Q8. Should Anti-Epileptic Drug (AED) treatment be started after first unprovoked seizure in non-specialist health settings?

Background

Unprovoked seizures and epilepsy are common treatable neurological conditions and there is considerable disagreement about the recurrence risk following a first seizure (Beghi et al, 2008). There is agreement that AED treatment should be started after a second seizure but, although the chances of entering remission seem to be unchanged by the use of AEDs, there may be a reduction in relapse rate after a first seizure if AEDs are commenced. AED treatment may be associated with adverse events as well as increased stigma (Beghi et al, 2008).

Estimates of the recurrence rates following the first seizure over two and three years have varied between 23% and 71% (Pearce & Mackintosh, 1979; Elwes et al, 1985); the risk of recurrence has been estimated at 14% at one year, 29% at three years and 34% at five years (Hauser et al, 1990). In a systematic review and meta-analysis including both prospective and retrospective observational studies, the pooled estimate of the risk of recurrence of a first unprovoked seizure at two years was 42% (95% CI 39 to 44).(Berg & Shinnar, 1991).

The more seizures an individual has had, the higher the risk of subsequent seizures; the risk of a recurrence following two seizures is approximately 73% and after three seizures is 76% (Beghi et al, 2008). There is agreement that antiepileptic drug treatment should be offered after a second seizure; however, the value of antiepileptic drugs (AEDs) for the treatment of a first unprovoked seizure has been a subject of debate. Evidence against treatment of the first seizure was provided by observational studies, which reported no difference in the risk of recurrence between treated and non-treated patients. Some randomized trials demonstrated that the AEDs can reduce the relapse of a first seizure; however, treatment of the first seizure and treatment of the relapse do not seem to affect the long-term prognosis of epilepsy, and antiepileptic drug treatment may be associated with adverse effects as well as increased stigma.

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

Population: adults and children with a first unprovoked seizure

Interventions: AED treatment offered after first seizure

Comparison: AED treatment offered only after a seizure recurrence

placebo

Antiepileptic drug treatment after first unprovoked seizure

Outcomes: time to first seizure

time to 2-year remission

adverse Effects

quality of life

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

A Cochrane review protocol for treatment for a first epileptic seizure has been published (Beghi et al, 2008). The author has kindly provided us with the articles found by the literature search. The meta-analysis has not yet been performed.

A meta-analysis (Wiebe et al, 2008) of treatment of a first seizure (probably considering short-term seizure recurrence, although it is not entirely clear) has also been published. This has been GRADEd (see below).

A practice parameter published in 2003 (Hirtz et al, 2003) considered the prevention of recurrences and long-term prognosis after a first unprovoked seizure in children. All the class I and II articles cited are included in the literature search for the Cochrane review.

A Clinical Evidence publication (Marson et al, 2009) also considered the use of AEDs after a single seizure. This did not provide pooled effects and included the articles selected for the Cochrane Review mentioned above.

A PubMed search using the terms (epilepsy AND first seizure AND treatment) AND systematic [sb] found no further systematic review.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Immediate AED treatment after a first seizure vs. treatment delayed until recurrence	Time to first seizure	Wiebe et al, 2008	Only recent study with meta-analytical results
		Time to seizure remission	No systematic reviews found	

Narrative description of the studies that went into the analysis

Wiebe et al, 2008 included 6 randomized studies have looked at immediate versus delayed treatment in patients with a single unprovoked seizure. Only one of these studies was double blind and placebo controlled. Two of the studies assessed only generalized seizures, and one only children. Neonates were included in a single trial.

Wiebe et al, 2008 reported that all randomized controlled trials showed that immediate treatment with an AED reduced the risk of a subsequent seizure in the short-term, but none showed that long-term AED treatment altered long-term outcomes. A problematic aspect highlighted by Wiebe et al, 2008 is that patients did not remain on their initial treatment group on the long term, that is, by 2 or 3 years, many patients in the untreated group were receiving treatment, and many in the treated group had stopped their treatment. So it is not clear if immediate treatment with an AED positively affects the long-term outcome of the condition.

One included study (Marson et al, 2005) had the longest follow-up (8 years). They looked at both time to first seizure and time to first tonic-clonic seizure. The largest differences occurred at 5 years, when 42% of treated and 51% of untreated patients experienced a second seizure, while 35% of treated and 44% of untreated patients experienced a tonic–clonic seizure. Two year remission rates were identical (92%) for both groups at 5 years, and almost identical (95% vs. 96%) at 8 years. Thus, long-term prognosis was not altered with early intervention.

Another study (First Seizure Trial Group, 1993) found that the overall risk of seizure recurrence was 50% lower in treated patients at 2 years (adjusted RR = 0.5, 95% CI 0.3–0.6). However, there was no significant difference between the groups in achieving a 1- or 2-year seizure-free period (RR 2-year remission 0.82, 95% CI 0.64–1.03) (Musicco et al, 1997), and both had a 64% chance of 5-year remission at 10 years (Leone et al. 2006).

a. Time to first seizure.

(Studies which are highlighted grey are not included in Wiebe et al, 2008 meta-analysis)

Reference	Design	Sample size and demographics	Comparison methods	Limitations	Results
Camfield et al,1989	Randomised, unblinded study. No detail provided on randomisation process. Children had afebrile	49 children eligible, 31 (14 boys) randomised. Mean age at entry 79 months (range not	Time to recurrent unprovoked afebrile seizure.	Non-blinded. 18 refused randomisation. 1 child randomised to cbz had a seizure after 5 days of no medication. One sided	2/14 randomised to cbz and 9/17 on no treatment had a seizure within one year of randomisation. Article gives one-sided Fisher's exact p = 0.0295 (but 2-sided

	seizures – any type except atonic, absence or myclonic.	provided).		analysis.	p=0.059). 2 children in each group had febrile seizures. 4 children stopped cbz due to somnolence (N=2) or rash (N=2).
Camfield 2002	Follow up of 26 of 31 patients in above study.	26 children traced after 15 years follow-up. 16/17 in control group and 10/14 in cbz group contacted.	Further seizures.	Five patients lost to follow-up.	12 controls and 5 on cbz had had at least one further seizure. 12/16 controls had received at least one AED.
Chandra 1992	Double blind comparison of 228 patients with a single seizure within 2 weeks of presentation. Excluded if seizure was due to neurological disease or intracranial tumour.	Adults (>16yrs) with single seizure, seen within 2 wks. Double blind placebo control using SVP four times daily.	Recurrence within 1st year of treatment.	No mention of randomisation. Code was broken if patient had a seizure. No mention of drop-outs.	5/115 in valproate group had recurrent seizures compared with 63/113 in placebo group. Ten mentions of side effects with valproate compared with 2 with placebo.
Das et al, 2000	Patients with single idiopathic generalised seizure. No history of febrile seizures or unprovoked seizures. Randomised into AED treatment or no treatment.	Originally 100 patients. 17 with abnormal CT excluded. 7 lost to FU. Any age. N=76 (56 male).	Recurrence during follow-up.	7 lost to follow-up. No mention of blinding.	4/36 treated had recurrence compared with 18/40 untreated. Duration of follow 12 to 24 months.
Gilad et al, 1996	Patients presenting to A&E within 24 hours of a single first unprovoked	N=91, but 4 not included in analysis. 42 men. 18 to 50 years.	Recurrence within 36 months.	4 patients dropped out – one patient from treated group dropped for lack of compliance. 3 from	During 3 year FU, 29 (71% of untreated group) and 10 (22%) of treated group had a further seizure.

	generalised tonic-clonic seizure. AED treatment (initially cbz, or valproate if side-effects).			untreated group lost to FU. Randomisation sequential. Unblinded.	
First Seizure Trial Group, 1993	People presenting to hospital within 7 days of first witnessed unprovoked tonic-clonic seizure. Randomised by telephone to immediate treatment or treatment following recurrence. AED chosen by clinician. Excluded if recurrence within 7 days before randomisation. ITT analysis.	N=397 (204 immediate treatment, 193 treatment only if recurrence). Age 2 years and older. 229 (58%) men.	Recurrence during follow-up.	Unblinded. No placebo group.	Recurrence of GTCS during FU in 36 (18%) treated group and 75 (39%) untreated group.
Marson et al, 2005	Randomised trial of immediate or deferred AED treatment in people with single seizures or early epilepsy. Unblinded. Choice of AED dependent on clinician choice.	N=1443 (826, 57% men). Age one month and over.	Comparison between immediate and deferred AEDs on: time to first seizure, time to first Tonic clonic seizure.	Unblinded. No restriction of choice of AED.	Of patients randomised to immediate treatment, 404 had single seizure before randomisation (deferred group, 408 had single seizure). Considering those with single seizures only: At 2 years 32% immediate group vs. 39% deferred treatment group had had further seizure.

b. Time to 2 year remission

Reference	Design	Sample size and demographics	Comparison methods	Limitations	Results
Camfield et al, 2002	Follow up of 26 of 31 patients in above study.	26 children traced after 15 years follow-up. 16/17 in control group and 10/14 in carbamazepine group contacted.	Further seizures.	Five patients lost to follow-up.	Terminal 2 year remission in 8/10 in treated group compared with 14/16 controls.
Musicco et al,1997	Longer FU of group in First Seizure Trial Group, 1993 (above). Sample size slightly larger. Endpoints seizure remission one year and two years.	N=419 (56% men). 215 randomised to immediate AED treatment, 204 to treatment only if recurrence.	One and two year seizure freedom attained.	Unblended. ITT analysis.	One year remission attained in 186 (87%) immediate treatment patients and 170 (83%) initially untreated patients. Two year remission attained in 146 (68%) immediate treatment patients and 122(60%) initially untreated patients. Both groups had the same time-dependent probability of achieving 1 and 2 seizure-free years.
Leone et al, 2006	Further follow-up of First Seizure Trial Group, 1993 (above).	N=419.	Two and five year seizure freedom attained.		After further follow-up, two year remission attained in 174 (81%) immediate treatment patients and 159 (78%) initially untreated patients. Five year remission attained in 86 (63%) immediately

					treated patients and 82 (64%) initially untreated patients.
Marson et al, 2005	Randomized trial of immediate or deferred AED treatment in people with single seizures or early epilepsy. Unblinded. Choice of AED dependent on clinician choice.	N=1443 (826, 57% men). Age one month and over.	Comparison between immediate and deferred AEDs on time to 2 year remission (and other outcomes).	Unblinded. No restriction of choice of AED.	Of patients randomised to immediate treatment, 404 had single seizure before randomisation (deferred group, 408 had single seizure). Considering those with single seizures only: Two year remission achieved by 69% (immediate) and 61% (deferred) by 2 years, 92% (immediate) and 92% (deferred) at 5 years and 95% (immediate) and 96% (deferred) by 8 years. At least one adverse event reported during follow-up by 39% of immediate group (including those with >1 seizure) and 31% of deferred group.

GRADE tables

Table 1

Author(s): G Bell, C Barbui, T Dua
Date: 2009-08-20
Question: Should antiepileptic drugs vs. no treatment be used for adults and children after first unprovoked seizure?
Settings:
Bibliography: Wiebe et al (2008). An evidence-based approach to the first seizure. *Epilepsia,* 49(Suppl1):50-7.

Antiepileptic drug treatment after first unprovoked seizure

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antiepileptic drugs	no treatment	Relative (95% CI)	Absolute		
seizure recurrence (Risk reduction)												
6[1]	randomised trials	serious[2]	very serious[3]	no serious indirectness[4]	no serious imprecision	none	130/819 (15.9%)[5]	0%	RR 0.34 (0.15 to 0.52)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
adverse effects												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Figure 1 of Wiebe et al, 2008.

[2] Only one out of six studies is double-blind and placebo controlled, and no data on dropouts are reported.

[3] Text states "substantial heterogeneity" (hence random effects meta-analysis was performed).

[4] Two studies assessed only GTCs. One study assessed only children.

[5] Table in Wiebe et al, 2008 gives the Ns for Marson et al, 2005 as 722 and 721. The rest of the date applies to seizure occurring at 6 mo in people with single seizures before randomization. Thus the Ns sould possibly be 404 and 408 respectively. It is unclear which data were used for the meta-analysis. Additionally, the risk difference in the text (used in the GRADE) is marginally different from that in the Figure 1.

Additional information that was not GRADEd

Two of the articles above mention that those in the immediate treatment group were more likely to report at least one adverse event (First Seizure Trial Group, 1993; Marson et al, 2005) . Side effects of AEDs are not inconsiderable and may involve serious risks as well as more minor inconveniences. Idiosyncratic reactions, teratogenesis and cognitive effects are well recognised. Additionally the costs of obtaining AED treatment must be considered, particularly when many people with a single seizure never have a further seizure. As well as the cost to the patients and families, the costs to the health service in providing resources must be considered.

Reference list

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First Seizure Trial Group (1993). Randomized clinical trial on the efficacy of antiepileptic drug in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology,* 43:478-83.

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Leone MA, Solari A, Beghi E (2006). Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy. *Neurology,* 67:2227-9.

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Pearce JL, Mackintosh, HT (1979). Prospective study of convulsion in childhood. *The New Zealand Medical Journal,* 89:1-3.

Wiebe S, Tellez-Zenteno JF, Shapiro M (2008). An evidence-based approach to the first seizure. *Epilepsia,* 49(Suppl 1):50-7.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	There is evidence in children and adults showing that early seizure recurrence is reduced by early initiation of AED treatment. However, there is no evidence showing that immediate treatment with an AED positively affects the long-term outcome of the condition. Retrospective and prospective observational studies indicate that the prognosis for the development of chronic epilepsy is not altered through early intervention. Antiepileptic drug treatment is associated with adverse effects.
Summary of the quality of evidence	The quality of evidence was VERY LOW
Balance of benefits versus	There is no evidence that treating the first unprovoked seizure will affect the

harms	long term prognosis. The risks (cognitive, behavioral, physical as well as psychosocial) of chronic AED therapy need to be weighed against the probable benefit in preventing a recurrence.
Values and preferences including any variability and human rights issues	Patient age, occupation, need to drive and personal preference are important factors to consider. Antiepileptic drug treatment may be associated with adverse effects. Antiepileptic drug treatment may be associated with increased stigma, although stigma may also be associated with the experience of seizure.
Costs and resource use and any other relevant feasibility issues	Carbamazepine, phenobarbital, phenytoin, and sodium valproate are included in the WHO list of essential medicines.
Final recommendation(s) Antiepileptic drugs should not be routinely prescribed to adults and children after a first unprovoked seizure. In adults and children with a high risk of recurrence (e.g. presence of neurological deficit, associated handicaps), referral should be made to specialist setting for further assessment. Strength of recommendation: STRONG	

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant.