**E U R E C A**
**EVIDENCE THAT IS UNDERSTANDABLE, RELEVANT, EXTENDIBLE, CURRENT, AND APPRAISED**
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# Tapering of Anticonvulsant Therapy in Children

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The following piece (in italics) is presented with kind permission from the *Archimedes* section of *Archives of Disease in Childhood*(1). This is followed by examination of the evidence along the lines of EURECA.

***ARCHIMEDES***

*Smith R, Ball R. Arch Dis Child 2002; 87: 259-260.*

***Clinical scenario:*** *A 12 year old girl with primary generalised epilepsy comes to clinic for review. She has been seizure free for two years on sodium valproate 600 mg twice daily. Following discussion with her and her mother, an agreement is reached to withdraw the medication. You advise that the medication should be tapered off over a six week period. At this point the mother informs you that when she had her own anticonvulsant medication withdrawn, this was reduced over a six month period. She questioned whether it was appropriate to reduce the medication so quickly and requested evidence to support the recommendation, raising concerns about the possibility of a higher risk of seizure recurrence.*

***Structured clinical question:*** *In a child with primary generalised epilepsy [patient] does the rate of withdrawal of anticonvulsants [intervention] affect rate of seizure recurrence or other adverse event [outcome]?*

***Search strategy and outcome:*** *The Cochrane library search terms "epilepsy" or "anticonvulsants" yielded no relevant systematic reviews or controlled trials of relevance. Using PubMed-"anticonvulsants/administration and dosage" (MESH) AND "drug administration schedule" (MESH) limits All child 0–18 years, English, clinical trial, there were 98 hits—one relevant RCT was found. A further search by Ovid 1966–2001 with search terms "anticonvulsants" OR "epilepsy" (MESH) AND "discontinuing" OR "stopping" OR "withdrawal" (keyword) limited to all child 0–18 was performed. There were 56 hits, the same single RCT was identified.*

***Commentary:*** *Guidelines based on expert recommendations from the 1980s for adults and children suggested discontinuation be undertaken slowly over months to minimise risk of relapse (level 5 evidence). A large textbook of paediatric neurology gave neither advice nor data. A general paediatric text suggested weaning should take place over 3–6 months because abrupt withdrawal may cause status epilepticus (level 5 evidence). The usual practice of two consultant paediatricians, one with an interest in epilepsy, was to withdraw therapy when appropriate over 6–8 weeks. There is a paucity of published randomised controlled trials on this subject. The seizure recurrence rate in children in this study was 40%, which is in the range of seizure recurrence rates (11–41%) seen in children but on the higher side. This may reflect a patient population in a tertiary centre with more severe epilepsy. The study identified was relatively small and therefore underpowered to detect potential differences as indicated by the wide confidence intervals. This would especially be so for detecting differences in subgroups of children with differing types of epilepsy and on different*

*anticonvulsants. To confirm an absolute risk reduction of 9%, a significance level of 0.05 and power of 80% would require 465 subjects in each group, clearly a much larger study. In this study the type of medication being tapered did not affect risk of seizure recurrence. The majority of patients in both groups were on either phenobarbitone or phenytoin; 66% in six week taper group and 65% in nine month taper group. There were only 9% and 8% in the respective groups on sodium valproate. There are differences in the pharmacology of these drugs which may affect rates of seizure recurrence on withdrawal. Currently, neither phenytoin and phenobarbitone are first or second choice anticonvulsants used by paediatricians in the UK.*

*They also randomised into two groups for duration of seizure free period (either two or four years seizure free) before tapering was begun. There was a trend towards a greater risk of seizure recurrence in the group that had been seizure free for two years before drug tapering was begun, although this was not significant. The optimum duration of treatment when seizure control has been achieved has not been established. The presence of mental retardation and the presence of spikes on pre-withdrawal electroencephalogram increased the likelihood of a recurrence of seizures in this and other studies. Our case had normal intelligence and it is not our routine practice to perform withdrawal electroencephalograms in patients with primary generalised epilepsy. The subject of this enquiry was tapered off valproate over six weeks and has remained seizure free at three month follow up.*

## EURECA

### Relevance

There is a general agreement on continuing anti-convulsant therapy in children with primary (idiopathic) generalized seizures and no significant risk factors for at least two seizure-free years(2-4). However, it is not clear over what time period such therapy should be withdrawn. Nelson Textbook cautions against abrupt withdrawal of anti-convulsant therapy for fear of provoking status epilepticus and recommends withdrawal over three to six months, although the basis for this is not described(5). Since anticonvulsant therapy is often associated with significant neuropsychological, cognitive and behavior related effects(6,7) besides being expensive, one would prefer rapid tapering and discontinuation. The clinical question raised in Archimedes is thus relevant since it leads to the decision question, *"Could (should) I rapidly taper and discontinue anticonvulsant therapy in children who are seizure-free?"* and also the issue of balancing efficacy and safety, in the context of an individual patient in our clinical setting.

### Current Best Evidence with Critical Appraisal

A 2006 Cochrane review on this question(8) included a comprehensive search till September 2004 and identified a single randomized controlled trial (RCT) in children(9). Therefore, an additional PubMed search beyond this date was conducted on 21 August 2008 using the terms *"antiepileptic withdrawal"* (501 citations), *"antiepileptic weaning"* (34 citations), *"antiepileptic taper"* (25 citations) and *"antiepileptic discontinue"* (34 citations). No limits were used. The search yielded one additional RCT(10), one comment(11) and twelve papers that appeared relevant, but did not pertain to this issue. No additional data was identified through searches in TRIP database and BestBETs.

As RCT is the most appropriate study design for this clinical question, data from the Cochrane review and additional RCT comprise current best evidence. The Cochrane review followed the usual methodology including independent analysis by two reviewers at every stage and intention-to-treat analysis. The authors' exclusion list does not have any trials which could provide additional data. As the review is due for updating, it is likely that the authors would include the additional trial and arrive at appropriate results..

***Table* I** shows the characteristics of the two RCTs. The new trial(10) presented data as a Kaplan Meir survival curve depicting percentage of seizure free children over time; absolute numbers had to be calculated from a blow-up of the graph. A meta-analysis of the data from the two RCTs was

**TABLE I** CHARACTERISTICS OF TRIALS INCLUDED IN THE EURECA META-ANALYSIS

| Trial | Tennison, *et al.* 1994(9) | Serra, *et al.* 2005(10) |
|---|---|---|
| Subjects | 149 children | 57 children (2-16 yr) |
| Seizure control duration | 18 mo | 2 yr |
| Participant characteristics | mean age at seizure onset:4 yr; tapering: 11 yr | majority of children had idiopathic seizures and required 1 drug for control |
| Normal EEG at start of tapering | 40% | 72% |
| Rapid tapering | 6 wk; 25% decrement every 2 wk (n=81) | 1 mo; 25% decrement every 10 d (n=30) |
| Slow tapering | 9 mo; 25% decrement every 3 mo (n=68) | 6 mo; 25% decrement every 2 mo (n=27). |
| Follow-up duration | 5 yr | 4 yr |
| Outcome variables | seizure recurrence, number of seizure free children | seizure recurrence |
| Randomization | by tossing a coin | not described |
| Allocation concealment | inadequate | not described |
| Drop-outs | >10% | none |
| Blinding | none | not described |
| Methodological quality | low | low |

conducted and the results are summarized in ***Table* II.** The risk of seizure recurrence in children whose anticonvulsant therapy is tapered rapidly (within 6 weeks) is comparable to those where tapering is slow (over 6 months or longer). It should be noted that this conclusion is drawn from only two methodologically poor RCTs with a small number of participants; the data is neither sufficiently robust nor adequately powered to detect a difference, should it exist.

### EXTENDIBILITY

Both the RCTs comprising current best evidence included only children; they had various types of seizure disorders (most frequently idiopathic) and were receiving different anticonvulsant therapy including multiple drugs in some patients. All children did not have normal EEG at the time of starting tapering. These facts suggest that the participants in both trials resemble the real-life clinical situation. Therefore, although neither of the trials was based in our population, the evidence can be extended to the Indian setting but evaluation of the seizure type and individual risk factors is important.

One point that is not clear is whether greater caution should be exercised for children who reside far from medical facilities/centers and may therefore be unable to report quickly in the event of seizure recurrence. In the absence of high quality evidence to support or refute rapid tapering, another unclear issue is judging the relative balance (in the

**TABLE II** EURECA META-ANALYSIS OF DATA FROM RCTs

| Seizure recurrence at | *n* | RR (95% CI) |
|---|---|---|
| 1 yr | 206 | 1.29 (0.90-1.84) |
| 2 yr | 206 | 1.00 (0.78-1.29) |
| 3 yr | 206 | 0.86 (0.72-1.04) |
| 4 yr | 206 | 0.86 (0.74-1.01) |
| 5 yr | 149 | 0.96 (0.86-1.07) |

*RR = relative risk; CI = confidence interval.*

**EURECA CONCLUSIONS IN THE INDIAN CONTEXT**

- The risk of seizure recurrence is similar with rapid or slow tapering of anticonvulsant therapy in children with uncomplicated seizures.
- This conclusion is based on only two methodologically unsatisfactory randomised controlled trials.

Indian setting) between the need to minimize anticonvulsant therapy against the risk of seizure recurrence. Although this has greater impact on the duration of anticonvulsant treatment rather than the rate of withdrawal, it could affect individual decisions in daily practice.

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