Review article

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Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors

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ABSTRACT – *Aim.* Many seizure-free patients consider withdrawal of antiepileptic drugs, both when seizure control is achieved by medication alone, or once they became seizure-free following epilepsy surgery. The risk of recurrence is consequently of very important prognostic value. However, estimations of recurrence risks are outdated for both populations. In addition, although many publications have reported predictors of seizure relapse, no comprehensive overview of prognostic factors is available.

Methods. A systematic review of the databases of PubMed and EMBASE was conducted, identifying articles on antiepileptic drug withdrawal in patient cohorts. Recurrence risk meta-analyses were performed for both populations at one, two, three to four, and five or more years of follow-up. Within the selected articles, studies presenting multivariable analysis of predictors were identified; all studied predictors were listed, as well as all significant independent predictors. The quality of separate analyses of predictors was assessed.

Results. There was no significant difference of long-term cumulative recurrence risk between surgical and medication-only populations, with respectively 29% and 34% recurrences. In medication-only treated patients, 25 factors have been reported as significant independent predictors; 12 have been reported in surgical cohorts. The quality of most analyses of predictors was low to moderate. No predictor was consistently found among all analyses, and for most predictors, study results were contradictory.

Conclusion. No consistent set of predictors could be identified because a large number of variables have been identified in the literature, many

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studies reported contradicting results, study populations varied considerably, and the quality of the original studies was often low. Meta-analysis of individual participant data is necessary, because it allows for (1) correction for differences in follow-up duration between subjects and studies, (2) a study of interaction effects, (3) calculation of more accurate estimates valid across several populations, and (4) the assessment of each predictor's effect size.

Key words: AED withdrawal, meta-analysis, predictors, recurrence, systematic review

Although antiepileptic drugs (AEDs) provide seizure freedom for the majority of people with epilepsy, nine out of ten patients experience at least one of the wide range of possible adverse effects (Perucca *et al.*, 2009). A long-term follow-up study of childhood epilepsy showed that patients who became completely AED-free had a higher quality of life (QOL) than those continuing AED treatment, independently of being in remission or not (Sillanpaa *et al.*, 2004). An important consideration for patients who become seizure-free, following either medical or surgical treatment, is whether or not an attempt should be made to stop AED treatment, with the risk of seizure recurrence. The significance of this decision is supported by the many reviews written on the subject (Berg and Shinnar, 1994; Shinnar and Berg, 1995; Buna, 1998; Greenwood and Tennison, 1999; Verrotti *et al.*, 2003; Specchio and Beghi, 2004; Shih and Ochoa, 2009; Beghi and Schmidt, 2013; Braun and Schmidt, 2014). While the benefits of stopping AED treatment are clear, safety is a much debated issue. Previous meta-analyses have addressed seizure recurrence risks of AED discontinuation in medically treated (Berg and Shinnar, 1994) and surgically treated patients (Ladino *et al.*, 2014). In the first study, cumulative recurrence rates at one and two years following start of withdrawal were 25% and 29%, respectively. Relapse rates at later time points were not provided. In the pooled analysis of postoperative withdrawal studies, 708 of 2,901 patients (24.4%) who withdrew AEDs had a seizure recurrence (Ladino *et al.*, 2014). Follow-up duration, however, was not accounted for. These studies did not systematically review the available evidence on predictors of seizure relapse. The independent predictive value of many clinical variables that have previously been reported to relate to seizure relapse remains debated, since studies have often revealed opposing results. When reviewing the available literature, the selection of studies referred to will therefore determine the conclusions reached by the reviewer. As an example, the predictive value of an EEG evaluation before the start of AED withdrawal is acknowledged by most authors but questioned in two articles (Verrotti *et al.*, 2003; Specchio and Beghi, 2004). The first objective of this study was to systematically review the literature and provide an updated meta-analysis of all available data in order to compare recurrence rates at different time intervals, including longer-term follow-up, after the start of AED reduction between two distinct populations: patients who became seizure-free with AEDs only (medically treated) and those who reached seizure freedom after epilepsy surgery (surgically treated). Second, we present an overview of possible predictors of seizure recurrence after AED withdrawal in both populations, as a first step towards an evidence-based estimation of recurrence risk in the individual patient.

Methods

Study selection

Studies were selected based on two steps: first, articles were selected for meta-analysis of recurrence rates, after which all included articles were screened for the analysis of predictors of seizure outcome.

To be eligible for inclusion in the meta-analysis of recurrence risks, manuscripts were required to be an original English full-text publication reporting a population of seizure-free epilepsy patients who attempted AED withdrawal. Both populations of medically treated and surgically treated patients were included (but analysed separately). The outcome of interest was seizure recurrence during or after AED withdrawal. Both retrospective and prospective observational studies were included, as well as randomized-controlled trials (RCTs). Excluded were case series and studies with <20 patients, cohorts that reinstituted AED therapy after an abnormal EEG (without having had a prior relapse), and publications on AED withdrawal in acute symptomatic seizures, neonatal seizures, or other populations that included patients not conforming to the 2014 ILAE definition of epilepsy (Fisher *et al.*, 2014) (which includes the 1993 definition of at least two unprovoked seizures occurring 24 hours apart [ILAE, 1993]).

The databases of PubMed and EMBASE were used until November 6, 2014; the full search string can be found in appendix 1. Duplicates were removed, after which two independent researchers (HJL and KG) screened the articles for eligibility based on above-mentioned criteria. All eligible articles were included in the meta-analysis, reference lists were checked for additional articles missed in the electronic search, and the articles were subsequently screened for the presence of multivariable analysis of risk factors for recurrence for inclusion in the systematic review.

Data collection

Full-text articles were screened by the first author to extract information on the following study characteristics and variables of interest: authors; publication year; geographical location; setting; publication type and in case of RCTs, the treatment and control groups; treatment (surgical versus medical); inclusion and exclusion criteria; number of participants; number of recurrences at one, two, three, four, and five or more years when available; duration of follow-up after start withdrawal (and, in some studies after surgery); predictors of seizure recurrence; potential for bias (see below); number of prognostic factors studied; and number and type of prognostic factors that were found to be significantly related to relapse.

Summary measures and risk of bias

A single group meta-analysis on recurrence risk after AED withdrawal was performed for both populations with different follow-up durations. Because less than half of studies on medical cohorts, and less than a third of studies on surgical cohorts, reported information on three- or four-year recurrence rates separately, these two follow-up times were combined, and when both were provided, the four-year recurrence rate was used. Similarly, the recurrence risks of all studies with follow-up of five or more years were averaged. To correct for differences in study sample size, meta-analysis was performed on the logit of the proportion of recurrence (logit=log[p/1-p], with variance[logit]=[1/number of recurrences]+[1/number of non-recurrences], where p equals the proportion of recurrences), according to Sutton *et al.* (2000). To correct for potential heterogeneity between studies, the meta-analysis was performed with a linear random effects model and additional Knapp and Hartung adjustments to obtain more accurate confidence intervals (Knapp and Hartung, 2003). Meta-analysis summary estimates and corresponding 95% confidence intervals were back-transformed from logits to proportions.

Heterogeneity between studies was assessed with the I^2 statistic according to Higgins and Thompson, where values between 50% and 75% are considered measures of moderate heterogeneity, and values >75% high heterogeneity (Higgins and Thompson, 2002). Statistical analyses were performed with R version 3.1.2 (R Core Team, 2014), using packages "metaphor" and "boot".

In the surgical cohorts, the main meta-analysis included only those studies reporting follow-up after initiation of withdrawal (six studies). Studies that only reported follow-up relapse rates in relation to duration after surgery (ten studies) were excluded from the primary analysis, because the interval between surgery and AED withdrawal varied between subjects and studies. An additional analysis on studies that reported follow-up after surgery is shown as supplementary information.

Considering the systematic review of predictors of relapse, we compared, for each possible predictor, the number of studies that reported a significant correlation with relapse with the total number of studies that included the variable in the analysis. The possibility to meta-analyse the separate prognostic factors was evaluated, but many articles did not present data on non-significant predictors, resulting in a large publication bias rendering any result from meta-analysis unusable for solid conclusions. Therefore, the choice was made to perform a descriptive systematic review instead.

Quality appraisal and assessment of risk of bias of each study was performed with the Quality in Prognosis Studies (QUIPS) method proposed by Hayden and colleagues (Hayden *et al.*, 2006). Six separate items are scored in this assessment: potential for bias in (1) study participation, (2) study attrition (loss to follow-up), (3) measurement of prognostic factors, (4) measurement of outcome, (5) measurement of, and accounting for, confounders, and (6) analysis and reporting. Since this is a descriptive systematic review of prognostic factors, no studies were excluded based on quality assessment.

Results

From 2,588 articles identified, 61 articles were included in the meta-analysis, of which 45 (7,082 patients) concerned medically treated patients (Emerson *et al.*, 1981; Holowach-Thurston *et al.*, 1982; Shinnar *et al.*, 1985; Overweg *et al.*, 1987; Arts *et al.*, 1988; Callaghan *et al.*, 1988; Alvarez, 1989; Ehrhardt and Forsythe, 1989; Matricardi *et al.*, 1989; MRC, 1991; Gherpelli *et al.*, 1992; Galimberti *et al.*, 1993; Shinnar *et al.*, 1994; Tennison *et al.*, 1994; Uesugi *et al.*, 1994; Delgado *et al.*, 1996; Dooley *et al.*, 1996; Tinuper *et al.*, 1996; Braathen and Melander, 1997; Caviedes and Herranz, 1998; Marcus, 1998; Altunbasak *et al.*, 1999; Gebremariam *et al.*, 1999; Verrotti *et al.*, 2000a; Verrotti *et al.*, 2000b; Bouma *et al.*, 2002; Lamdhade and Taori, 2002; Specchio *et al.*, 2002; Cardoso *et al.*, 2003; Ohta *et al.*, 2004; Camfield and Camfield, 2005; Geerts *et al.*, 2005; Serra *et al.*, 2005; Sillanpaa and Schmidt, 2006; Lossius *et al.*, 2008; Olmez *et al.*, 2009; Ramos-Lizana *et al.*, 2010; Vurucu

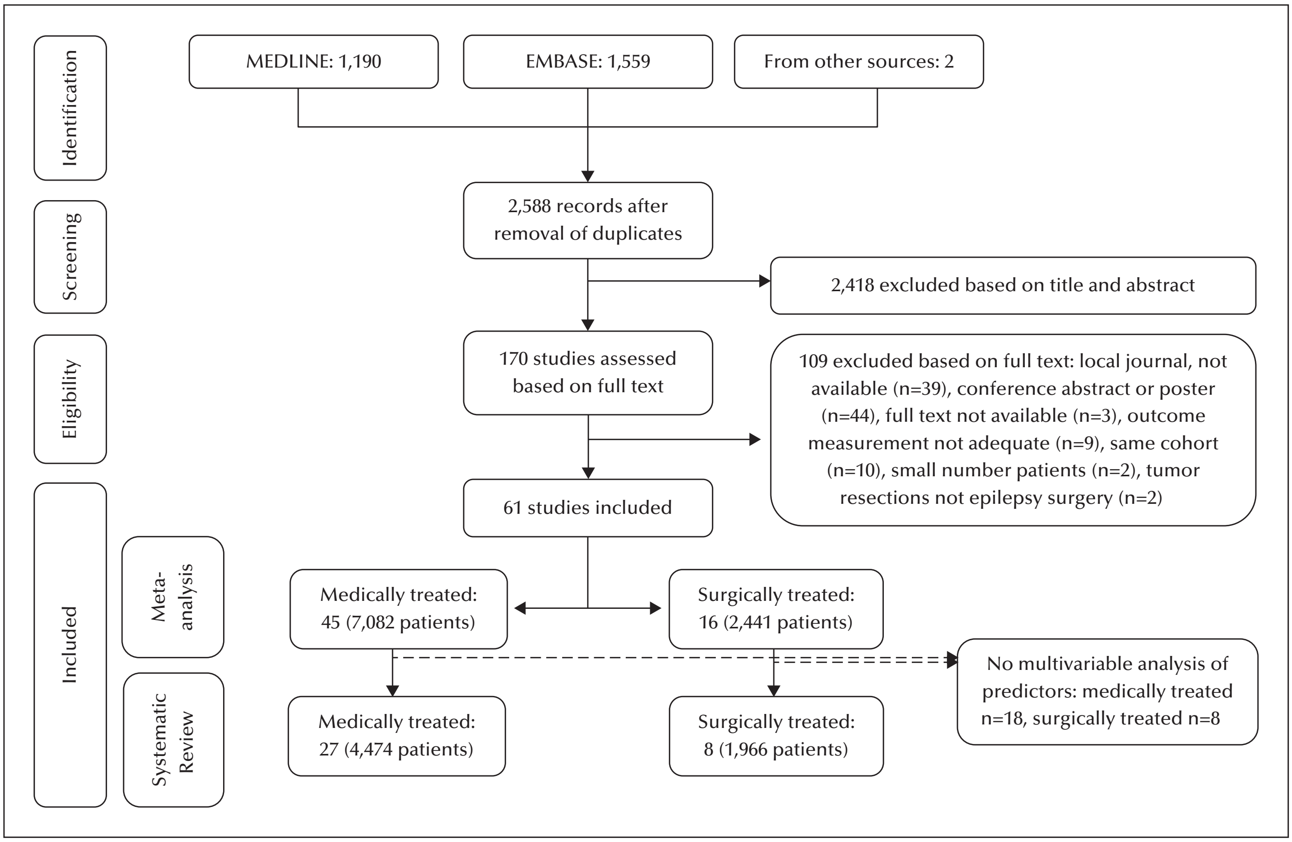

Figure 1. Flow-chart of selection of publications.

et al., 2010; Afshari and Moradian, 2012; Pavlovic *et al.*, 2012; Verrotti *et al.*, 2012; Su *et al.*, 2013; Yang *et al.*, 2013; Gafoor *et al.*, 2014; Li *et al.*, 2014), and 16 (2,441 patients) surgical cohorts (Murro *et al.*, 1991; Schiller *et al.*, 2000; Griffin *et al.*, 2004; Kim *et al.*, 2005; Berg *et al.*, 2006; Al-Kaylani *et al.*, 2007; Sinclair *et al.*, 2007; Lachhwani *et al.*, 2008; Lee *et al.*, 2008; Kerling *et al.*, 2009; Park *et al.*, 2010; Rathore *et al.*, 2011; Boshuisen *et al.*, 2012; Menon *et al.*, 2012; Zeng *et al.*, 2012; Yardi *et al.*, 2014) (see *figure 1* for full flow chart). A multivariable analysis of prognostic variables was performed in 27 studies on medically treated patients and in eight studies on surgical cohorts.

Meta-analysis of recurrence risk (*table 1*, *figure 2*)

Meta-analysis was performed on different subsets of articles, depending on the availability of data for the specific duration of follow-up (*e.g.* 36 medical cohorts with one-year follow-up data, see *table 1*).

In medically treated patients, the cumulative recurrence rate climbed from 22% (95% confidence interval [CI] 19%-26%) at one year, to 28% (24%-32%) at two years, and 34% (28%-40%) at three or four years. At five or more years of follow-up, the cumulative recurrence rate taken from 19 articles was lower, with an average of 27% (23%-32%). Subgroup analysis of articles providing information on recurrences both at three to four years and at five or more years of follow-up, showed that recurrences after five years only occurred in less than 1% (*supplementary table 1*). The heterogeneity between studies was high, with I^2 between 87% and 92% at different follow-up durations.

The cumulative recurrence rate in surgical cohorts increased from 14% (4%-37%) at one year after initiation of AED withdrawal, to 21% (8%-45%) at two years, 24% (13%-42%) at three to four years, and 29% (0%-100%) at five or more years. Six studies (1,172 patients) reported follow-up starting at the initiation of AED withdrawal and 11 studies (1,303 patients) started follow-up at surgery (one article reported both follow-up after surgery and after AED withdrawal). Meta-analysis of recurrence rates after AED withdrawal in these latter 11 articles is presented in *supplementary table 2*. Heterogeneity between studies was high, with I^2 of 88% to 94%.

At all time points, there was no significant difference between the surgical and medical cohorts, but average recurrence rates were lower in surgical cohorts. Within the medical cohorts, 66% of recurrences occurred in the first year of follow-up. For surgical cohorts, this was 48%.

Table 1. Meta-analysis of recurrence risk after AED withdrawal. Separate meta-analyses were performed for the different follow-up durations. Follow-up started at initiation of AED withdrawal. If a study provided information on e.g. one-year and five-year seizure outcome, it was only included in these two meta-analyses.

Follow-up after start of withdrawal		No. studies (no. patients)	Recurrence risk (95% CI)	Heterogeneity I^2 (95% CI)
Medical cohorts (45 studies; 7,082 patients)	1 year	36 (5,215)	22.1% (18.7-26.0)	88.8 (82.3-93.5)
	2 years	35 (5,283)	27.5% (23.7-31.6)	89.0 (82.5-93.5)
	3 or 4 years	26 (3,697)	33.7% (28.1-39.8)	91.5 (85.8-95.8)
	5 or more years	19 (3,653)	27.2% (22.8-32.2)	87.3 (77.5-94.5)
Surgical cohorts (6 studies; 1,172 patients)	1 year	5 (1,115)	13.7% (4.1-37.0)	94.1 (83.0-99.2)
	2 years	5 (1,115)	21.0% (7.9-45.3)	94.4 (84.2-99.3)
	3 or 4 years	5 (1,025)	24.1% (12.5-41.6)	88.4 (67.5-98.4)
	5 or more years	2 (913)	28.5% (0.0-100.0)	88.4 (0.7-98.4)

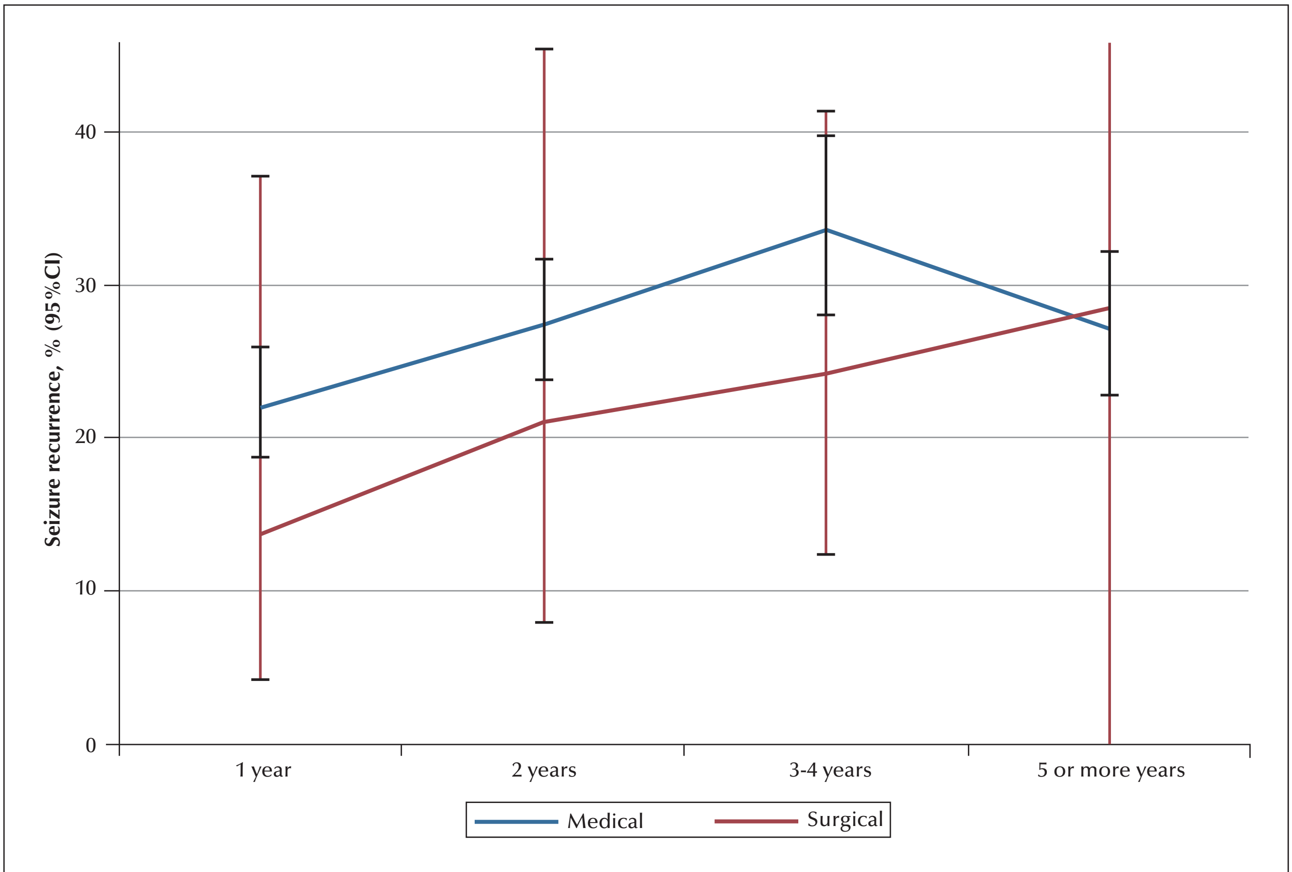

Figure 2. Cumulative recurrence risk after AED withdrawal in medical and surgical cohorts. Error bars indicate 95% confidence interval. See *table 1* for exact recurrence rates with 95% CI.

Study characteristics

For the systematic review of predictors, study characteristics, seizure recurrences, and number of prognostic factors studied are listed in *tables 2 and 3*. In almost all cohorts of medically treated patients, a minimum of two years of seizure freedom was required before considering AED withdrawal, whereas this ranged from no minimum to a minimum of one year in the surgical articles. Clinical characteristics of included patients varied largely between cohorts, as evident from the different inclusion and exclusion criteria.

Table 2. Characteristics of medically treated cohort studies.

Reference	Population - study design	Minimal seizure freedom (years)	Inclusion / exclusion criteria	No. subjects	No. of patients with seizure recurrence (%)	Follow-up (months)	Factors significant/ studied
Li, 2014	A&C – pro	2	-	162	37 (22.8%)	mean 29	1/8
Su, 2013	A&C – pro	2	in: - ex: specific seizure types/ syndromes (absence, myoclonic seizures, atonic seizures, LGS, West, JME, BECTS), progressive disease or systemic illness, pregnant or lactating	86	43 (50.0%)	mean 25	1/14
Pavlovic, 2012	A&C – retro	2	in: cryptogenic focal epilepsy, age onset<16 years ex: follow-up <2 years	52	19 (36.5%)	median 48	4/15
Verrotti, 2012	C – pro	2	in: age onset <15 years ex: neonatal onset, BECTS, abnormal neurological findings, developmental delay	168	48 (28.6%)	mean 126	3/7
Ramos-Lizana, 2010	C – pro	2	in: age onset <14 with new-onset epilepsy ex: metabolic cause, neurodegenerative disorder, previous AED treatment	216	56 (25.9%)	mean 59	4/16
Vurucu, 2010	C – retro	2	in: - ex: follow-up <2 years	266	51 (19.2%)	minimum 24	1/12
Olmez, 2009	C – retro	2	in: age at onset <15 years ex: neonatal onset, follow-up <1 year	200	54 (27.0%)	mean 40	2/19
Lossius, 2008	A – RCT: withdrawal versus non-withdrawal	2	in: age 18-67 years, in case of unsuccessful prior withdrawal attempt 5 years of seizure freedom ex: polytherapy, JME, epileptiform EEG in patients with primary generalized epilepsy, >1 prior withdrawal attempt, pregnant or seeking pregnancy, intellectual disability, progressive neurological disease, other serious disease, co-medication	72	11 (15.3%)	median 47	2/8

Table 2. (*Continued*).

Reference	Population - study design	Minimal seizure freedom (years)	Inclusion / exclusion criteria	No. subjects	No. of patients with seizure recurrence (%)	Follow-up (months)	Factors significant/ studied
Ohta, 2004	C – retro	3	in: age at onset <15, cryptogenic localization-related epilepsies ex: follow-up <5 years, epileptiform EEG prior to withdrawal	82	8 (9.8%)	mean 55	2/12
Cardoso, 2003	A&C – RCT: reduction versus complete discontinu-ation	2	in: partial or GTCS, age at inclusion 14 years or more ex: idiopathic epilepsies, polytherapy	45	14 (31.1%)	protocolised 24	1/13
Specchio, 2002	A&C – pro	2	in: - ex: polytherapy	225	113 (50.2%)	mean 48	4/7
Altunbasak, 1999	C – retro	2	in: - ex: progressive CNS disorder, any inborn error of metabolism or febrile convulsion	97	20 (20.6%)	range 24-48	2/12
Caviedes and Herranz, 1998	C – retro	2	-	226	55 (24.3%)	mean 70	6/7
Peters, 1998	C – RCT, 6 months treatment versus 12 months treatment	0.5	in: - ex: progressive neurological disorder, JME, infantile spasms, photosensitivity	161	84 (52.2%)	protocolised 48	3/14
Braathen and Melander, 1997	C – RCT: 1 year AED treatment versus 3 years AED treatment	1	in: - ex: major neurologic disability, mental retardation, infantile spasms, LGS, previous AED treatment	161	60 (37.3%)	mean 70	4/20
Dooley, 1996	C - pro	1	in: - ex: polytherapy, JME	97	38 (39.2%)	mean 32	4/16

Table 2. (*Continued*).

Reference	Population - study design	Minimal seizure freedom (years)	Inclusion / exclusion criteria	No. subjects	No. of patients with seizure recurrence (%)	Follow-up (months)	Factors significant/ studied
Shinnar, 1994	C - pro	1	-	264	95 (36.0%)	mean 58	5/17
Galimberti, 1993	A&C - pro	2	in: - ex: idiopathic partial epilepsy	136	71 (52.2%)	mean 38	3/5
MRC, 1993	A&C – RCT: withdrawal versus no withdrawal	2	in: - ex: progressive neurological disorder	510	221 (43.3%)	median 36	7/22
Matricardi, 1989	C- pro	2	-	446	71 (15.9%)	mean 96	5/9
Arts, 1988	C - retro	2	in: - ex: abnormal EEG	146	37 (25.3%)	mean 52	5/10
Callaghan, 1988	A&C - pro	2	in: - ex: polytherapy	92	31 (33.7%)	mean 26	4/11
Bouma, 1987	C - retro	2	in: age onset <17 years ex: seizure free >2.5 years	198	40 (20.2%)	median 71	1/14
Overweg, 1987	A - pro	3	in: age < 60 years ex: IQ<70, neurological deficit, psychiatric disorder, pregnancy, somatic disease	62	41 (66.1%)	not reported	3/5
Shinnar, 1985	C - pro	2	in: - ex: seizure free >4 years	88	22 (25.0%)	mean 22	4/7
Holowach-Thurston, 1982	C - pro	4	-	148	41 (27.7%)	minimum 216	5/13
Emerson, 1981	C - retro	4	-	68	18 (26.5%)	mean 32	2/14

MRC Medical Research Council Antiepileptic Drug Withdrawal Study Group; A: adults; C: children (in most studies: age at withdrawal, sometimes age at onset of epilepsy); Pro: prospective study; Retro: retrospective study; RCT: randomized controlled trial; LGS: Lennox-Gastaut syndrome; JME: juvenile myoclonic epilepsy; BECTS: benign childhood epilepsy with centro-temporal spikes; SR: seizure recurrences.

Table 3. Characteristics of surgical cohort studies.

Reference	Population -study design	Minimal seizure freedom (years)	Inclusion / exclusion criteria	No. subjects	N SR (%)	Follow-up (months)	Factors significant/ studied
Yardi, 2014	A&C – retro	-	in: temporal lobe epilepsy surgery ex: -	380	112 (29.5%)	mean*55	2/?
Boshuisen, 2012	C - retro	-	in: age at withdrawal <18 years ex: <1 year postoperative follow-up, continuing postoperative seizures (including auras)	766	95 (12.4%)	mean 62	6/9
Menon, 2012	A&C - retro	0.25	in: extratemporal surgery ex: hemispherectomy, temporal surgery only	94	44 (46.8%)	mean*55	2/13
Rathore, 2011	A&C - pro	0.25	in: anterior temporal lobectomy for mesial temporal lobe epilepsy ex: neoplasms, vascular malformations	258	64 (24.8%)	mean*96	2/5
Park, 2010	A&C - retro	-	in: neocortical resection ex: reoperation	147	78 (53.1%)	mean 73	4/13
Lachhwani, 2008	C - retro	0.5	in: age at surgery <18 years ex: follow-up <12 months after discontinuation	68	11 (16.2%)	median*37	0/6
Lee, 2008	A&C - retro	0.1	in: anterior temporal lobectomy ex: neocortical lesions, bilateral hippocampal lesions, critical incongruent ictal semiology or ictal EEG findings	124	65 (52.4%)	mean*69	4/13
Berg, 2006	A&C - pro	1	in: age at surgery >=12 years ex: >=3 AEDs at time withdrawal, previous epilepsy surgery	129	41 (31.8%)	not reported	1/11

A: adults; C: children (in most studies: age at withdrawal, sometimes age at onset of epilepsy);
Pro: prospective study; Retro: retrospective study; SR: seizure recurrences.
*follow-up from surgery, not from initiation of AED withdrawal.

Follow-up duration ranged from 22 to 216 months (median 48) after start of AED withdrawal in medically treated patients, and between 12 and 73 (median 61) after start of withdrawal in surgically treated patients and between 24 and 96 (median 58) months since surgery.

Quality assessment

The articles that presented prognostic factors were assessed for potential bias. The quality was low to moderate in the majority of articles, as summarized in *supplementary table 3*. In most studies, the potential for bias in confounding measurement and account, and in analysis and reporting, was scored as moderate to high. In almost all articles, exploratory analyses were performed, in which the selection of variables into the multivariable model depended on the dataset and not on previous studies of prognostic factors. Because many of the potential predictors (or confounders) were not systematically included in each multivariable analysis, this increases potential for bias in confounding measurement and account (Hayden *et al.*, 2006). The potential for bias in analysis and report is largely explained by the low number of included patients in most studies, compared to the large number of factors studied, resulting in low statistical power which leads to underestimation or false representation of predictive factors (Harrell *et al.*, 1996). Another reason for this large bias is that many articles did not fully report the results. In general, most articles had one or more flaws that increased the risk for bias, decreasing the scientific reliability of each of the individual studies.

Prognostic factors

Tables 4 and 5 list all variables that have been studied as possible risk factors for recurrence. The second column summarizes the number of studies in which a significant predictive value for a certain factor was identified compared to the number of studies that investigated the factor of interest. For example, 21 studies investigated the predictive value of female sex, and four concluded that this was a significant independent predictor for seizure recurrence.

In medically treated patients, 25 variables have been reported as significant independent predictors by at least one study, and 12 variables in surgical cohorts.

Prediction models

In addition to identification of predictors, some publications have created a clinical prediction model (Overweg *et al.*, 1987; MRC, 1993; Dooley *et al.*, 1996; Braathen and Melander, 1997; Geerts *et al.*, 2005). These five models are compared in *table 6*, two of which reported c-statistics (0.73 and 0.78) (MRC, 1993; Geerts *et al.*, 2005). The populations vary (see also *table 2*), largely with respect to the inclusion of children or adults, the inclusion of subjects with mental or neurological impairment, and the required duration of seizure freedom. Therefore, most models are only applicable in highly specific populations; a general population with children and adults was used only in the model from the Medical Research Council (MRC, 1993), although this model was built both on patients who withdrew AEDs and on those who continued AED treatment. There was no single predictive variable that was included in all models.

Discussion

In this meta-analysis, the maximum cumulative recurrence risk at five or more years following the start of reduction was 34% in medically treated patients, and 29% in surgical cohorts. It can be concluded from the quality appraisal of studies that there is a moderate to high chance of bias (and therefore non-representative results) in most of the articles that reported on predictive factors of relapse. Concerning the existing prediction models on recurrence risk after AED withdrawal, we observed that no single predictor variable was included in each of the five models.

Recurrence rates

The presented recurrence rates for medically treated patients roughly resemble the outcome of a 20-year-old meta-analysis (Berg and Shinnar, 1994) in which one-year and two-year recurrence rates of 25% (95% CI: 21%-30%) and 29% (24%-34%) were reported, respectively, which is only a few per cent higher than the results presented here. The current analysis adds longer-term seizure outcomes at three to four, and five or more years, revealing that seizures can recur after an interval longer than two years following the start of AED withdrawal, although this only happens in 6% of patients. Because our meta-analysis includes all available studies on recurrence risk after AED withdrawal until 2014, the average recurrence risks of 22% at one year, 28% at two years, and 34% at three or four years are the most accurate estimate currently available.

Seizure outcomes after AED withdrawal in surgical cohorts have recently been reviewed by Ladino *et al.* (Ladino *et al.*, 2014). Despite the comprehensive overview given, results are difficult to interpret, most importantly because the included articles had such a large range of follow-up durations, and only the recurrence rate at latest follow-up was used in their analysis. Cumulative relapse rates at specific time points were not provided. We therefore chose to determine the recurrence risk at different follow-up durations. We also used different inclusion criteria than those of Ladino *et al.* (2014), excluding more articles from analysis, such as those describing only cohorts of patients who primarily underwent tumour resections.

Table 4. Risk factors for relapse in medically treated patients, showing significant findings based on multivariable models. Non-significant predictors that were only investigated by a single study were: age at initiation of treatment, time from first to second seizure, history of brain trauma, changes in seizure pattern over time, seizures only on awakening, seizures only while asleep, epilepsy severity, history of febrile seizures in patients with previously afebrile seizures, compliance, and previously attempted AED withdrawal. Correlations with different ethnic groups were studied in two articles and not found to be significant.

Predictor	No. of studies showing significance/total no. of studies	References of significant findings
Patient		
Female sex	4/21	1-4
Age and Time		
Age at onset	8/22	2, 5-11
Age at withdrawal	4/13	4, 12-14
Age at last seizure	1/2	15
Time from first seizure to start of treatment	0/6	
Time to seizure control (start of treatment to last seizure)	3/12	6, 16, 17
Time from first seizure to last seizure (duration of active disease)	1/8	18
Time from start of treatment to AED reduction (duration of therapy)	2/6	11, 19
Time from last seizure to start of AED reduction (duration of seizure freedom)	3/10	13, 14, 18
Diagnostics		
Neuroimaging (CT/MRI)	0/8	
EEG abnormality before withdrawal	8/21	9-11, 13, 19-21
EEG abnormality or aggravation during/after withdrawal	7/9	3, 4, 9, 14, 21-23
Aetiology		
Remote symptomatic aetiology*	3/13	1, 8, 24
Neurological deficit from clinical examination	6/13	1, 2, 12, 17, 21, 25
Developmental delay	4/12	10, 12, 17, 21
History of perinatal anoxia	0/3	

Table 4. *(Continued)*.

Predictor	No. of studies showing significance/total no. of studies	References of significant findings
Seizure Characteristics		
Seizure type**	9/24	2, 8, 9, 11- 13, 17, 19, 21
Multiple types of seizures	3/7	17, 23, 24
Seizure frequency/amount of seizures before treatment	2/16	20, 26
History		
History of febrile seizures	3/13	10, 23, 24
History of neonatal seizures	1/3	24
History of status epilepticus	0/7	
Psychiatric abnormality	1/3	18
Family history of epilepsy	2/17	1, 10
Antiepileptic Drugs		
Number of AEDs	4/13	1, 13, 15, 27
Type of AED	2/6	12, 19
Serum level of AED	1/5	15
Seizures after start AED treatment	1/6	13
Taper duration	1/5	5
Number of medication changes before remission	0/3	

*unprovoked seizures related to static encephalopathy resulting from previous insult to the CNS (*e.g*. infection, CNS trauma, cerebrovascular disease) (ILAE, 1993)
**various seizure types have been reported as significant predictors, including partial seizures, absence seizures, rolandic seizures, "jacksonian seizures" and myoclonic seizures.
[1]Arts *et al*., 1988; [2]Dooley *et al*., 1996; [3]Olmez *et al*., 2009; [4]Pavlovic *et al*., 2012; [5]Altunbasak *et al*., 1999; [6]Ohta *et al*., 2004; [7]Bouma *et al*., 1987; [8]Peters *et al*., 1998; [9]Shinnar *et al*., 1985; [10]Shinnar *et al*., 1994; [11]Braathen and Melander, 1997; [12]Caviedes and Herranz, 1998; [13]MRC *et al*., 1993; [14]Galimberti *et al*., 1993; [15]Overweg *et al*., 1987; [16]Li *et al*., 2014; [17]Holowach-Thurston *et al*., 1982; [18]Specchio *et al*., 2002; [19]Callaghan *et al*., 1988; [20]Emerson *et al*., 1981; [21]Matricardi *et al*., 1989; [22]Su *et al*., 2013; [23]Verrotti *et al*., 2012; [24]Ramos-Lizana *et al*., 2010; [25]Lossius *et al*., 2008; [26]Cardoso *et al*., 2003; [27]Vurucu *et al*., 2010.

Table 5. Risk factors for relapse in surgically treated patients, showing significant findings based on multivariable models. Non-significant predictors that were investigated only in a single study were: sex, age at surgical evaluation, time to complete discontinuation, poorly versus well-defined focal lesions, post resection ECoG spikes, SPECT preoperative ictal contralateral localization, PET preoperative contralateral localization, preoperative intracranial monitoring during evaluation, contralateral seizure semiology, persistent auras, temporal localization, lobar localization, type of surgery (lesionectomy versus bi/multilobar), MRI diagnosis of hippocampal sclerosis, tumour, and focal radiation.

Predictor	No. of studies showing significance/ total no. of studies	References of significant findings
Age and Time		
Age at onset epilepsy	0/2	
Age at start of withdrawal	1/1	1
Age at surgery	0/3	
Time from surgery to reduction	3/3	1-3
Duration of epilepsy before surgery	2/4	3, 4
Diagnostics		
Absence of focal MRI abnormalities	1/1	3
Multifocal MRI lesions	1/1	2
EEG: preoperative contralateral interictal spikes	0/3	
EEG: postoperative interictal epileptiform discharges prior to withdrawal	4/5	2, 4, 5, 6
Seizures		
Generalized tonic-clonic seizures	0/2	
Seizure frequency/amount of seizures before treatment	1/4	6
History of febrile seizures	0/2	
Seizures between surgery and withdrawal	2/4	3, 7
Acute postoperative seizures*	0/3	
Surgery Location		
Lobar surgery	0/2	
Left-sided surgery	0/2	
Hemispherectomy	1/1	2
Aetiology		
Aetiology**	1/5	5
Therapy		
Incomplete resection	1/2	2
Number of AEDs	0/3	
Multiple resections	1/1	2

*seizures within one week or two weeks after surgery, or seizures before hospital discharge
**significant for definite hippocampal sclerosis in a series of mesial temporal lobectomies
[1]Lee *et al.*, 2008; [2]Boshuisen *et al.*, 2012; [3]Park *et al.*, 2010; [4]Menon *et al.*, 2012; [5]Rathore *et al.*, 2011; [6]Yardi *et al.*, 2014; [7]Berg *et al.*, 2006.

Bearing these differences in mind, we present recurrence rates of 14% at one year, 21% at two years, 24% at three or four years, and 29% at five or more years of follow-up after initiation of AED withdrawal.

Predicting seizure recurrence

In this systematic review, we listed the available evidence for different predictors of seizure recurrence after AED withdrawal. Although for some factors it seems likely that they predict relapse, for every variable there are also studies that found the opposite, and for some variables only few studies have reported significantly predictive values. Because most of the original studies reviewed here have several limitations, drawing definite conclusions from the presented data is not possible, and this may be the most important inference from this review.

An important issue, regarding the long lists of possible predictors, is how to decide which ones are relevant for

Table 6. Existing prediction models for seizure recurrence after AED withdrawal.

Reference	Population	Included variables
Overweg *et al.*, 1987	age between 18-60 years (*n*=62), without mental or neurological disability, seizure free >3 years	(1) number of AEDs, (2) serum level of AEDs, (3) age at last seizure, (4) duration of seizure-free period
MRC, 1993	adults and children (*n*=1003), seizure free >2 years. Half of participants randomized to maintain AED treatment	(1) age at withdrawal, (2) polytherapy, (3) seizures after start of AED therapy, (4) history of tonic-clonic seizures, (5) history of myoclonic seizures, (6) abnormal EEG in previous year, (7) no EEG available, (8) duration of seizure-free period
Dooley *et al.*, 1996	children (*n*=97), seizure free >1 year	(1) female sex, (2) age at seizure onset, (3) seizure type (generalized versus partial), (4) neurological abnormalities
Braathen and Melander, 1997	children without mental or neurological disability (*n*=161), seizure free >1 year	(1) seizure type and epilepsy type (complex partial, simple partial, absence epilepsy, generalized tonic clonic seizures, rolandic seizures, benign epilepsy with centrotemporal spikes), (2) age at onset, (3) type of EEG abnormality
Geerts *et al.*, 2005 (cohort of Peters *et al.*, 1998)	children (*n*=161), seizure free >6 months	(1) age at onset of epilepsy, (2) absence aetiology, (3) idiopathic aetiology, (4) abnormal EEG, (5) post-ictal signs

clinical practice. An attempt to identify the most important predictors from this list is ill advised, because every method of doing so will have its limitations. As an example, it is tempting to presume that those factors that were most often reported as being significantly related to relapse are the strongest predictors. However, because of the limitations within all separate studies discussed below, conclusions will be weak at the least. Also, factors that have not been studied by many different groups would not be identified through this method, possibly unjustly so. In 1994, Berg and Shinnar performed a meta-analysis in which they studied only three predictors of seizure outcome after AED withdrawal and concluded that age at onset of epilepsy, symptomatic aetiology, and an abnormal EEG result, before AED withdrawal, significantly predicted seizure recurrence (Berg and Shinnar, 1994). However, this was a meta-analysis based on univariable data, and therefore possible multicollinearity between these cannot be formally ruled out.

An obvious solution to this problem is a multivariable meta-analysis of all possible predictors. We have tried to meta-analyse the existing literature of predictors, but the large differences in presented outcome measures between studies made this impossible, given the mix of risk ratios, odds ratios and hazard ratios. A superior method of studying predictors is a meta-analysis of individual participant data (IPD), in which groups collaborate to create an aggregated dataset with predictor data at individual subject level which can be analysed multivariably (Riley *et al.*, 2010). Only in this way, it becomes possible to study a large number of variables in a large dataset. This allows identification of predictors with accuracy which is not possible with other methods of meta-analysis, because the analysis can impute missing values on an individual patient level, detailed follow-up data is available, and (maybe most importantly) the analysis can be carried out in a standardized way across all included studies, while correcting for baseline characteristics (Riley *et al.*, 2010). We have recently initiated a collaborative effort to perform such an IPD meta-analysis of all possible predictors of seizure relapse following AED withdrawal in both medically and surgically treated patients, as identified through this review.

Limitations

The recurrence risks calculated in our meta-analysis show estimates based on a relatively large number of articles and patients. Although many articles were included, not all presented useful information for risk estimation at each individual time point. In particular, in the surgical cohorts, only six of 16 articles presented follow-up starting from initiation of AED withdrawal, rendering ten articles inappropriate for primary analysis. The data derived from the analysis of the latter are not useful in daily practice, because the interval between surgery and withdrawal is different between individual patients and between centres.

In the medically treated patients, the cumulative recurrence risk after five or more years, calculated from all studies that included outcome at this follow-up duration, was lower than that after three to four years. The explanation for this discrepancy is that most articles presenting long-term follow-up did not include information also on the one- to four-year follow-up time point, and had a lower overall recurrence rate. For this reason, the presented data should not be taken as exact hazard functions; this would only be possible when all studies provided information on recurrences at all time points, or even better, when individual patient data were aggregated into a large IPD meta-analysis. In an additional analysis of studies that contained data from both follow-up time points, we showed that relapse rate at five or more years after start of AED withdrawal was virtually identical to that at three to four years.

The current presentation of evidence concerning predictors of relapse has several limitations. First, several factors have been measured or defined variably across the different studies. As an example, age at onset of epilepsy was measured both as a continuous variable and dichotomized, and the cut-off age ranged between 2 and 12 years. Second, the inconsistency between study results may be caused by low sample sizes, as mentioned before. Third, there might be true differences in predictors between different populations. Fourth, the methodology of statistical analysis varied greatly between studies, and different variables were included in the multivariable models leading to heterogeneous results; effects of multicollinearity may be present in one but absent in another model because of inclusion or exclusion of certain variables. As argued by John Ioannidis (Ioannidis, 2005), several factors increase the possibility of "false positive findings"; amongst others: small sample sizes, high possibility for bias, hypothesis-generating studies (compared to confirmatory designs), and greater flexibility in design, analysis and reporting. All these factors are present in the different studies included here, increasing the chance that some of the findings are in reality not true. The way forward is to perform larger, bias-free studies or meta-analyses with collaboration, more appropriate statistics, and standardization (Ioannidis, 2005; Ioannidis, 2014).

Concerning the existing prediction models presented in *table 6*, several limitations also exist. To start with, the populations on which the models have been based on raise questions of generalizability. Three articles have based their model on a paediatric population, one on an adult population, and one on a population with children and adults. It has been shown before (Berg and Shinnar, 1994) that adolescent age at onset of epilepsy has a higher risk of recurrence than both childhood and adult-onset epilepsy. By excluding an age group, this effect might be less prominent or even absent. Also, two articles excluded patients with low intelligence quotient or neurological deficits. These two factors, which can be seen as signs of symptomatic aetiology, seem to be predictors of worse outcome based on the results listed in *table 4*, and also on a previous meta-analysis (Berg and Shinnar, 1994). By excluding these patients from analysis, the validity of the model is restricted. In addition, the required duration of seizure freedom before the start of AED reduction varied between six months and three years, whilst three reports suggested that this time is important in determining recurrence risk (*table 4*). The above-mentioned observations illustrate that a narrative systematic review is only the first step in determining which factors will ultimately aid decision-making in the clinic. Unfortunately, no conclusions can yet be drawn concerning each separate predictor. Future research in the form of larger and well-designed analyses or IPD meta-analysis is needed to be able to predict recurrence risk in individual patients.

Lastly, an important limitation to the current review is the absence of effect sizes. Even if the conclusion would be that a certain factor predicts seizure recurrence, this review does not give insight into the strength of that prediction. Future quantitative analyses should provide answers to the question of effect sizes.

Conclusion

Survival analyses revealed that cumulative risk of seizure recurrence after AED withdrawal is 29% in surgically treated and 34% in medically treated patients. Many factors have been identified as possible predictors of seizure recurrence after AED withdrawal, but the evidence is inconclusive. To determine which variables are truly and independently predictive, and to assess effect sizes, the findings from this systematic review should be incorporated into a large meta-analysis of individual patient data. □

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

Disclosures.
None of the authors have any conflicts of interest to disclosure.

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TEST YOURSELF

(1) For patients with successful treatment with AEDs and seizure freedom for two years, what is the average risk of seizure recurrence after AED withdrawal?

(2) Following successful epilepsy surgery, what is the risk of seizure recurrence after AED withdrawal?

(3) Which factors independently predict seizure recurrence after AED 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".