Original Article

Seizure relapse based upon withdrawal period of antiepileptic drugs in pediatric epilepsy patients

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ABSTRACT

Aim: This study was carried out to quantify risk of seizure recurrence after discontinuation of antiepileptic drugs (AEDs) after varying duration of seizure remission in children with epilepsy and to assess the variables modifying the risk of seizure recurrence. **Materials and Methods:** Randomized controlled trials that evaluate withdrawal of AEDs after varying periods of seizure remission in pediatric epilepsy patients, which could be unblinded, single-blind, or double-blind. The database searching included Cochrane Epilepsy Group Specialized Register, MEDLINE, EMBASE, CINAHL, WHO Clinical trial register, and the Cochrane Central Register of Controlled Trials. Two independent authors extracted the data and assessed trials for quality. **Results:** The pooled relative risk ratio (RR) for early AEDs withdrawal and late AEDs withdrawal was assessed as 1.22 (95% confidence intervals [CI]: 0.94–1.57), for type of epilepsy pooled relative risk was 1.52 (95% CI: 0.96–2.41), electroencephalogram (EEG) relative risk was assessed as 1.65 (95% CI: 1.08–2.51) and the underlying etiology relative RR was assessed as 1.65 (95% CI: 1.08–2.51). **Conclusion:** The high-grade evidence of this study supports that discontinuing AED medication prior to at least 2 seizure free years is associated with higher seizure recurrence risk than waiting for two or more seizure free years in children.

Key words: Antiepileptics, epilepsy, pediatrics, relapse rate, tapering

INTRODUCTION

Epilepsy is a disorder that is best viewed as an indication of disturbed electrical activity in the brain, which may be instigated by an extensive variation of etiologies. After 2 or 5 years of efficacious treatment, drugs can be withdrawn in about 70% of children and 60% of adults with relapse. People with epilepsy sometimes prefer to continue to take antiepileptic drugs (AEDs) lifelong rather than risk a seizure relapse. Thus, a challenging problem ascends as to the timing of withdrawal of drugs.

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Often the clinicians anticipating AEDs withdrawal encounters two important questions; timing of withdrawal and mode of withdrawal. According to guideline drafted by American Academy of Neurology recommended optimal timing of AEDs discontinuation was 2–5 seizure free years.[1] In another study from UK the required seizure free period was at least 2 years.[2,3] Although the data lack on the mode of withdrawal many studies for reviewing tapering of AEDs from rapid to slow withdrawal spreads over a period of 2 years.[4-8]

Although in recent studies the taper period has shrieked to 3–6 months depicting change in the prescribing patterns.[9-12] Consequently whether AEDs may be safely discontinued earlier than 2 years remain unresolved in this study, we had two main objectives. First, to evaluate the risk of seizure recurrence in the pediatric population with epilepsy was depending upon duration of remission. Secondly, effect of

variables affecting risk of seizure recurrence. The objective of this study was to measure risk of seizure recurrence after discontinuation of AEDs after varying duration of seizure remission in children with epilepsy and to assess the variables modifying the risk of seizure recurrence.

MATERIALS AND METHODS

The study included randomized controlled trials that assess withdrawal of AEDs after varying times of seizure remission on pediatric epilepsy patients which could be unblinded, single-blind and double-blind. Studies involving highly specific patient samples such as neonates were excluded. Children excluding neonates of any age with history of diagnosis of epilepsy and who have been seizures free for a described period of time; epilepsy onset may have occurred at any age and the epilepsy could be either partial or generalized. Studies involving withdrawal of any antiepileptics drug randomizing subjects to differing duration of AED treatments were included. The rapid versus later antiepileptic drug discontinuation was cardinal part of studies. Seizure relapse rates following randomization with seizure remission period treated as dichotomous variable between rapid and slow tapering period of AED; time of seizure relapse following withdrawal; risk of status epilepticus; mortality risk.

The primary outcomes were relapse risk between early and late discontinuation, relapse risk in people with early discontinuation of AEDs by electroencephalogram (EEG), relapse risk in people with early discontinuation by epilepsy type. Secondary outcomes were mortality risk, neurological deficit.

This study used as an initial basis of results of previously published studies. We searched the following database, Cochrane Epilepsy Group Specialized Register (10 August 2013); this register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (issue 10 of 12, September 2013), MEDLINE (Ovid) (1948 to September, 2013) using the advanced search strategy. In addition, CINAHL (10 June 2013), EMBASE (1998 to August 2013), WHO International Clinical Registry platform search portal (September 2013) were searched. No linguistic limitations were imposed on our searching activities.

Statistical analysis

Two authors screened titles and abstracts of the electronic search results independently. After screening the electronic searches, bibliographic searches, hand searches, two authors independently selected trials, which met defined inclusion criteria and abstracted study attributes and outcomes, including information on their outcome measures.[13] The results were assessed as relapse risk and risk difference with 95% confidence interval (CI) for dichotomous outcomes. The statistical heterogeneity was assessed using the I^2 test where a value >50% indicated substantial heterogeneity.[14] A fixed effect model was utilized for generating data provided no significant heterogeneity was present. The random effect model was employed in case of significant heterogeneity. Aggregate data methods[15,16] were employed for time to event outcomes (time to seizure recurrence) in the first instance and results were presented as hazards ratios with 95% CI.

RESULTS

All of the identified trials were randomized trial studies conducted on children. Eight eligible randomized controlled trials were included in the analysis representing a total of 1202 children [Table 1].

36 of randomized controlled trial (RCT) records were identified through database searching; additional 10 similar study records were identified through other sources. Braathen and Melander[17] published in 1997 was excluded because of no additional data from the trials were represented in comparison to study[18] published in 1996. 45 identified data records were screened for the appropriate inclusion criteria, 30 of these were excluded cause of noncompliance with the inclusion criteria. Fifteen full text articles were assessed for all the eligibility and 7 of these were excluded as a reason of various

Table 1: Seizure relapses after <2 years of seizure remission versus 2 or more years of seizure remission

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Relapse risk between early and late discontinuation	6	1073	RR (M-H, random, 95% CI)	1.22 (0.94, 1.57)
Seizure relapse rate in people with early discontinuation of AEDs by EEG	3	528	RR (M-H, random, 95% CI)	1.65 (1.08, 2.51)
Seizure relapse rate in people with early discontinuation by epilepsy type	2	180	RR (M-H, random, 95% CI)	1.52 (0.96, 2.41)
Association between seizure relapse risk and underlying etiology	3	287	RR (M-H, random, 95% CI)	2.67 (1.1, 5.3)

RR=Risk ratio, AEDs=Antiepileptic drugs, EEG=Electroencephalogram, CI=Confidence interval

biases such as selection bias (e.g. random sequence generation, allocation concealment), performance bias, detection bias, reporting bias, attrition bias, and publication bias [Figure 1].

There were eight RCT records, which were thoroughly screened for assigned inclusion criteria [Table 2]. Emerson *et al*.[12] conducted a study over 68 children randomly assigned a study group of rapid and late withdrawal that showed the best predictor outcomes where the EEG at cessation of medication and the number of seizures before control. Another included trial Todt[22] undertook 40 participants with history of one seizure who are randomized, showed weaning of seizure drugs after 1, 2, 3, and 4 seizure free years. Andersson *et al*.[18] were the first of the published manuscripts, which primarily documented relationship between relapse risk and how epilepsy and seizure type modify relapse risk. Whereas Tennison *et al*.[19] enrolled 149 children with average age of 11 years randomly assigned to two groups by coin tosses. In this study, EEG and drug tapering were the main interventions.[19] Three trials Gebremariam *et al*.,[20] Peters *et al*.,[21] Verrotti *et al*.[23] studies had 2 years of follow-up periods, outcome was measured continuously in all studies, but presented as an aggregated number of individuals who had a seizure relapse at fixed time point depending on the follow-up duration of trial. Another study conducted by Gherpelli *et al*.[24] assigned 70 children, experienced at least 2 seizures before the age of 12 years excluding neonatal seizure and febrile seizure.

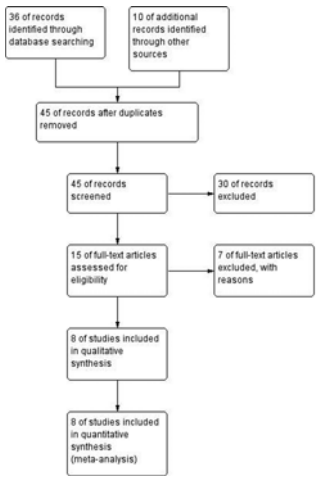

Figure 1: Study flow diagram

In terms of seizure prevention, the number of individuals with early withdrawal (<2 seizure free years) of AEDs and late withdrawal (more than 2 seizure free years) was available for 8 trials representing 1202 randomized children. The pooled relative risk

Table 2: Included study characteristics

First author	Year	Intervention		Outcomes
		Rapid tapper withdrawal of drugs	Slow tapper withdrawal of drugs	
Tennison *et al.*[19]	1994	6 weeks (*n*=70)	9 months (*n*=63)	EEG, underlying etiology
Andersson[18]	1996	After 1-year of seizure freedom. All drugs were tapered during a 3-month period	After 3 years of seizure freedom. All drugs were tapered during a 3-month period	Seizure relapse and risk factors including seizure type, serum concentrations of seizure drug
Gebremariam *et al.*[20]	1999	After an 18 seizure-free months	After 24 seizure-free months	Seizure relapse and risk factors including multiple medications, neurological deficit, family history of epilepsy, EEG, mental retardation
Peters *et al.*[21]	1998	After 6 months of seizure freedom. Withdrawal of drug was conducted over a period of 4 weeks in both groups	After 12 months of seizure freedom. Withdrawal of drug was conducted over a period of 4 weeks in both groups	Seizure relapse and risk factors including: Age; seizure type; epilepsy type; imaging; etiology and EEG data
Todt[22]	1984	After 2 seizure free years during 1, 3, 6, and 12 moths	After 4 seizure free years during 1, 3, 6, and 12 moths	Seizure relapse and risk factors including: sex, family history, epilepsy/seizure type, duration of epilepsy, age at onset, IQ, duration of taper, and EEG data
Verrotti *et al.*[23]	2000	After 1 seizure free year. Withdrawal of drug was conducted over 6 months to 1 year	After 2 seizure free years. Withdrawal of drug was conducted over 6 months to 1 year	Seizure relapses, type of epilepsy
Gherpelli *et al.*[24]	1992	After 6 months of seizure freedom	After 24 months seizure freedom	EEG, underlying etiology and seizure relapse rate
Emerson *et al.*[12]	1981	Before 24 months	After months 24	Underlying etiology and seizure relapse rate

EEG=Electroencephalogram, IQ=Intelligence quotient

ratio (RR) for early AEDs withdrawal and late AEDs withdrawal was assessed as 1.22 (95% CI: 0.94–1.57). 167 subjects had seizure relapse event out of 381 exposed to early withdrawal, whereas 243 seizure relapse events documented over 692 subjects exposed late withdrawal [Figure 2]. Braathen study group[18] showed RR 1.64 (M-H Random 95% CI: 1.08–2.47); Tennison study group[19] showed RR 0.87 (M-H random 95% CI: 0.58–1.29); Todt 1984 showed RR 1.69 (M-H random 95% CI: 1.29–2.21); Gebremariam study[20] showed RR 0.82 (M-H random 95% CI: 0.43–1.54); Peters study group[21] showed RR 1.12 (M-H random 95% CI: 0.83–1.50); Verrotti study group[23] showed RR 1.16 (M-H random 95% CI: 0.58–2.30).

There was no statistical heterogeneity between trials ($\chi^{2:}$ 12.08; degree of freedom = 5 [P = 0.03] I^2 = 59%) there by test overall effect was Z = 1.48 (P = 1–14).

In terms of EEG the three studies Andersson *et al*.[18] Tennison *et al*.,[19] Todt[22] groups were based on seizure relapse RR in relation to their withdrawal periods of AEDs among pediatric epileptic patients with total of 528 participants. The pooled relative RR was assessed as 1.65 (95% CI: 1.08–2.51). A total of 232 subjects were exposed to early withdrawal out of which 108 had documented episodes of seizure relapse. On the other hand, 296 subjects were exposed to late AEDs withdrawal where 83 of them had seizure relapse. All the trial supported a similar effect favoring a normal EEG for rapid withdrawal of AEDs [Figure 3].

Braathen study group[18] showed RR 1.23 (M-H random 95% CI 0.86–1.76); Tennison *et al*.[19] showed RR 1.55 (M-H random 95% CI 0.80–3.01); Todt group[22] showed RR 2.24 (M-H, random 95% CI 1.64–3.06); Two trials Gabrimariam *et al*.,[20] Peters *et al*.[21] have reported relapse risk without providing any data on total number of subjects in each group.

In terms of seizure types, Two trial Braathen study group,[18] Verrotti study group[23] provided data on epilepsy type and its relationship to seizure relapse after early and late withdrawal of AEDs representing 180 subjects. The pooled relative risk was 1.52 (95% CI: 0.96–2.41) at 2 years of follow-up. Both trials included the number of randomized children with partial seizure [Figure 4].

Braathen study group[18] showed RR 1.86 (M-H, random 95% CI: 1.04–3.34); Verrotti study group[23] showed RR 1.16 (M-H, random 95% CI: 0.58–2.30); The early withdrawal group had 50% seizure relapse rate versus 37% in the late withdrawal group although Peters 1998 provided a relapse risk, but did not sate the total number of subjects. Only one trial[18] included number of participants with generalized seizure and found no statistical difference in seizure relapse between rapid and slow withdrawal. However, rapid withdrawal group had 46.55% seizure relapse rate versus 28% in the slow withdrawal group. One additional trial Peters study group[21] provided relapse risk, but the data on the total number of participant was ambiguous, there were declining the evidence scoring of generated data. There was no significant statistical heterogeneity between included trials.[25]

In terms of underlying etiology the total of three randomized controlled trials Emerson study group,[12] Gherpelli study group,[24] Tennison study group[19] were included for assessing the association between the seizure relapse risk and underlying etiology with the total of 287 subjects [Table 3]. The pooled relative risk was 2.67 (95% CI: 1.1–5.3); Emerson study group[12] showed RR 4.9 (M-H, Random 95% CI: 1.77–9.45 with 39% of recurrence); Gherpelli study group[24] showed RR 2.07 (M-H, random 95% CI: 0.942–4.57 with 29% of recurrence); Tennison study group[19] showed RR 1.05 (M-H, random 95% CI: 0.59–1.88

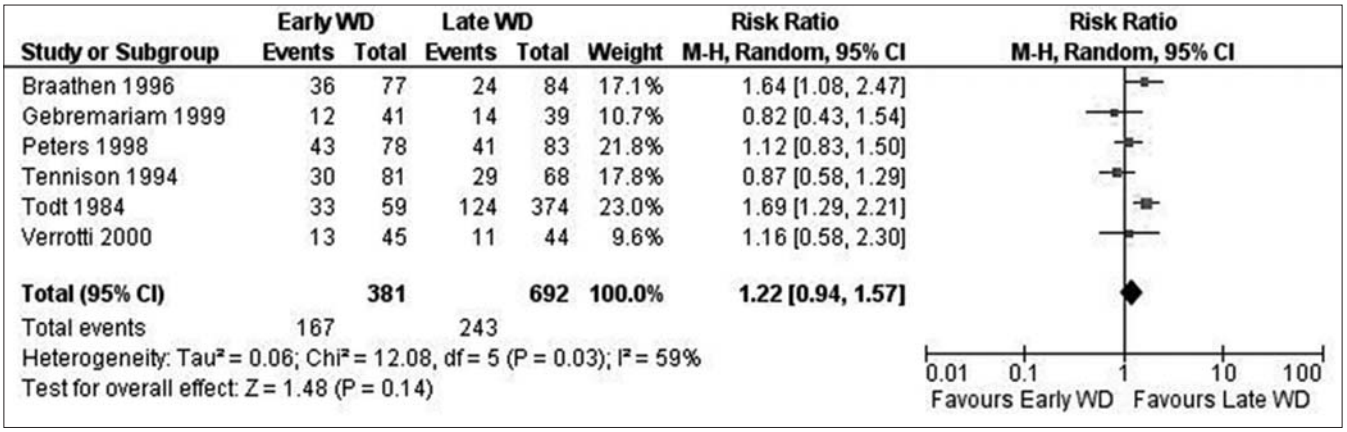

Figure 2: Forest plot of comparison of relapse risk between early and late discontinuation

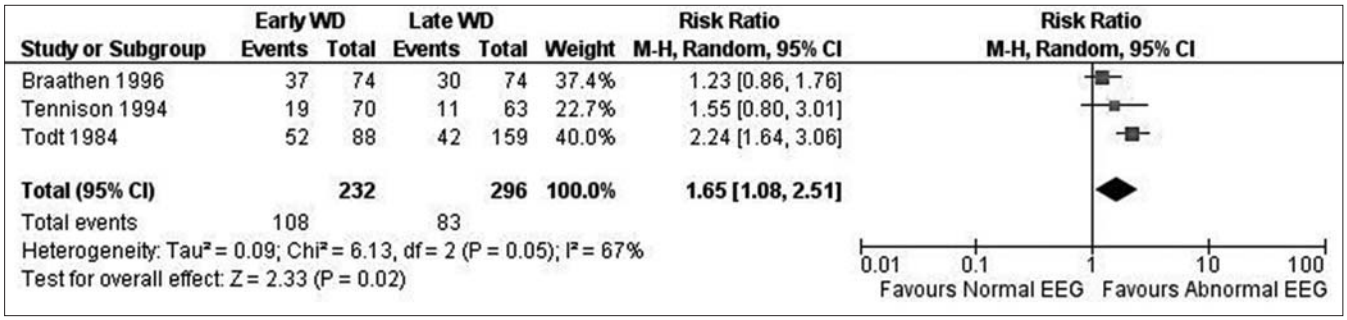

Figure 3: Forest plot of comparison between seizure relapse rates in children with early discontinuation of antiepileptic drugs by electroencephalogram

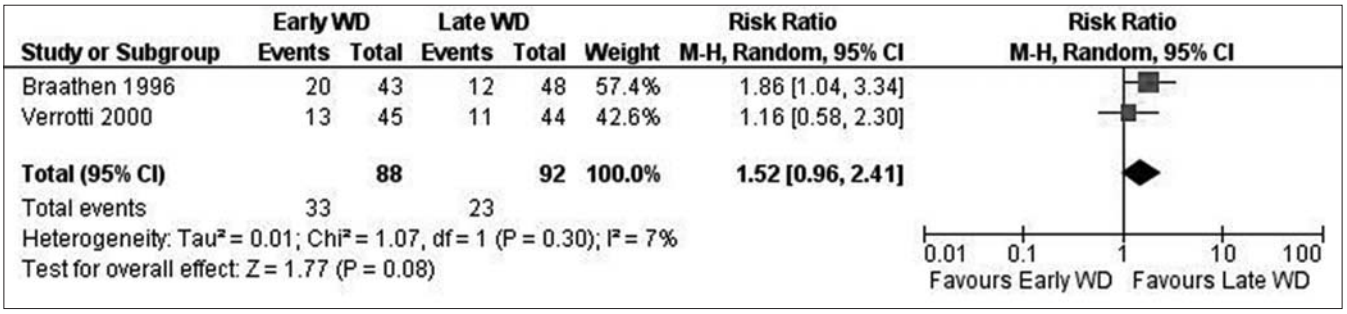

Figure 4: Forest plot of comparison between seizure relapse rates in children with early discontinuation by epilepsy type

Table 3: Seizure relapse rate in children with early discontinuation of AEDs by underlying etiology

Author	Year	Population	Relative risk	95% CI	Recurrence (%)
Emerson *et al.*[12]	1981	68	4.9	1.77, 9.45	52 (39)
Gherpelli *et al.*[24]	1992	70	2.07	0.94, 4.57	20 (29)
Tennison *et al.*[19]	1994	149	1.05	0.59,1.88	18 (26)
Total		287	Average 2.67		

AEDs=Antiepileptic drugs, CI=Confidence interval

with 26% of recurrence). The seizure relapse risk and the underlying etiology was associated with recurrence rate of 90/287 subjects (31.35%) of the study population and the quality of evidence was graded as moderate [Figure 5].

DISCUSSION

Others attributes such as age at seizure onset, neurological deficits, duration of epilepsy, intelligence quotient, mortality. We were unable to get any data regarding the above outcome measures and the data were not adequate to form any firm conclusion from the various solitary studies. Two trials Gabrimariam study group,[20] Todt study group[22] included some of the variable, but the data were presented as relapse risk for entire study population without comparing rapid versus slow AED withdrawal groups. Many of the studies had weak methodology, low sample size or highly biased making it difficult to come up with any firm conclusion, Protocol violation and lost to follow-up further reduce the reliability of results. We did not find any trials examining the mortality or intelligence quotient between early and late withdrawal of AEDs. These results represent exclusively relapse RR based upon withdrawal period of AEDs and do not take into account variables such as epilepsy type, EEG data, or underlying etiology.

The moderate quality of evidence supported late AED withdrawal in children with partial seizures. Another moderate grade quality scoring supported a strong association in higher seizure relapse risk and underlying etiology in association to the rapid AEDS withdrawal. On an overall conclusion, the high quality of evidence supports later AED tapering after 2 years of seizure remission over the slow AEDS (<2 years).

CONCLUSION

This descriptive study was envisioned with unique sole purpose to illustrate and quantify the relapse risk association with earlier AEDs discontinuation (<2 years) versus to the late AEDs discontinuation in pediatric epileptic population. All the included trials only to children excluding the highly specific group such as neonates. Only eight studies met the inclusion criteria. We found that all trials except Gabrimariam study group[20]

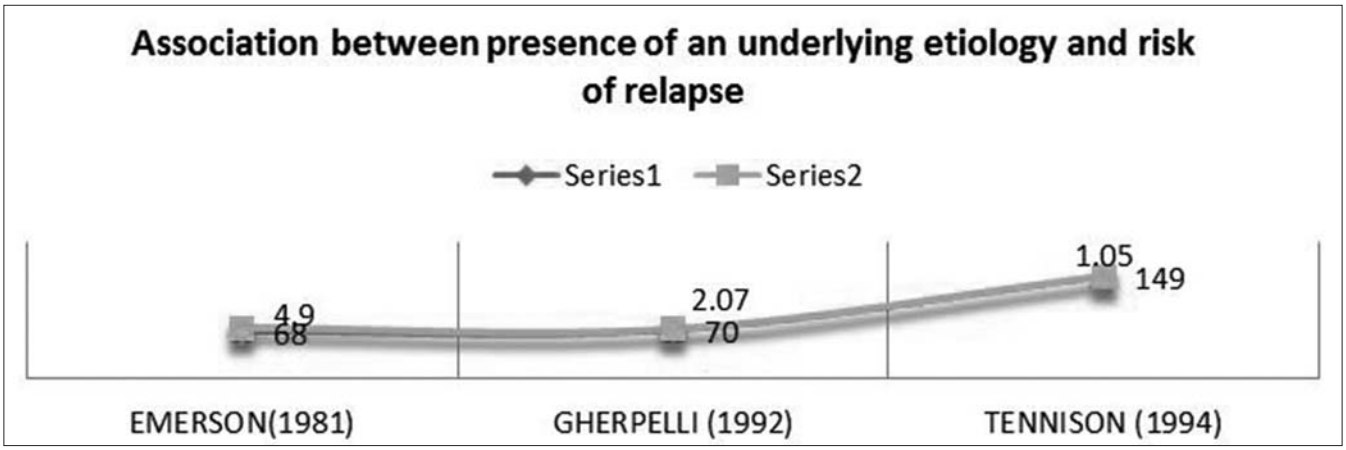

Figure 5: Association between presence of an underlying etiology and risk of relapse for antiepileptic drugs

Table 4: Summary of findings tables

Patient or population: Patients with epilepsy in pediatrics. Intervention: AEDs tapering associated seiazure relapse after 2 years of seizure remission versus <2 years of seizure remission

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (Grade)
	Assumed risk	Corresponding risk			
	Control	AEDs tapering associated seizure relapse after 2 years of seizure remission versus<2 years of seizure remission			
Relapse risk between early and late discontinuation Follow-up: 2-5 years		Study population	RR 1.22 (0.94-1.57)	1073 (6 studies)	⊕⊕⊖⊖ moderate
	351/1000	428/1000 (330-551)			
		Moderate			
	345/1000	421/1000 (324-542)			
Seizure relapse rate in children with early discontinuation of AEDs by EEG Follow-up: 2-5 years		Moderate	RR 1.71 (1.37-2.13)	528 (3 studies)	⊕⊕⊖⊖ low
	335/1000	573/1000 (459-714)			
Seizure relapse rate in children with early discontinuation by epilepsy type Seizure relapse follow-up: 2-5 years		Study population	RR 1.52 (0.96-2.41)	180 (2 studies)	⊕⊕⊖⊖ low
	250/1000	380/1000 (240-603)			
		Moderate			
	250/1000	380/1000 (240-603)			
Association between seizure relapse risk and underlying etiology Seizure relapse follow-up: 2-5 years		Study population	RR 2.67 (1.1-5.3)	287 (3 studies)	⊕⊕⊕⊖ moderate
		Recurrence 90/287 (31.35%)			
		Moderate			

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Grade: Working group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. CI=Confidence interval, RR=Risk ratio, AEDs=Antiepileptic drugs

supported waiting withdraw AEDs in children with seizure remission. The relationship between seizure relapse rate and EEG was favoring a normal EEG for successful weaning of AEDs in <2 seizure free years [Table 4].

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