysed.

See Online for appendix

The course of AED withdrawal was divided into the time interval between surgery and start of drug withdrawal (time to reduction [TTR]) and the time interval from surgery to complete discontinuation of AEDs (time to discontinuation [TTD]). The study outcome measures were (1) seizure recurrence during or after AED withdrawal, (2) seizure freedom at final follow-up, defined as seizure freedom without auras for at least 1 year, regardless of AED use (Engel class 1 or International League Against Epilepsy class 1),[22,23] and (3) cure at final follow-up, defined as being seizure free and off AEDs for at least 1 year.

Statistical analysis

Previously identified predictors of seizure outcome[1,6–21] were first tabulated against start and completion of drug withdrawal by Cox proportional hazard regression models to assess which factors were associated with the timing of AED withdrawal and could therefore be deemed potential confounders of the relation between timing and seizure outcome. Second, the crude associations between TTR and TTD and the three outcome measures were analysed by Cox proportional hazard regression models. We then adjusted for the earlier identified potential confounders. Continuous variables were introduced as such in the models; for categorical variables, we both calculated a main effect and created indicator variables. Separate models were used for TTR and TTD because these were highly correlated. Data from patients who did not achieve 12 months of follow-up after the start of drug withdrawal and who remained event-of-interest free were

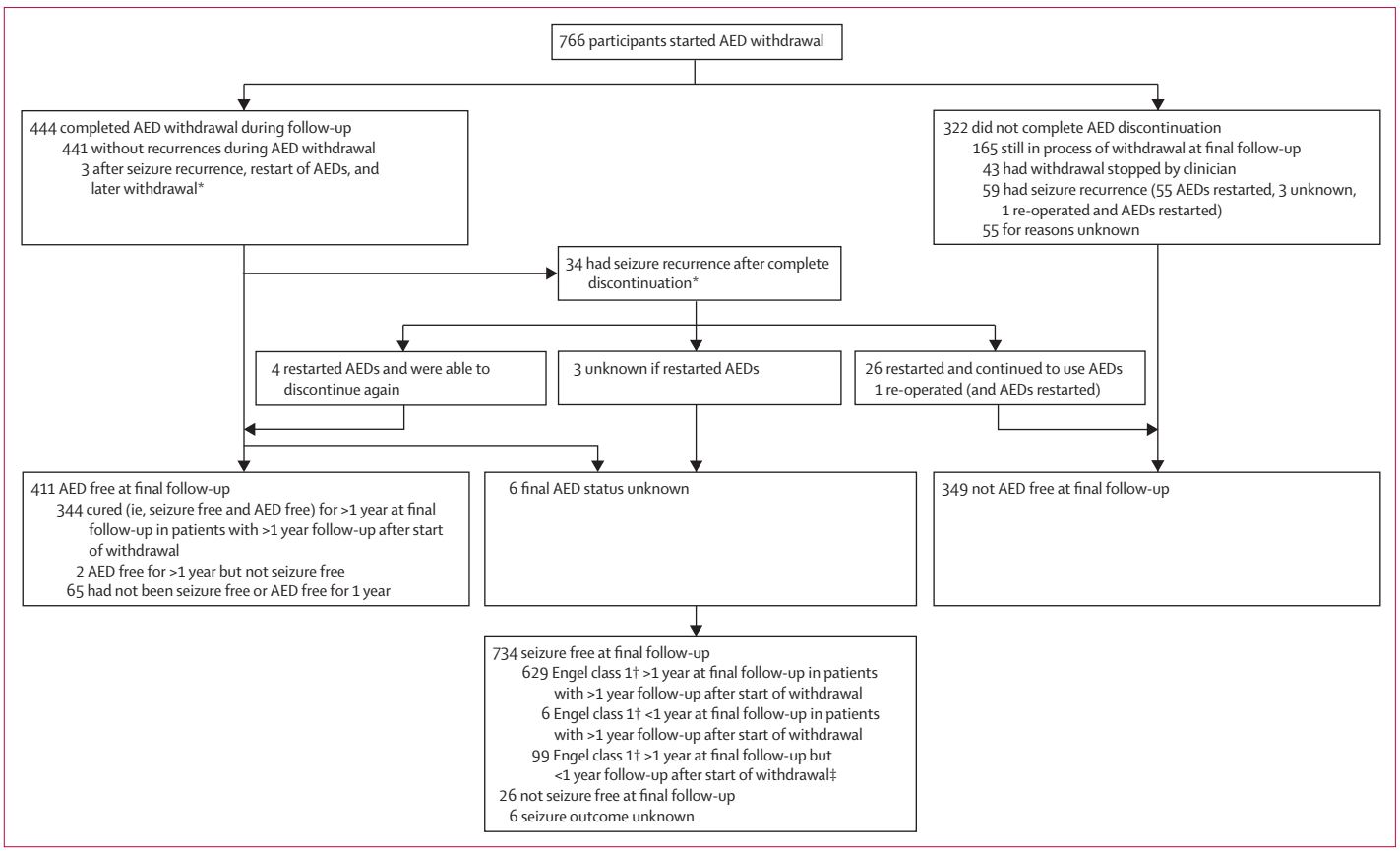

Figure: **Study profile and postoperative AED withdrawal**
AED=antiepileptic drug. *One of the patients had two recurrences, one during AED withdrawal and one after complete AED withdrawal. †Engel class 1 (patients could also have been classified as International League Against Epilepsy class 1): seizure freedom without auras, regardless of AED use. ‡Censored for final outcome measures.

censored 1 year before final follow-up; findings from all other patients were censored at final follow-up. In the group of children with seizure recurrence, we analysed the crude association between time intervals and regain of seizure freedom. We used SPSS Statistics version 17.0. Results are reported as hazard ratios (HRs) with 95% CIs. Additionally, we ran a random effects Cox regression analysis to exclude possible clustering effects within centres that could bias our data, using Stata SE version 11.1. p values were based on two-sided tests with 0·05 as the cutoff level for statistical significance.

Role of the funding source

The sponsor of the study, the Dutch National Epilepsy Fund (NEF 08-10), had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. KB and KPJB had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We included 766 patients in the study. The appendix lists patient characteristics, surgical procedures, and other preoperative and perioperative variables. Mean follow-up time was 61·6 months (SD 29·7, range 12·0–117·4) after surgery, 44·3 months (28·5, 0·3–114·9) after start of drug withdrawal, and 41·6 months (25·9, 0·0–104·9) after complete discontinuation of AEDs. The figure shows the pattern of postoperative AED withdrawal and seizure outcomes. 766 patients started AED reduction; median TTR was 12·5 months (95% CI 11·9–13·2). 62 patients had seizure recurrence during AED withdrawal. 444 (58%) of 766 patients achieved complete discontinuation of drugs; median TTD was 28·8 months (95% CI 27·4–30·2). After complete AED discontinuation, 34 patients had seizure recurrence, one of whom also had a recurrence during AED withdrawal but discontinued the drug afterwards, giving a total of 95 patients (12%) who had seizure recurrence overall. Of the 87 patients who restarted AEDs, 26 (30%) did not regain seizure freedom despite restart of drugs. At latest follow-up, 411 patients were AED free and 349 patients were still on AEDs.

With regard to the long-term outcome measures, at latest follow-up, 629 of 766 patients (82%) were seizure free for more than 1 year and had been followed up for at least 1 year since start of drug withdrawal and 344 (45%) were cured. 32 children (4%) still had seizures (n=26) or had not reached 1 year of seizure freedom (n=6).

	Number	Start of AED withdrawal (n=766)		Complete AED withdrawal (n=444)	
		HR (95% CI)	p value	HR (95% CI)	p value
Multifocal MRI lesions	66/747	0·73 (0·56–0·95)	0·02	0·73 (0·49–1·09)	0·12
Cause of epilepsy*	760	1·00 (0·94–1·06)	0·87	1·06 (0·97–1·16)	0·23
Malformations of cortical development	270	..	..	..	..
Tumour	266	1·00 (0·83–1·21)	0·98	1·38 (1·02–1·87)	0·04
Vascular lesions	87	1·28 (1·00–1·64)	0·06	1·25 (0·84–1·87)	0·27
Hippocampal sclerosis	112	0·92 (0·73–1·15)	0·45	1·12 (0·76–1·67)	0·57
Rasmussen's encephalitis	9	1·26 (0·63–2·51)	0·52	3·68 (1·63–8·30)	<0·0001
Other	16	0·83 (0·46–1·50)	0·54	1·55 (0·67–3·60)	0·31
Number of AEDs used at time of surgery	754	1·30 (1·18–1·43)	<0·0001	0·71 (0·61–0·83)	<0·0001
Type of surgery	754	..	..	1·14 (0·97–1·33)	0·12
Lobar resection	583	..	..	..	..
Hemispherectomy	108	..	..	2·17 (1·43–3·30)	<0·0001
Multilobar resection	63	..	..	0·85 (0·55–1·31)	0·46
Immediate postoperative seizure freedom†	700/757	1·36 (1·01–1·83)	0·05	1·46 (0·96–2·22)	0·08
Previous surgery	35/710	..	..	0·54 (0·30–0·97)	0·04
Postoperative EEG findings	745	1·08 (0·98–1·19)	0·18	1·05 (0·90–1·23)	0·51
No epileptic abnormalities	511	..	..	..	..
Epileptic abnormalities	147	0·80 (0·66–0·98)	0·03	0·63 (0·47–0·83)	<0·0001
No EEG done	87	1·45 (1·13–1·86)	<0·0001	1·30 (0·93–1·81)	0·13
Resection of the anatomical lesion	760	1·08 (0·98–1·19)	0·12	1·14 (0·99–1·30)	0·07
Proven complete resection of the anatomical lesion	507	..	..	..	..
Proven incomplete resection of the anatomical lesion	112	1·02 (0·83–1·27)	0·83	0·87 (0·62–1·20)	0·39
Not determined	141	1·19 (0·97–1·45)	0·10	1·51 (1·14–2·01)	<0·0001

Data were analysed by multivariable Cox regression. For the categorical variables both the main effect of the variable and the effect per category using indicator variables are given. The indicator variable is always the first subcategory shown. Because the other subcategories are compared to this variable no HRs and p values are given. For type of surgery and time to reduction, no multivariable analysis was done because univariable analysis did not show a significant correlation. For categorical variables, numbers of patients are given as the total with data available for that category or by the number in each category; for non-categorical variables, numbers of patients are shown over the total number for whom information was available. AED=antiepileptic drug. HR=hazard ratio. EEG=electroencephalogram. *Malformations of cortical development: focal cortical dysplasia (n=213), hemimegalencephaly (n=20), tuberous sclerosis complex (n=26), other (n=11); tumour: dysembryoplastic neuroepithelial tumour (n=97), ganglioglioma (n=120), astrocytoma (n=32), meningioma (n=2), other (n=15); vascular lesions: ischaemic lesion (n=27), porencephalic cyst (n=31), cavernoma (n=5), Sturge-Weber syndrome (n=15), arteriovenous malformation (n=2), (old) haemorrhage (n=7). †Not having had any seizures since surgery.

Table 1: **Independent predictors of timing of withdrawal**

99 children (13%) had been seizure free for at least 1 year at final follow-up, but data from these patients were censored for analysis of the outcome measures because they had less than 1 year of follow-up since the start of AED withdrawal.

Between the onset of seizures and surgery, children had trialled a mean of 4·5 AEDs (SD 2·4, range 0–15). Immediately before surgery, patients were taking a mean of 1·8 AEDs (0·8, 0–5); two patients were using five AEDs before surgery, 21 were using four, 112 were using three, 305 were using two, 313 were using one, and seven patients were already off AEDs. For six patients the latest number of preoperative AEDs was unknown.

The first drug to be reduced was analysed in relation to the patients who used this specific AED preoperatively. The appendix shows for every AED the percentage of children who withdrew that drug first. The three drugs that were most frequently reduced first were primidone (in 8 of 9 patients using this AED the time of surgery; 89%), vigabatrin (in 34 of 47 patients; 72%), and phenytoin (in 24 of 37 patients; 65%).

Multifocal MRI lesions and epileptic EEG abnormalities decreased the chance of starting AED withdrawal, whereas a high number of AEDs used at time of surgery, immediate postoperative seizure freedom, and no postoperative EEG increased that chance (table 1; appendix). Tumours, Rasmussen's encephalitis, hemispherectomy, and completeness of resection of the anatomical lesion not having been determined increased the chance of achieving complete withdrawal of AEDs, whereas a high number of AEDs used at surgery, previous surgery, and epileptic abnormalities on postoperative EEG decreased the chance of achieving complete withdrawal of AEDs (table 1; appendix).

In table 2, the relation between timing of withdrawal and the three outcome measures—seizure recurrence, seizure freedom, and cure—is given, with separate adjustment for confounders. In the unadjusted analysis, shorter TTR increased the risk of seizure recurrence during or after AED withdrawal by 5% per 3 months. TTR did not correlate with seizure freedom at final follow-up or cure. Shorter TTD increased the risk of

	Seizure recurrences during or after AED withdrawal				Seizure freedom at end of study (Engel class 1 >1 year)				Cure at end of study (Engel class 1 and AED free >1 year)			
	Crude model		Adjusted model*		Crude model		Adjusted model*		Crude model		Adjusted model*	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
TTR (per 3 months)	0·95 (0·90–1·00)	0·05	0·94 (0·89–1·00)	0·05	1·01 (0·93–1·09)	0·91	0·97 (0·89–1·07)	0·55	1·00 (0·97–1·03)	0·96	0·97 (0·97–1·03)	0·84
TTD (per 3 months)	0·91 (0·85–0·98)	0·01	0·90 (0·83–0·98)	0·02	1·04 (0·94–1·14)	0·42	1·03 (0·93–1·14)	0·55	0·99 (0·96–1·03)	0·65	0·98 (0·94–1·02)	0·31

Data were analysed by Cox regression analysis. AED=antiepileptic drug. HR=hazard ratio. TTR=time to start of AED reduction. TTD=time to complete discontinuation of AEDs. *Corrected for number of AEDs used at time of surgery, completeness of resection of the anatomical lesion, postoperative electroencephalogram findings, multifocal MRI lesions, immediate postoperative seizure freedom, previous surgery, cause of epilepsy, and type of surgery.

Table 2: **Adjusted and unadjusted relation between timing of antiepileptic drug withdrawal and seizure outcome measures**

	Seizure recurrence		Regain of seizure freedom		Long-term Engel class 1*		Long-term cure†	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Time to start of AED reduction (per 3 months)								
Multifocal MRI abnormalities	0·87 (0·76–1·01)	0·06	0·87 (0·71–1·06)	0·17	1·02 (0·86–1·21)	0·79	1·03 (0·95–1·12)	0·44
Hemispherectomy	0·96 (0·83–1·11)	0·57	0·72 (0·48–1·07)	0·11	0·87 (0·77–0·99)	0·04	0·96 (0·89–1·03)	0·25
Previous surgery	1·10 (0·94–1·28)	0·24	1·17 (0·96–1·43)	0·11	1·12 (0·64–1·96)	0·70	0·98 (0·88–1·09)	0·69
Epileptic abnormalities on EEG	0·95 (0·87–1·03)	0·21	1·04 (0·94–1·16)	0·45	1·04 (0·91–1·20)	0·57	0·99 (0·94–1·03)	0·58
Incomplete resection of the anatomical lesion	0·97 (0·89–1·06)	0·48	1·03 (0·88–1·21)	0·69	1·05 (0·90–1·21)	0·54	1·03 (0·97–1·09)	0·30
Incomplete resection of the epileptogenic zone	0·76 (0·56–1·03)	0·08	1·22 (0·62–2·40)	0·56	1·28 (0·82–2·00)	0·28	0·97 (0·90–1·06)	0·53
Complete cohort (unadjusted)	0·95 (0·90–1·00)	0·05	0·98 (0·92–1·05)	0·62	1·01 (0·93–1·09)	0·91	1·00 (0·97–1·03)	0·96
Time to complete discontinuation of AEDs (per 3 months)								
Multifocal MRI abnormalities	0·80 (0·60–1·08)	0·15	0·30 (0·02–5·38)	0·41	1·26 (0·82–1·95)	0·29	1·20 (0·97–1·47)	0·09
Hemispherectomy	0·96 (0·79–1·17)	0·69	0·85 (0·63–1·15)	0·30	0·96 (0·80–1·15)	0·64	0·98 (0·91–1·06)	0·59
Previous surgery	0·30 (0·03–2·83)	0·29	..	..	..	..	1·70 (0·98–2·93)	0·06
Epileptic abnormalities on EEG	0·84 (0·71–1·01)	0·06	0·64 (0·29–1·42)	0·27	1·15 (0·91–1·45)	0·24	0·97 (0·90–1·03)	0·30
Incomplete resection of the anatomical lesion	0·93 (0·82–1·04)	0·21	0·89 (0·64–1·24)	0·51	1·04 (0·88–1·23)	0·61	1·02 (0·94–1·11)	0·60
Incomplete resection of the epileptogenic zone	0·79 (0·47–1·33)	0·38	..	..	..	..	0·98 (0·78–1·22)	0·83
Complete cohort (unadjusted)	0·91 (0·85–0·98)	0·01	0·93 (0·83–1·05)	0·26	1·04 (0·94–1·14)	0·42	0·99 (0·96–1·03)	0·65

Crude Cox regression analysis of the relation between timing and seizure outcome measures in the identified high-risk patients. EEG=electroencephalogram. HR=hazard ratio. AED=antiepileptic drug. ..=analyses that could not be undertaken because of small numbers. *Seizure freedom at end of study (Engel class 1 >1 year). †Cure at end of study (Engel class 1 and AED free >1 year).

Table 3: **Relation between timing of AED withdrawal and seizure outcome in subgroups of patients at high risk of recurrence**

seizure recurrence during or after AED withdrawal by 9% per 3 months. TTD did not affect the chance of seizure freedom or cure at final follow-up. Adjustment for potential confounders did not change the risk estimates or significance levels for seizure recurrence during or after AED withdrawal, long-term seizure freedom, or cure. Additional analyses accounting for possible clustering effects within centres did not reveal substantial changes (data not shown). TTR and TTD were not related to the chance of regaining seizure freedom after restart of drug treatment in children who had seizure recurrence during or after withdrawal (crude analysis, n=87; HR 0·98, 95% CI 0·92–1·05, p=0·62; and 0·93, 0·83–1·05, p=0·26 per 3 months, respectively).

The appendix shows how each of the predictors of timing of start and completion of AED withdrawal was associated with the three outcome measures in a multivariable analysis. The risk of seizure recurrence was increased in patients with multifocal MRI lesions, hemispherectomy, epileptic abnormalities on post-operative EEG, incomplete resection of the anatomical lesion, and previous surgery. The chance of reaching seizure freedom at follow-up was decreased in patients who used more AEDs at time of surgery and in patients with incomplete resection of the anatomical lesion. The chance of cure at final follow-up was decreased in children who used more AEDs at time of surgery, with incomplete resection of the anatomical lesion, and with previous surgery and was increased in hemispherectomy patients. For patients who achieved complete withdrawal of drugs, incomplete resection of the anatomical lesion increased the risk for seizure recurrence and decreased the chance of reaching seizure freedom or cure at follow-up, and Rasmussen's encephalitis decreased the chance of reaching cure (appendix).

For each of the identified high-risk groups of patients, we studied the association between timing of AED withdrawal and seizure outcome measures. The only

significant influence of time intervals on seizure outcome was noted in children who underwent hemispherectomy. Their chance of reaching Engel class 1 at follow-up was decreased with later start of withdrawal (HR 0·87, 95% CI 0·77–0·99, p=0·04; table 3). In all other groups of patients with risk factors for unfavourable outcome (multifocal MRI abnormalities, previous surgery, postoperative epileptic EEG abnormalities, and incomplete resection), early withdrawal was not associated with long-term seizure outcome, although later complete discontinuation showed weak evidence of increasing the chance of cure in children with previous surgery (HR 1·70, 95% CI 0·98–2·93, p=0·06).

Discussion

This study confirms that several, but not all, of the known predictors of seizure outcome also determine timing of AED withdrawal. Immediate postoperative seizure freedom had previously been associated with AED reduction.[20] Higher number of AEDs at the time of surgery increased the probability of early withdrawal, possibly suggesting that clinicians were less concerned about the risk of recurrence because of the protective effect of the remaining AEDs or were keen to reduce the high drug load, which is supported by the finding that AEDs with severe side-effects were most often withdrawn first. If surgical success is anticipated, postoperative EEG recordings might not be done, which explains the higher chance of early AED reduction in children in whom no EEG was done. Similarly, for children in whom postoperative EEGs were done, those with epileptic abnormalities started and completed AED withdrawal later.

Complete discontinuation of drug treatment was more likely in patients who underwent hemispherectomy, which is in accordance with the high rate of seizure freedom in this population,[24] showing the complete removal or disconnection of the epileptogenic lesion. Although we expected that in children with complete resection, in whom successful surgery could be anticipated, drug treatment would be withdrawn earlier, incomplete resection of the anatomical lesion was not independently related to timing of withdrawal. One explanation is that completeness of resection is difficult to judge in daily practice and might therefore not have influenced AED withdrawal policy. An alternative explanation is that awareness of this important outcome predictor is relatively recent,[11,13] and many of the patients in our cohort started withdrawal before publication of these findings.

Although shorter TTR and TTD increased the risk of seizure recurrence during the study, timing of withdrawal did not affect the chance of regaining seizure freedom after restart of drugs or of reaching seizure freedom or cure for at least 1 year at final follow-up (panel). Findings from studies in adults have suggested that early discontinuation increases the risk of seizure recurrence.[8,21] In children, the risk of recurrence was increased in those who discontinued AEDs within 6 months compared with those who remained on drug treatment.[7] Less and slower AED withdrawal were the main predictors of seizure freedom 2 years after surgery.[5] Schmidt and colleagues[6] reviewed the published work in adults and showed that delaying discontinuation more than 2 years after surgery did not improve safety. Nowadays, starting withdrawal of AEDs at least 1 year after surgery is regarded safe.[6,7,25] The safety of earlier AED withdrawal is an important point of discussion. We and others have suggested that timing of withdrawal itself does not predict seizure recurrence but that other factors, such as delayed remission after surgery, continuing auras, and completeness of resection, increase the risk for seizure recurrence in patients who withdraw AEDs.[20,26] In this study, we show not only that the risk of seizure recurrence seems to increase with earlier AED withdrawal, but also, and more importantly, that there was no association between timing variables and seizure freedom or cure at final follow-up. These findings support our hypothesis that early AED withdrawal identifies the need for postoperative AEDs earlier in patients who are not completely cured by surgery, without affecting their long-term seizure outcome.

Regain of seizure freedom after restarting drug treatment in children with recurrence was not affected by timing of withdrawal. In adults who withdrew AEDs, seizure freedom rates were higher than in those who continued drug treatment, and seizures that recurred in patients who withdrew were more responsive to AEDs (63%) than those in patients who continued on AEDs (10%), suggesting that seizure reccurence during or after withdrawal might be regarded relatively benign.[27] The rate of regaining seizure freedom (70%) in our study was comparable to previously published data.[7,20,25–27]

The effect of early withdrawal on recurrence risk is partly inherent to the present withdrawal policy in clinical practice; withdrawal of AEDs is generally considered only in patients who are seizure free after surgery. Most recurrences after paediatric epilepsy surgery occur during the first postoperative year.[5,26] The later the decision to start withdrawing AEDs is made, the longer the child has potentially been seizure free and, thus, the longer surgery has been able to prove its success. Therefore, the group of children who withdrew late inevitably consists of fewer patients with incomplete surgical success and has a better prognosis than those who withdrew early after surgery.

In our study cohort, several factors affected seizure outcome. Incomplete resection of the anatomical lesion has previously been identified as one of the most important predictors for unfavourable seizure outcome after surgery.[1,11,13,28] The association between incomplete resection and all outcome measures suggests that AEDs are needed in patients with incomplete surgery to protect them from the epileptogenicity of the remaining lesion. The same notion might be applicable to patients with

Panel: **Research in context**

Systematic review

References for this study were identified through searches of PubMed for articles published between Jan 1, 1980, and June 1, 2012, and were restricted to publications in English. Search terms were "epilepsy surgery", "pediatric" or "paediatric", "outcome", "seizure freedom", "AED", "antiepileptic drugs", "anticonvulsants", "withdrawal", or "discontinuation". A secondary search for missed references was done by reviewing the reference lists of the original articles and published reviews.

Interpretation

Previous publications on postoperative drug withdrawal in children drew conflicting conclusions. Most agreed that tapering off drug treatment after 1 year of postoperative seizure freedom is safe,[7,9,25,26] although others claimed that slow withdrawal of antiepileptic drugs (AEDs) is the most important factor associated with better surgical outcome rates.[5] Drug withdrawal within 1 year of postoperative seizure freedom has been investigated in only small groups and success rates differed between studies.[5,7,9,26] With this study, we provide more insight into the postoperative drug policy in children and its relation to seizure outcome. This study has three clinical messages. First, most of the identified predictors for timing intervals have previously been reported to affect postoperative seizure outcome; anticipation of surgical success thus determines postoperative drug policy. Second, although in this seizure-free postoperative paediatric cohort earlier AED withdrawal increased the risk for seizure recurrence, this increase was not at the cost of seizure freedom or cure in the longer term. Third, the strongest predictor for seizure outcome and cure was incomplete resection of the anatomical lesion; early AED withdrawal seems safe in the group of patients with presumed complete resection of the anatomical lesion.

multifocal MRI lesions, in whom the risk for seizure recurrence was increased. Multifocal MRI lesions have previously been associated with unfavourable outcome.[1,11] In a recent study of patients who had undergone hemispherectomy, significant MRI abnormalities in the remaining hemisphere were associated with unfavourable outcome.[29] Remaining MRI abnormalities seem to harbour epileptic potential, and reduction of AEDs should be done with more caution in these patients. Epileptic abnormalities on postoperative EEG predict seizure recurrence.[12] In clinical practice, EEG has often been used to estimate the risk of recurrence before starting AED reduction in non-surgical cohorts.[30] We now show that epileptic abnormalities on EEG also predict seizure recurrence after epilepsy surgery but not long-term seizure outcome or cure. The total number of AEDs used at time of surgery predicted both seizure freedom and cure. This finding suggests that the more drugs trialled, the more refractory the epilepsy and the less the chance of surgical success.

The rate of cure at final follow-up was 45% (344 of 766), which is higher than that reported 5 years after surgery in the cohort of Hemb and colleagues (36%; 27 of 75).[5] In their study, seizure freedom at 2 years after surgery was more frequent in patients who underwent surgery after 1997 compared with those who underwent surgery before 1997. However, the number of seizure-free children who were off AEDs after 2 years was significantly lower in the more recently operated patients, leading to a lower cure rate (24%; 27 of 113) than the pre-1997 cohort (53%; 44 of 83). At 5 years after surgery, seizure freedom rates were still significantly higher in the post-1997 group, but cure rates (36%; 27 of 75) were similar to those in the pre-1997 cohort (44%; 27 of 61). Hemb and colleagues' findings[5] support the hypothesis that AED withdrawal does not affect long-term outcome.

Our study has several limitations. First, as agreed by the study group, only patients who withdrew AEDs after having reached postoperative seizure freedom were included in the study. In this selected subgroup of children, surgical success was anticipated and unfavourable predictors of postoperative seizure outcome were expected to be less common than in the total group of children who undergo epilepsy surgery. Therefore, the results of this study cannot be extrapolated to all children who undergo epilepsy surgery. Although early withdrawal of AEDs did not significantly affect long-term seizure outcome in the total cohort of children, or in subgroups of high-risk patients (table 3), further prospective studies are warranted to establish to what extent early withdrawal influences long-term seizure status in children who are particularly at risk for unfavourable outcome.

Second, timing of withdrawal probably largely depends on subjective factors, such as the individual preference of treating physicians, side-effects of the drug, and the request of parents to discontinue AEDs. Unfortunately, these factors were not documented systematically in the patient files and therefore their effect on withdrawal decisions could not be investigated.

Third, since we included only patients who achieved postoperative seizure freedom and withdrew AEDs, the predictors of seizure outcome identified here are applicable only to children in whom AEDs are tapered postoperatively. Nevertheless, our findings on outcome predictors are similar to those in studies that investigated determinants of outcome in general surgical cohorts.

In this large collaborative study we found that early withdrawal of drug treatment unmasked incomplete surgical success and AED dependency sooner, but not at the cost of long-term seizure outcome. Unnecessary long-term continuation of drugs can be prevented in a large number of children when starting withdrawal of drugs early after surgery. Those who need continued medical treatment will be identified earlier, with the same chance of regaining seizure freedom as they would have had when AEDs were withdrawn late. The implications of our study cannot be extrapolated to adults, in whom the possibly increased relapse rate associated with early AED withdrawal has a greater effect than in children, because it can lead to temporary suspension of the patient's driving licence, stigmatisation, and detrimental effects on professional careers. However, for children, the slightly increased risk of recurrences and their consequences does not, in our opinion, outweigh the well known neurocognitive side-effects of AEDs,[3,4,31] and early AED withdrawal might have cognitive benefits. The findings of this study justify the undertaking

of a future randomised controlled trial to study the possible benefits and confirm the safety of early AED withdrawal after epilepsy surgery in children.

Contributors

KB collected the data, wrote the manuscript, and did the statistical analysis. AA, JHC, TP, and OvN contributed data and commented on and amended the content of the manuscript. CSPMU commented on the manuscript and supervised the statistical analysis. KPJB contributed data, commented on and amended the content of the manuscript, assisted with the statistical analysis, and supervised the study.

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Conflicts of interest

In the past 36 months, AA has received speaker's or consultancy fees or research grants, or both, from Cyberonics, Eisai, GlaxoSmithKline, Pfizer, Sanofi-Aventis, Schwartz Pharma, UCB Pharma, and Valeant. In the past 5 years, JHC has received speaker's or consultancy fees or research grants, or both, from Eisai, GlaxoSmithKline, Sanofi, and UCB. In the past 36 months, TP has received speaker's or consultancy fees from Eisai, Desitin, and UCB. KB, CSPMU, OvN, and KPJB declare that they have no conflicts of interest.

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