For a year now, Archimedes has sought to assist practising clinicians to give the best care to patients and families; paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family by providing "evidence based" answers to common questions which are not at the forefront of research, but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Mackway-Jones and the group at the Emergency Medicine Journal—"BestBets".

A word of warning. The topic summaries are not systematic reviews, though they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What Archimedes offers are practical, best evidence based answers to practical, clinical questions.

The format of Archimedes may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching, and gaining answers.) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question. A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett and Moyer may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra topics. The previously published topics will hopefully be available soon from the same site, published as "rapid responses" to the original article.

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REFERENCES
4 http://cebim.r2.ox.ac.uk/docs/levels.htm [accessed April 2001].

In this anniversary issue, we highlight four questions which Archimedes considers should have evidence based answers—but don’t. These are:
- How quickly can you withdraw antiepileptic medicines?
- Does melatonin help developmentally delayed children with sleep problems?
- Should children with glue ear get grommets (ventilation tubes)?
- Are children with perianal dermatitis more likely to have been sexually abused?

Readers wishing to submit their own questions—with best evidence answers, or indeed lack of answers—are encouraged to review those already proposed at www.bestbets.org. If your question still hasn’t been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com.

Additional information on each of the topics is available on the ADC website (www.archdischild.com)
Discontinuing anticonvulsant medication in children

Report by Robert Smith and Robin Ball, Consultant Paediatricians, York District Hospital, UK

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. 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. See table 1.

Commentary
Guidelines based on expert recommendations from the 1980s for adults and children suggested discontinuation be undertaken slowly over a period of 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. This indicates 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 468 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 phenobarbital 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.

<table>
<thead>
<tr>
<th>Table 1 Discontinuing anticonvulsant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citation</td>
</tr>
<tr>
<td>Tennison et al (1994)</td>
</tr>
<tr>
<td>Study group</td>
</tr>
<tr>
<td>149 children with epilepsy randomised to 6 week or 9 month taper after 2 or 4 year seizure free interval</td>
</tr>
<tr>
<td>Study type (level of evidence)</td>
</tr>
<tr>
<td>Prospective, randomised unblinded trial (level 1b)</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Seizure recurrence</td>
</tr>
<tr>
<td>Key results</td>
</tr>
<tr>
<td>No difference in seizure recurrence rate between 6 week and 9 month taper (p=0.38) Relative risk reduction = 8% 95% CI -34% to +50%</td>
</tr>
</tbody>
</table>

► CLINICAL BOTTOM LINE

- Many factors need to be taken into consideration when considering withdrawing anticonvulsant medication in children with epilepsy; not least the views of the parents and child, which often do not accord with their physician’s view.

- With regard to the rate of withdrawal of anticonvulsants for a child with primary generalised epilepsy, this study indicated that tapering treatment over six weeks did not give a significantly higher risk of recurrence of seizures than tapering over a longer period.

- Further studies are required to determine the specific recurrence risk on withdrawal for sodium valproate.

Is melatonin likely to help children with neurodevelopmental disability and chronic severe sleep problems?

Report by

Caroline Willey, Staff Grade Community Paediatrician, Central Manchester PCT, UK
Bob Phillips, Associate Fellow, Centre for Evidence-based Medicine, Oxford, UK

A girl aged 3 years 6 months has neurofibromatosis with significant visual impairment and mild to moderate learning difficulties. She has always been difficult to settle to sleep and has frequent nocturnal wakings.

A sleep programme with specific behavioural management techniques has been used, as have sedative medications such as trimipramine, which caused deterioration in concentration and daytime sleepiness. Should she be tried on melatonin?

Structured clinical question

In a preschool child with visual impairment and mild to moderate learning difficulties, in whom conventional treatments have failed [patient] is melatonin [intervention] likely to improve her sleep pattern [outcome]?

Search strategy and outcome

Secondary sources

Cochrane Library: Systematic Reviews—0, Abstracts of Reviews of Effectiveness—0, Controlled Trials Register—six papers of which two relevant (same papers found through search detailed below).

Primary sources: Medline 1966 to present—using OVID interface
Melatonin.mp AND Sleep disorders.mp (and exploded) AND Learning disabilities (and exploded) AND Limit to: Children <0 to 18 years> Human, English language.

This gave 90 references; all titles checked—15 considered, six included. Nine excluded as three non-systematic reviews, two other conditions, one non-delayed children, one slow release melatonin, two abstracts only.

Embase 1980 to present: searched with same strategy—no additional papers.

See table 2 for summary of the six included papers.

Commentary

Most studies had small numbers of participants with significant drop out rates or non-randomisation in larger studies. Very few of the studies give p values or confidence intervals—they appear far too small to give statistically meaningful effects. One of the trials (Camfield et al) is very different in design, an “N-of-1” study. These trials are designed for each individual patient, and allow for interpersonal variation in drug effect. Classically an N-of-1 trial has three blocks; during each block the patient receives sequentially therapy and placebo under double blind conditions with an appropriate washout period. Response in two or three blocks is considered positive; less than this, caused by chance alone.

Even allowing for the difficulty of recruitment and objective assessment of outcomes in children with multiple difficulties, there is currently little good quality evidence for the effectiveness of melatonin. The startling increase in seizures noted by the Sheldon paper is of great concern, especially in the UK where melatonin is often given in an uncontrolled way with overseas imports of the drug. A large multicentre placebo-controlled randomised controlled trial is needed to try to clarify which children and what types of sleep disorder are most amenable to treatment, and to define the likely side effect profile.

Clinical bottom line

• Melatonin may be effective in sleep onset difficulties, but not in fragmented sleep or early morning wakening, though evidence is poor quality.
• There is little evidence regarding melatonin’s long term safety profile.
• Melatonin should be used with caution in any child with epilepsy in view of increased seizure frequency in one study; “N-of-1” methods may be considered.

Do grommets prevent language delay?

Report by

Vidya Sudhakar-Krishnan, Paediatric Registrar, St James’s University Hospital, Leeds, UK
Mary Rudolf, Consultant Community Paediatrician, Leeds General Infirmary, Leeds, UK

A mother brings her 2 year old daughter to your clinic. She is concerned about her speech which she feels is poor for her age. Her daughter has failed two consecutive audograms. On otoscopy she has signs of bilateral otitis media with effusion (OME) which you have confirmed on a previous occasion two months ago. Should you refer for insertion of grommets?

Structured clinical question

In preschool children with OME (glue ear) [patient] does the insertion of ventilation tubes (grommets) [intervention] as...
possibility of uneven allocation. The large numbers of studies have problems with small study populations leaving the need to be addressed. The results of a further randomised controlled trial are awaiting publication.

Commentary

The use of language development as an outcome measure is problematic because of confounding factors, such as age, maternal education, and comorbid conditions. These studies have attempted to overcome this by randomisation, but still have problems with small study populations leaving the possibility of uneven allocation. The large numbers of the watchful waiting group being treated despite the study protocol may bias the results, reducing the apparent effect of ventilation tubes. These problems need to be taken into consideration when interpreting the studies.

In the UK, screening is not routinely carried out for OME, so the patient population in two of the studies is not similar to the UK population. The inclusion of “asymptomatic” children is likely to reduce the effectiveness of ventilation tubes, should any truly exist. The large unintentional crossover in some studies highlights the major problem in that there are no clear indications for the insertion of grommets.

Taken as a whole, there does seem to be some improvement in language skills a few months after the treatment. It is not evident that these effects persist long term and the differences seem to diminish with time, as one would expect with the natural history of the condition.

As grommet insertion is the most common elective operation in preschool children, concerns both about risks of the anaesthesia and cost-benefit analysis of the procedure need to be addressed. The results of a further randomised controlled trial are awaiting publication.

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**Table 2** Melatonin in sleep disorders

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Level of evidence</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan et al (1994)</td>
<td>15 children aged 6 months to 14 years, mean 8.8</td>
<td>Double blind placebo controlled trial (level 1b), crossover study</td>
<td>Sleep charts</td>
<td>No adverse effects</td>
<td>6 (40%) not randomised</td>
</tr>
<tr>
<td></td>
<td>with epilepsy, 9 visually impaired, Melatonin 2.5–5 mg</td>
<td></td>
<td>Parental interview</td>
<td>No response in 2/15</td>
<td>Type of sleep disturbance described</td>
</tr>
<tr>
<td>O’Callaghan et al</td>
<td>7 children aged 2–28 years with tuberous sclerosis and epilepsy + SUD</td>
<td>Crossover randomised double blind trial (level 1b)</td>
<td>Sleep diary</td>
<td>Mean improvement in total sleep time of 0.55 h (CI 0.088 to 1.01)</td>
<td>Short treatment time for any adverse effects to become apparent</td>
</tr>
<tr>
<td>(1999)</td>
<td>Randomised to placebo or 5 mg melatonin 20 min prior to bedtime</td>
<td></td>
<td>Total sleep time</td>
<td>No effect on fragmented sleep</td>
<td>No effect noted on seizure frequency</td>
</tr>
<tr>
<td>Dodge and Wilson</td>
<td>20 children with moderate to severe developmental disabilities (4/20 visual impairment), age range 1–12 years</td>
<td>Randomised double blind placebo controlled trial (level 2b)</td>
<td>Sleep latency</td>
<td>Sleep latency improved in all but 2 children on MLT (p&lt;0.05); more marked in those with greater sleep latency on baseline measure</td>
<td>No side effects reported large drop out rate but no reported differences in diagnosis, age, epilepsy, etc in those not completing</td>
</tr>
<tr>
<td>(2001)</td>
<td>36 recruited but only 20 completed study</td>
<td></td>
<td>Duration of sleep</td>
<td>Dose of melatonin but no different from placebo</td>
<td>No baseline data for type or severity of sleep problems in those dropping out</td>
</tr>
<tr>
<td>Camfield et al</td>
<td>6 children aged 3–13 years blind with at least moderate learning disability, using 0.5–1 mg melatonin</td>
<td>“N-of-1” double blind placebo trial (level 2b)</td>
<td>Sleep diary</td>
<td>Found MLT to be ineffective in 5/6</td>
<td>Low dose used</td>
</tr>
<tr>
<td>(1996)</td>
<td></td>
<td></td>
<td>Average numbers hours sleep per 24 hours</td>
<td>Timing in relation to desired sleep time may have been too long</td>
<td></td>
</tr>
<tr>
<td>Palm et al (1997)</td>
<td>8 aged 3–23 years (6 children aged 18 or less) All functionally blind, M/S learning disabilities 0.5–2 mg melatonin, age dependent</td>
<td>Open study (level 4)</td>
<td>Sleep diaries for 6 weeks prior to treatment and several months during treatment MLT levels in 7 children</td>
<td>“Dramatic” response in all 8</td>
<td>No side effects reported</td>
</tr>
<tr>
<td>Sheldon (1998)</td>
<td>6 children, 9 months to 18 years Multiple neurological deficits and chronic sleep disorders with 5 mg at bedtime</td>
<td>Open study, consecutive recruitment (level 4)</td>
<td>Wrist actigraph</td>
<td>“N-of-1” double blind placebo trial (level 2b)</td>
<td>No side effects reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Changes in sleep onset latency, nocturnal wakeings Total sleep time</td>
<td>Marked improvement in all 3 measures in 5/6</td>
<td>Study stopped due to increased or new seizure type activity on melatonin in 4/6</td>
</tr>
</tbody>
</table>

MLT, melatonin.

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possibility of uneven allocation. The large numbers of studies have problems with small study populations leaving the need to be addressed. The results of a further randomised controlled trial are awaiting publication.
Is perianal dermatitis a sign of sexual abuse?

Report by

Joanna Thomas, Staff Grade in Community Child Health, Leeds Community and Mental Health Trust, UK

Mary Rudolf, Consultant Paediatrician in Community Child Health, Leeds Community and Mental Health Trust, UK

### CLINICAL BOTTOM LINE
- No evidence has been found to support or refute the association of perianal dermatitis and sexual abuse.

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