

[When to discontinue antiepileptic drug treatment in adults and children](#)**Q9. In adults and children with convulsive epilepsy in remission, when should treatment be discontinued?****Background**

Antiepileptic drugs (AED), which are used to prevent seizures have long term adverse effects. Thus when epilepsy is in remission, it may be in the individual's best interest to consider discontinuation of medication. Timing of withdrawal is a difficult question. Such decisions are fraught with the uncertain balance between the risk of seizure recurrence and its consequences versus the long term adverse effects. Various textbooks and guidelines report optimal timing for AED withdrawal as a range between two and five years seizure freedom.

Long term AED use is associated with other implicit and explicit costs. These include alteration of one's daily activities to remain compliant, psychosocial stigma of AED use, financial cost of drug purchase, regular clinical monitoring, and burden on health systems in terms of human and other resources. Despite the arguments in favour of early discontinuation, the decision to do so is not an easy one due to consequences of seizure recurrence, and such as impact on quality of life for example by loss of driving license, loss of employment, loss of confidence and sense of control.

Consequently the issue whether AED should be withdrawn earlier than two years is not resolved.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population: children or adults with epilepsy in remission

Interventions: early discontinuation (less than 2 year seizure-free period)

Comparison: less than or equal to 1 year seizure-free period/ more than 1 year seizure-free period for children only

Outcomes: seizure relapse rate

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mortality

adverse effect of AEDs

quality of life

stigma

risk of intractable epilepsy after AED withdrawal

List of the systematic reviews identified by the search process

Sirven J, Sperling MR, Wingerchuk DM (2001). Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews*, (3):CD001902.

PICO table

| Serial No | Intervention/Comparator | Outcomes | Systematic reviews | Comments |
|-----------|--|----------------------|---|---|
| 1. | Less than 2 year seizure-free period/ More than 2 year seizure-free period | Seizure relapse rate | Sirven et al, 2001 (Cochrane review updated 2007) | Additional relevant studies: MRC 1991, Lossius et al, 2008 |
| | | Mortality | Sirven et al, 2001 (Cochrane review updated 2007) | No evidence found in the systematic review Additional relevant studies: MRC 1991 (RCT); Callaghan et al, 1988; Camfield & Camfield 2005, and Lossius et al, 2008 (observational studies and reviews) |
| | | Adverse effects of | Not assessed by the Cochrane | Information gathered from |

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| | | | | |
|----|--|---|-------------------------------------|--|
| | | AEDs | review by Sirven et al, 2001 | primary studies included in the systematic review |
| | | Quality of life | Not assessed by the Cochrane review | None reported in primary studies Additional relevant studies (Jacoby et al, 1992; Lossius et al, 2008) |
| | | Stigma | Not assessed by the Cochrane review | None reported in primary studies Additional relevant studies (Jacoby et al) |
| | | Risk of intractable epilepsy after AED withdrawal | Not assessed by the Cochrane review | Additional relevant studies (Shinnar et al, 1994; Arts et al, 1988; Callaghan et al, 1988; Matricardi et al, 1989; Camfield & Camfield, 2005; Schmidt & Löscher, 2005) |
| 2. | Less than or equal to 1 year seizure-free period/ More than 1 year seizure-free period | Seizure relapse rate | | New systematic search performed |

GRADE tables

Table 1

Author(s): G Bell, T Dua, N Huynh

Date: 2009-04-28

Question: Should AED treatment be discontinued before two seizure-free years vs. discontinued after two seizure-free years be used for epilepsy in children?

Settings:

Bibliography: Sirven J, Sperling MR, Wingerchuk DM (2001). Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews*, (3):CD001902.

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| Quality assessment | | | | | | | Summary of findings | | | | | Importance |
|---|-----------------------|----------------------|---------------------------------------|-------------------------|------------------------|----------------------|---|---|-----------------------|---|----------|------------|
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | | Effect | | Quality | |
| | | | | | | | AED treatment be discontinued before two seizure-free years | discontinued after two seizure-free years | Relative (95% CI) | Absolute | | |
| seizure relapse rate (clinical grounds) | | | | | | | | | | | | |
| 5 ¹ | randomized trials | serious ² | no serious inconsistency ³ | no serious indirectness | no serious imprecision | none | 137/300 (45.7%) | 214/624 (34.3%) | RR 1.32 (1.02 to 1.7) | 110 more per 1000 (from 7 more to 240 more) | MODERATE | CRITICAL |
| mortality | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | Not estimable | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | CRITICAL |
| adverse events | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | CRITICAL |
| | | | | | | | 0% | | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| quality of life (Better indicated by lower values) | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0 | 0 | - | MD 0 higher (0 to 0 higher) | | IMPORTANT |
| stigma (Better indicated by lower values) | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0 | 0 | - | MD 0 higher (0 to 0 higher) | | IMPORTANT |

¹ Cochrane review updated 2007 (Sirven et al, 2001), page 11 (Analysis 1.1).

² All five studies are randomized. Two out of five studies were not blind but the outcome was a hard and robust parameter. Allocation concealment was unclear in all five studies according to the Cochrane Review.

³ heterogeneity is I squared = 48%.

⁴ In the Cochrane review, none of the included trials examined mortality as an outcome.

Table 2

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Author(s): G Bell, T Dua, N Huynh

Date: 2009-04-28

Question: Should AED treatment be discontinued before two seizure-free years vs. discontinued after two seizure-free years be used for epilepsy in adults?

Settings:

Bibliography: Sirven J, Sperling MR, Wingerchuk DM (2001). Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews*, (3):CD001902

| Quality assessment | | | | | | | Summary of findings | | | | | Quality | Importance |
|--|-----------------------|----------------------|---------------------------------------|---------------------------|------------------------|----------------------|---|---|-----------------------|---|--|----------|------------|
| | | | | | | | No of patients | | Effect | | Relative (95% CI) | | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | AED treatment be discontinued before two seizure-free years | discontinued after two seizure-free years | | | | | |
| seizure relapse rate (clinical grounds) | | | | | | | | | | | | | |
| 5 ¹ | randomized trials | serious ² | no serious inconsistency ³ | very serious ⁴ | no serious imprecision | none | 137/300 (45.7%) | 214/624 (34.3%) | RR 1.32 (1.02 to 1.7) | 110 more per 1000 (from 7 more to 240 more) | VERY LOW | CRITICAL | |
| mortality | | | | | | | | | | | | | |
| 0 ⁵ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | | |
| | | | | | | | | 0% | | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| adverse events | | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | | |
| | | | | | | | | 0% | | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| quality of life | | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | | |
| | | | | | | | | 0% | | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| stigma | | | | | | | | | | | | | |
| 0 ⁴ | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0) | | | |

Seizure relapse rate

Additional information from RCTs not meeting the criteria of systematic review:

- MRC 1991 - Randomized study of epilepsy patients of all ages seizure-free for at least 2 years into AED withdrawal and non-withdrawal groups. The 2-year seizure relapse rate was 22% among non-withdrawers, compared to 41% in withdrawers (RR = 0.537, 95% CI 0.44 to 0.65 - our calculation)

Mortality

Description of the observational data/ Additional information from studies not meeting the criteria of systematic review:

- MRC 1991 (RCT): 15 patients died out of 1013 patients, 2 deaths were seizure related, both adults and in AED non withdrawal group.
- Callaghan et al .1988 - In epilepsy patients (both adults and children) withdrawn from AED after at least 2 seizure-free years, there was no mortality during a mean follow up period of 26 months (6-62).
- Camfield & Camfield 2008 - Non-systematic review of 3 studies of childhood epilepsy of 1777 patients followed for 5-20 years, 4 deaths due to seizure related causes, none had discontinued AEDs. The individual results of 3 studies are presented below.
- Camfield et al, 2002 - 26 deaths of 692 children with epilepsy, 1 SUDEP death and 1 status epilepticus, AED status not reported.
- Callenbach et al. 2001 - 9 deaths in 472 children with epilepsy, none due to seizure, 1 child not on AED.
- Shinnar et al. 2005 - follow up of 407 children after first unprovoked seizure for a mean of 14.2 years; 9 deaths, 4/9 not on AED, death related to seizure in 4 subjects and all of them taking AED at the time of death.

Adverse events due to AEDs

- None of the included trials in the Cochrane review studied the adverse events of AED between early and late withdrawal of AEDs. In one of the included trials (Braathen et al, 1996), at one study hospital, 84% of children (82 of 98 patients) on AEDs had adverse reaction.

Quality of life

- None of the included trials in the Cochrane review studied quality of life as an outcome between early and late withdrawal of AEDs.
- Jacoby et al, 1992 study on psychosocial outcomes of antiepileptic drug discontinuation reported little evidence of substantial effects of withdrawal after at least 2 seizure-free years vs. no withdrawal on psychosocial outcomes. But seizure recurrence since randomization was associated with increased distress on several measures. However receiving AEDs to control seizures was also associated with increased distress on these measures.

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- Gross Thur et al. 1993 - School performance and/or behaviour often improve when anticonvulsants are withdrawn even in asymptomatic children.

Stigma

- None of the included trials in the Cochrane review studied stigma as an outcome between early and late withdrawal of AEDs.
- Jacoby et al. 1992 follow up study on psychosocial outcomes of antiepileptic drug discontinuation - being randomized to slow withdrawal vs. no withdrawal was associated with slight decrease in feelings of stigma (NS) whereas a seizure recurrence or receiving AEDs increased it.

Intractable epilepsy subsequent to AED withdrawal from well-controlled patient

Not much evidence is available from RCTs and very few prospective studies have looked at this outcome. Moreover studies had variable follow up rates and variable definitions of intractable epilepsy thus it is difficult to reach any conclusion.

RCTs

- Gebremariam et al. 1999: "all children with relapse received within a few days of seizure recurrence the same anti-convulsant medication they had received previously and all responded well(0/12 in early withdrawal and 0/14 in late withdrawal)"
- Todt 1984: of patients who relapsed, 86% became seizure-free after reinstatement of formerly effective medicines. The remaining 14% did not respond immediately to former medicines, and presumably were managed with a change in treatment regimen. Only 1 patient developed intractable epilepsy. 14 patients who relapsed were left without any AED, and none had further seizures over the next 3 years. (seizure-free rates not provided for two treatment arms)

PROSPECTIVE STUDIES

- Camfield & Camfield 2005: 3 of 260 children (1%) who stopped AEDs and had 5+ year follow-up data developed intractable epilepsy, one of whom went into remission again 7 years later. The authors estimated that if all children with 2 year remission had stopped AEDs, 3% (98%CI 2.3-5.5%) would have eventually developed intractable epilepsy in a minimum of 5 years of observation.

RETROSPECTIVE STUDIES

- Arts et al, 1988: 37 of 146 children suffered relapse after AED withdrawal. 36 of 37 were restarted on AEDs, 12 of these were later withdrawn successfully. At study end, 6 of the 24 remaining on AEDs had difficulty with seizure control (other 18 were seizure-free at least 6 months). 6/36 had intractable epilepsy (16.7%)
- Callaghan et al, 1988: 31 of 92 patients (adults and children) suffered relapse after AED withdrawal. 4 patients were lost to follow up. All were reinstated on AED, but 7 continued to have seizures despite AED reinstatement. 7/27 had intractable epilepsy (25.9%)

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- Matricardi et al. 1989: 50 of 425 children suffered relapse after AED withdrawal. Ultimately only 6 were unable to regain seizure control after AED reinstatement. In these 6, all had "long duration" of disease, 4 had EEG abnormalities prior to first relapse, and 4 had neurologic abnormalities or etiologic factors present. 6/50 had intractable epilepsy (12%)
- Schmidt and Löscher 2005 (systematic review): reports intractable epilepsy rates of up to 20% in adults and 25% in children who quit AEDs. *Caveat*: percentages reported are relative to number of patients who both stopped AEDs and relapsed, not just patients who stopped AEDs (artificially inflates the rates since most people who quit AEDs do not have relapse)

II Adults

Seizure relapse rate

Information from RCTs not meeting systematic review criteria:

- Lossius et al, 2008 - Randomized double blind study of adult epilepsy patients seizure-free for more than 2 years on monotherapy into AED withdrawal and non-withdrawal group. Seizure relapse at 12 months occurred in 15% of the withdrawal group and 7% of non-withdrawal group (RR 2.46; 95% CI 0.85-7.08; p=0.095). At 2 years, relapse rate in withdrawers was 19%.
- MRC 1991 - Randomized study of all ages epilepsy patients seizure-free for at least 2 years into AED withdrawal and non-withdrawal group. The 2-year seizure relapse rate was 22% among non-withdrawers, compared to 41% in withdrawers (RR = 0.537, 95% CI 0.44 to 0.65 - our calculation)

Mortality

In the Cochrane review none of the included trials examined mortality as an outcome. Description of the observational studies:

- MRC 1991 (RCT): 15 patients died out of 1013 patients, 2 deaths were seizure related, both adults and in AED non withdrawal group.
- Lossius et al. 2008 (RCT) - adult study of 160 patients, 4 died, 2 of supposed SUDEP. One died weeks after withdrawal, one 4 years post withdrawal.
- Callaghan et al. 1988 - In epilepsy patients (both adults and children) withdrawn from AED after at least 2 seizure-free years, there was no mortality during a mean follow up period of 26 months (6-62 months).

Adverse events due to AEDs

- Lossius et al, 2008 - patients withdrawn from AEDs after 2 or more seizure-free years have significantly improved neuropsychological function compared to nonwithdrawal group.

Quality of life

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- Lossius et al, 2008 - patients withdrawn from AEDs after 2 or more seizure-free years had no statistical significant improvement in quality of life. The double blind design of the above trial excludes one known positive effect of being off medication; namely not having to take drugs regularly.
- Jacoby et al, 1992 study on psychosocial outcomes of antiepileptic drug discontinuation reported little evidence of substantial effects of withdrawal after at least 2 seizure-free years vs. no withdrawal on psychosocial outcomes. But seizure recurrence since randomization was associated with increased distress on several measures. However receiving AEDs to control seizures was also associated with increased distress on these measures.

Stigma

- Jacoby et al, 1992 study on psychosocial outcomes of antiepileptic drug discontinuation reported little evidence of substantial effects of withdrawal after at least 2 seizure-free years vs. no withdrawal on psychosocial outcomes. But seizure recurrence since randomization was associated with increased distress on several measures. However receiving AEDs to control seizures was also associated with increased distress on these measures.

Factors associated with risk of seizure relapse

Specchio & Beghi 2004 - In a critical review 28 studies accounting for 4571 patients (2758 children, 1020 adults and a combined group of 793), most with at least 2 years of seizure remission, the proportion of patients with relapses during or after AED withdrawal ranged from 12 to 66%. Using life-table analysis, the cumulative probability of remaining seizure-free in children was 66–96% at 1 year and 61–91% at 2 years after withdrawal of AEDs. The corresponding values in adults were 39–74% and 35–57%, respectively. The relapse rate was highest in the first 12 months (especially in the first 6 months) after withdrawal and tended to decrease thereafter.

Based on a previously published meta-analysis of data published up to 1992, the pooled relapse risk was 25% (95% CI 21, 30%) at 1 year and 29% (95% CI 24, 34%) at 2 years after AED withdrawal. The factors associated with a higher-than-average risk of seizure relapse included adolescent-onset epilepsy, partial seizures, the presence of an underlying neurological condition, and abnormal EEG findings at the time of AED withdrawal in children. Factors associated with a lower-than-average risk were childhood-onset epilepsy, idiopathic generalized epilepsy and – for children – a normal EEG. Factors associated with a lower-than-average risk are childhood-onset epilepsy, idiopathic generalized epilepsy and – for children – a normal EEG. Selected epilepsy syndromes (e.g. benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) may be associated with significantly different outcomes after AED withdrawal.

Reference List

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Medical Research Council (MRC) Antiepileptic Drug Withdrawal Study Group (1991). Randomized study of antiepileptic drug withdrawal in patients with remission. *Lancet*, 337:1175-80.

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Schmidt D, Löscher W (2005). Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurologica Scandinavica*, 111:291-300.

Shinnar S, O'Dell C, Berg AT (2005). Mortality following a first unprovoked seizure in children: a prospective study. *Neurology*, 64:880-2.

Shinnar S et al (1994). Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Annals of Neurology*, 35:534-45.

Sirven J, Sperling MR, Wingerchuk DM (2001). Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews*, (3):CD001902.

Specchio LM, Beghi E (2004). Should antiepileptic drugs be withdrawn in seizure-free patients? *CNS Drugs*, 18:201-12.

Todt H (1984). The late prognosis of epilepsy in childhood: results of a prospective follow-up study. *Epilepsia*, 25:137-44.

Verrotti A et al (2000). Discontinuation of anticonvulsant therapy in children with partial epilepsy. *Neurology*, 55:1393-5.

From evidence to recommendations

| Factor | Explanation |
|---|--|
| Narrative summary of the evidence base | In children, discontinuing AED treatment at least after two seizure-free years is associated with statistically significant lower seizure relapse rate compared to early discontinuation. However, the lower confidence interval is close to no effect (RR 1.32, 95% CI 1.02 to 1.70). No data from randomized trials are available in adults. |
| Summary of the quality of evidence | Five RCTs with almost 1000 patients providing results for seizure relapse rate only (MODERATE quality evidence). No randomized evidence was |

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| | |
|---|---|
| | <p>available for the other critical and important outcomes including mortality, adverse events due to AEDs, quality of life and stigma.</p> <p>Observational evidence suggest that the risk of death following a relapse after discontinuation of AED is extremely small. Long term AED use is associated with dose related morbidities in one-third of cases, and cognitive and metabolic consequences. The risk of intractable epilepsy subsequent to AED withdrawal has not been systematically assessed. However, observational evidence suggests that this risk seems low.</p> |
| Balance of benefits versus harms | <p>Early withdrawal will decrease the adverse effects associated with long term use, improve the quality of life as daily administration requires alteration in life style to remain compliant and decrease stigma associated with AED use. However the risk of seizure relapse is more with early withdrawal with its associated psychosocial consequences and distress.</p> <p>The factors associated with a higher-than-average risk of seizure relapse included myoclonic epilepsy, partial seizures, the presence of an underlying neurological condition, and abnormal EEG findings at the time of AED withdrawal in children. Factors associated with a lower-than-average risk are childhood-onset epilepsy, idiopathic generalized epilepsy and – for children – a normal EEG.</p> |
| Values and preferences including any variability and | <p>Important issues are seizure relapse and its consequences, quality of life and concerns about long term effect of AEDs.</p> |

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| | |
|---|---|
| human rights issues | <p>Some people with epilepsy are keen to stop the daily AED treatment due to concerns about side-effects of treatment, parental anxiety of effect of AEDs on maturing nervous system, wish to feel "cured", and to feel free of the burden of taking medication daily. Others wish to continue treatment because of concern about the impact of another seizure on their life style (sense of loss of control, loss of employment, driving possibilities), potential effect of seizure on developing nervous system or even dying during recurrence.</p> <p>In presence of risk factors for recurrence, the decision to stop AED needs to be taken on a case by case basis.</p> |
| Costs and resource use and any other relevant feasibility issues | <p>There are resource use and costs associated with drug purchase, laboratory monitoring and clinical examinations.</p> |
| Final recommendation(s) <p>In children and adults with epilepsy, discontinuation of antiepileptic drug treatment should be considered after two seizure-free years. After a two year seizure-free period, the decision to withdraw or continue antiepileptic drugs in a seizure-free patient, should be made after consideration of relevant clinical, social and personal factors and with the involvement the patient and the family.</p> <p>Strength of recommendation: STANDARD</p> | |

Limitations

Lack of data in adults is a major limitations, as well as lack of data on some critical and important outcomes.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

Sirven J, Sperling MR, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD001902. DOI: 10.1002/14651858.CD001902.