groups. Xylitol may still have some effect on the number of pneumococci growing in the nasopharynx, which we were not able to estimate in this study.

Being a polyol, xylitol is slowly absorbed by the gut wall and may cause osmotic diarrhoea when ingested in large amounts. Children can tolerate daily doses up to 45 g of xylitol without gastrointestinal symptoms.¹⁴ Two children in our trial stopped using xylitol because of complaints of diarrhoea. Yet the recorded number of episodes of diarrhoea and the mean duration of diarrhoea were similar in both groups.

The use of xylitol in the prevention of dental caries is widely accepted in Scandinavia. There are day care nurseries where chewing gums containing xylitol are given regularly after each meal. We thus did not change the current Finnish habits of using xylitol sweets in our trial. The chewing gum was given for only two months and always immediately after a meal or a snack. We found no difference in dental caries between the treatment groups four months after our trial. A large 40 month follow up trial showed that sucrose chewing gum increases the risk of dental caries only marginally.¹⁵

The episodes of acute otitis media were diagnosed by several doctors who used pneumatic otoscopy in diagnosis. The accuracy of pneumatic otoscopy in detecting middle ear effusion in a child with respiratory symptoms has been found to be over 80%.¹⁶ Inaccuracy in diagnosis would cause estimates of the efficacy of xylitol in our trial to be too low.

The mean age of 5 years of the children in our study was older than that of most patients with acute otitis media as the peak incidence occurs at the age of 6-15 months.^{17 18} The children participating in our trial had to be able to chew gum without swallowing it, which resulted in the selection of older children. Most of the children had previously had several episodes of acute otitis media and many had undergone adenoidectomies. Thus, our estimate of the efficacy of xylitol may be too optimistic and not directly applicable to unselected series of younger children.

Respiratory infections, especially acute otitis media, in children are the main reason for the use of oral antimicrobials. The emergence of multidrug resistant strains of *S pneumoniae* substantiates the need for new approaches in the prevention of bacterial infections. We have been able to show that xylitol, a well tolerated food additive, is an effective approach.

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Key messages

- Xylitol, a widely used food sweetener, is effective in preventing dental caries and inhibiting the growth of *Streptococcus mutans*
- It also inhibits the growth of *S pneumoniae*
- When given to children with recurrent otitis media chewing gum xylitol reduced the occurrence of otitis media by about 40%
- The daily dose required is not known, but 8.4 g given daily in a chewing gum seems to be effective
- Xylitol had no effect on the nasopharyngeal carriage of pneumococci

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Commentary: What about the ethics?

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The substitution of xylitol for sucrose in the diet has been of considerable interest since the report of a two year study in Turku, Finland, which studied a young adult population and showed a significant reduction in dental caries.¹ As total substitution of dietary sucrose by xylitol was deemed impossible in children, studies were subsequently limited to partial substitution in confectionery and chewing gum.^{2 3} These studies have demonstrated significant reductions in dental caries in schoolchildren when conducted over periods of two to three years. Xylitol is now accepted as non-cariogenic, and undoubtedly reduces the growth of *Streptococcus mutans*. It remains uncertain, however, to what extent this microbial effect on the oral flora is responsible for

the cariostatic properties of xylitol seen in these clinical trials. It has also been observed that chewing xylitol gum increases salivary flow, thus aiding remineralisation of carious lesions and that this may be the main mechanism of its anticaries effect.⁴ The fact that xylitol has also been shown to suppress in vitro the growth of *S pneumoniae* in a manner similar to that for *S mutans* and that this led to the present clinical trial of xylitol chewing gum, which has shown a significant reduction in episodes of acute otitis media, is clearly fascinating. The failure to demonstrate a reduction in pneumococcal carriage rates between study and control groups leaves doubts as to the precise mode of action of xylitol, not too dissimilar to that met in dentistry.

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The main point of this commentary, however, is to review the ethical decision to use chewing gum containing sucrose for the children in the control group. There are several reasons why an ethics committee based in the United Kingdom might have taken a different view from that reached in Finland.

Firstly, the use of chewing gum containing sucrose was not without risk to the dental health of children susceptible to caries in the control group. The previous study on xylitol that used a sucrose chewing gum in a control group was in older children (average age 10.2 years) and did not test the effect on the primary dentition which may be at greater risk.⁵ Admittedly this risk was small considering the very limited time of the experiment.

Secondly, the researchers seemed to be aware of the risk and therefore excluded children in whom caries was "noticed" when they took the first nasopharyngeal samples. They did not employ a dentally trained person to undertake this baseline examination, however, and may well have missed several children already suffering from the disease. This can be inferred from the observations of the dental nurse who, four months after the end of the trial, noted 44 children with dental decay. It is extremely unlikely that a fifth of the children developed new carious lesions in the six months in question, particularly when 21 children in the study group received xylitol chewing gum for the first two months.

The precise nature of this examination by the dental nurse is not stated but probably did not include the use of dental radiographs. Without these further lesions may have been missed specifically on the proximal surfaces of the molar teeth, surfaces particularly at risk from sucrose in the diet.

Thirdly, children in the control group already suffering from caries would have been subjected to increased risk of new or extended carious lesions. Such a risk would be considered by many too great to justify the possible benefits likely to accrue from the clinical trial. Furthermore, it seems to take little account of the guidance that "parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may carry some risk of harm."⁶

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Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome

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New antiepileptic drugs have a pivotal role in the successful treatment of the 20-30% of patients with epilepsy that is resistant to drug treatment. They are considered to be effective in such patients if they reduce the frequency of seizures by 50% or more because few patients are rendered seizure free.¹ Despite these drugs' apparent success with this outcome measure,^{2,3} the question still remains whether new antiepileptic drugs affect the long term prognosis of refractory epilepsy as measured by mortality and freedom from seizures.¹ We report our follow up audit of patients recruited from 1987 to 1989 into two uncontrolled open label clinical studies of lamotrigine and vigabatrin.^{2,3}

Patients, methods, and results

The two open label trials in 128 patients (vigabatrin) and 125 patients (lamotrigine) were both described in detail in 1990.^{2,3} All patients had confirmed severe medically refractory epilepsy and were evaluated as inpatients or outpatients at the Chalfont Centre for Epilepsy or the National Hospital for Neurology and Neurosurgery. After the trials the patients could continue the trial drugs, which were licensed in 1989 (vigabatrin) and 1991 (lamotrigine). By using hospital records and by contacting general practitioners, referring physicians, and the patients directly, we determined (a) how many patients were free of seizures, (b) how many were still taking the trial drug, and (c) how many had died. When appropriate the data on lamotrigine and vigabatrin were compared with the χ^2 test.

We successfully followed up 120 (96%) and 124 (97%) of the patients in the vigabatrin and lamotrigine trials respectively. Four of the five lost to follow up in the lamotrigine group and two of the four lost to follow up

Table 1—Long term outcome in patients with refractory epilepsy entered into open label studies of vigabatrin and lamotrigine as additional treatment

Outcome	Lamotrigine (n = 125)	Vigabatrin (n = 128)
Responded to treatment*	26	41
Lost to follow up	5	4
Seizure free	1	2
Continuing to take trial drugs	11	9
Stopped but restarted trial drugs	3	4
No longer taking trial drugs	89	96
Died	16	13

*50% or greater reduction in frequency of seizures.

in the vigabatrin group were no longer taking their respective trial drug. Table 1 shows details of the patients. A total of 16 (13%) of the lamotrigine group and 13 (10%) of the vigabatrin group had died in about 850 patient years. Of those living, 89 (86%) of the lamotrigine group and 96 (86%) of the vigabatrin group were no longer taking their respective trial drug, although 26 (21%) of the lamotrigine group and 41 (31%) of the vigabatrin group had responded to treatment. One patient was seizure free while taking lamotrigine and two were seizure free while taking vigabatrin. There were no significant differences at $P < 0.05$ between the lamotrigine and vigabatrin groups.

Comment

Of those successfully followed up 6-8 years after recruitment into open label trials for vigabatrin and lamotrigine, three patients were rendered seizure free. Indeed, 86% of those still living were no longer taking

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