

# Anaesthetic–analgesic ear drops to reduce antibiotic consumption in children with acute otitis media: the CEDAR RCT

Alastair D Hay,<sup>1\*</sup> Harriet Downing,<sup>2</sup> Nick A Francis,<sup>3</sup> Grace J Young,<sup>4</sup> Clare Clement,<sup>4</sup> Sue D Harris,<sup>1</sup> Aideen Ahern,<sup>4</sup> Behnaz Schofield,<sup>3</sup> Tammy E Thomas,<sup>5</sup> Jeremy Horwood,<sup>1,4</sup> Peter S Blair,<sup>4</sup> William Hollingworth,<sup>6</sup> Victoria Wilson,<sup>1</sup> Chris Metcalfe,<sup>4</sup> Peter Stoddart,<sup>7</sup> Desmond Nunez,<sup>8</sup> Mark D Lyttle,<sup>7</sup> Paul Little<sup>5</sup> and Michael V Moore<sup>5</sup>

<sup>1</sup>Centre for Academic Primary Care, Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK

<sup>2</sup>National Institute for Health Research Biomedical Research Centre, Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK

<sup>3</sup>Division of Population Medicine, Cardiff University, Cardiff, UK

<sup>4</sup>Bristol Randomised Trials Collaboration, Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK

<sup>5</sup>Primary Care and Population Sciences, University of Southampton, Southampton, UK

<sup>6</sup>Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK

<sup>7</sup>Bristol Royal Hospital for Children, Bristol, UK

<sup>8</sup>Division of Otolaryngology, Department of Surgery, University of British Columbia, Vancouver, BC, Canada

\*Corresponding author [alastair.hay@bristol.ac.uk](mailto:alastair.hay@bristol.ac.uk)

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## Scientific summary

### **The CEDAR RCT**

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# Scientific summary

## Background

Acute otitis media (AOM) is a common, painful condition of childhood that has an impact on the family because of disrupted sleep and time off work and school. Primary care consultation and antibiotics have been the mainstay of management; one UK study found that between 80% and 84% of children presenting to primary care with AOM were prescribed an antibiotic during the years 1995–2011 (Williamson I, Bengt S, Mullee M, Little P. Consultations for middle ear disease, antibiotic prescribing and risk factors for reattendance: a case-linked cohort study. *Br J Gen Pract* 2006;**56**:170–5). This is despite the available evidence of benefit being restricted to children < 2 years old with bilateral AOM, and those with otorrhoea, leading the National Institute for Health and Care Excellence (NICE) to conclude that these are the only children warranting a same-day full-course antibiotic treatment. For other children, the use of a 'wait-and-see' strategy, with or without a delayed prescription for an antibiotic, has been shown to be safe in terms of treatment failure and in the frequency of complications of AOM. Selective antibiotic prescribing in AOM is also recommended by other national guidelines, including the American Academy of Family Physicians and American Academy of Pediatrics, Dutch College of General Practitioners, Scottish Intercollegiate Guideline Network and French Health Products Safety Agency.

Judicious use of antibiotics seeks not only to counter the risks of antibiotic side effects (such as diarrhoea, rashes and anaphylaxis) but to also counter the risk of increasing antibiotic-resistant bacterial strains, which have been shown to increase substantially after antibiotic use. In view of AOM's prevalence, and the high level of associated antibiotic use, strategies to facilitate a reduction in antibiotic use in this condition in the UK are urgently required. Anaesthetic–analgesic ear drops are widely used in some countries and, if effective for controlling ear pain, could reduce dependence on antibiotics. However, there is little evidence regarding their effectiveness as an analgesic and no evidence on how their use affects antibiotic consumption.

## Objectives

The primary aim of the study was to determine if providing topical anaesthetic–analgesic drops [benzocaine–phenazone otic solution (Auralgan®), currently manufactured by Pfizer Consumer Healthcare] leads to a reduction in antibiotic consumption within the first 8 days of AOM diagnosis.

The secondary objectives were to answer the following questions:

- Are anaesthetic–analgesic ear drops more effective than placebo (key secondary question) and usual care in controlling AOM ear pain?
- Are children and their parents satisfied with using ear drops?
- Are anaesthetic–analgesic ear drops cost-effective?
- Do the drops improve the child's quality of life?
- What are the parents' beliefs and expectations in relation to AOM and its treatment?

## Methods

The Children's Ear Pain Study (CEDAR) was a multicentre, randomised three-group (anaesthetic–analgesic drops, placebo drops and usual care) randomised controlled trial (RCT). Owing to investigational medicinal product (IMP) supply problems, recruitment was initially to a two-group (anaesthetic–analgesic drops vs.

usual care) RCT. General practice surgeries in the primary care research network within the areas of Bristol, Cardiff and Southampton agreed to participate. The study was co-ordinated by the Bristol study centre.

Children were eligible if they met all of the following criteria:

- They were aged between 12 months and 9 years.
- They presented within 1 week of suspected AOM onset.
- They had parent-reported ear pain in 24 hours pre enrolment.
- They had clinician diagnosis of AOM.
- They were immunocompetent.
- A clinician was willing to use a NICE-recommended 'no' oral antibiotic prescribing strategy or a 'delayed' oral antibiotic prescribing strategy (as per NICE guidelines) [National Institute for Health and Care Excellence. *Respiratory Tract Infections (Self-Limiting): Prescribing Antibiotics*. Clinical Guideline CG69. London: National Institute for Health and Care Excellence; 2008].
- A parent or legal guardian is able to give informed consent.

Children were excluded from the study if they:

- were severely ill
- were unable to meet NICE delayed or no antibiotic for AOM criteria
- were at a high risk of serious complications
- were unfit to use topical ear drops
- were allergic to the components of the active drop
- had an alternative cause for ear ache
- required antibiotics for a coexisting condition.

The IMP for this trial was a benzocaine–phenazone otic solution (Auralgan). This is an oil-based, combined local anaesthetic (benzocaine) and analgesic (phenazone, also known in the USA as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54 mg (5.4%) of phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinoline sulphate). Despite an absence of published evidence of effectiveness, it is available as a pharmacy medicine in Australia and has been marketed since 1947 under Auralgan and other brand names. For this trial we intended to test Auralgan sold in 15-ml bottles. The placebo was glycerine (Albany Molecular Research Ltd, Glasgow, UK), with identical packaging to the active drops.

Randomisation was stratified by centre in blocks of 30 packs, each block having the packs arranged in a random and consecutively numbered sequence. The IMP supplier provided the pharmacy with medicine packs which had each been prelabelled with the patient identifier (ID) and medicine pack ID numbers. Each pack contained two bottles of active medicine, two bottles of placebo medicine or no bottles but a non-medicinal item of similar weight. Patients were enrolled by their general practitioner (GP) or research nurse who, at the stage of enrolment, was unaware of the contents of the next treatment pack in the sequence (maintaining allocation concealment). When the informed consent process was completed and signed, the trial pack was opened and allocation to active drops, placebo drops or no drops was confirmed. It was not clear if antibiotic prescribing decisions were made before or after opening the pack.

During the 8 days following randomisation, parents completed a daily questionnaire that asked about antibiotic use; ear pain on days 1 and 2; analgesic (e.g. ibuprofen or paracetamol) consumption; symptom presence and severity (e.g. episodes of crying, disturbed sleep and fever); adverse events; new or worsening symptoms (asked only on last day); satisfaction with, and opinion of, treatment allocation and future intention to use drops; costs; preference-based quality of life using the CHU-9D questionnaire and child's quality of life using the OMQ-14 questionnaire.

The net incremental costs to the NHS and society of using active ear drops compared with usual care (no drops) in the short (8 days) and medium term (3 months) were assessed. NHS resource use (e.g. antibiotic

or analgesic use, GP visits) and societal costs (school/nursery absences, parent lost productivity and other family expenses) were reported by parents in the 8-day questionnaire. Medium-term NHS resource use was collated from a review of the child's GP records.

All parents agreeing to participate were asked, at the time of consent, if they were willing to be contacted about taking part in a telephone interview. In-depth telephone interviews were conducted with parents 14 days after randomisation. Lines of questioning focused on views and experiences of the disease, its diagnosis, treatment and recovery, information and support needs, and views and experiences of participation within the trial. Interviews also explored the potential implications of making the CEDAR drops available over the counter, which means that the costs will shift from the NHS to the individual. Health-care professionals were to be interviewed to explore their views and experiences of the trial, information and support needs, and their attitudes to the future implementation of treatments. A flexible interview topic guide was used to ensure that primary issues were covered during all interviews, but without dictating data collection. The interviewer used open-ended questioning techniques to elicit participants' experiences and views of key events, and participants were asked to provide examples.

Based on existing literature, an antibiotic consumption rate of 80% was assumed for the usual treatment (no drop) group. To show an absolute 20% reduction in antibiotic consumption from a baseline of 80% (thought likely to have important effects on antimicrobial resistance), with 90% power at the 5% significance level, the trial would require 119 patients in each group. Allowing for a 20% loss to follow-up, the target sample size was adjusted to 149 patients in each group.

The primary outcome of antibiotic consumption was analysed using logistic regression, adjusting for whether or not the child had received a delayed antibiotic script at baseline. Secondary outcome measures were compared between the study groups using an appropriate regression model. Health economic analysis was undertaken primarily for active ear drops versus usual care comparison of the NHS, family and societal cost per antibiotic consumption avoided during the AOM episode. The qualitative interview data were subjected to thematic analysis using an inductive approach to identify major themes.

## Results

Owing to a delay in procurement of a suitable placebo, the study (especially the three-group study) was delayed and ultimately had to be closed prior to achieving recruitment targets and prior to collecting 3-month follow-up measures. A total of 74 (active drops,  $n = 38$ ; and usual care,  $n = 36$ ) patients were recruited into the two-group study and 32 (active drops,  $n = 12$ ; placebo drops,  $n = 10$ ; and usual care,  $n = 10$ ) were recruited into the three-group study between October 2016 and June 2017. Among patients allocated between anaesthetic–analgesic ear drops and usual care, the only apparent baseline difference was delayed antibiotic prescribing in 11% of the usual-care group and 31% of the active drop group. More differences were expected to occur by chance in the three-group study owing to the modest sample size; differences were apparent in sex, accompanying adult's age and employment status, living in an area of deprivation, breastfeeding status at 3 months, episodes of distress/crying and disturbed sleep.

In the two-group study, 1 out of 29 (3%) and 9 out of 30 (30%) children in the active drop and usual-care groups, respectively, consumed antibiotics. In the three-group study, the corresponding numbers were 0 out of 10 (0%) and 2 out of 8 (25%) children. Combining data from the two-group and three-group studies gives pooled estimates of the odds ratio, comparing active drops with usual care, of 0.09 [unadjusted, 95% confidence interval (CI) 0.02 to 0.55;  $p = 0.009$ ] and 0.15 (adjusted for prescription of delayed antibiotic at recruitment, 95% CI 0.03 to 0.87;  $p = 0.035$ ).

The mean (standard deviation) parent-reported ear pain scores at day 2 were 3.10 points (2.23), 2.14 points (1.07) and 5.00 points (1.73) in the active drops, placebo drops and usual-care groups of the three-group study, respectively. Compared with placebo drops ( $n = 7$  children), slightly greater ear pain was apparent in

the active drop group ( $n = 10$ ; adjusted difference in means 0.67; 95% CI  $-1.44$  to  $2.79$ ), although this difference could have arisen by chance.

There were no differences seen in the use of analgesic consumption or illness duration, but overall symptom burden was slightly reduced in the active group compared with both placebo and usual-care groups. Health economic analysis revealed a statistically significant intergroup difference in antibiotic costs of £0.38 ( $p = 0.01$ ) but the overall health-care costs associated with the AOM were similar at £75.07 and £76.92 in the active and usual-care groups, respectively.

There was a single, unrelated, serious adverse event (breathing problems) in the usual-care group. We found no difference in reporting of adverse events between groups.

Three interviews were conducted with participating trial parents. Key findings include that parents:

- felt that the trial was a good idea and were happy for their child to participate
- described that wanting to help relieve their child's ear pain was the main reason for consulting
- did not express any preconceptions about the need for antibiotics
- spoke positively about the trial drops and stated that they would be happy to purchase the drops over the counter from a pharmacy, provided that pharmacist advice was available.

## Conclusions

This study has provided evidence that anaesthetic–analgesic ear drops significantly reduce antibiotic consumption in childhood otitis media. The key weakness of this study is the small sample size and the consequent low statistical power to detect a true effect of the intervention. The small sample size for both the quantitative and qualitative aspects of this study resulted from a much shorter recruitment period than was planned. Despite this, CEDAR provides evidence of a substantial treatment effect in reducing antibiotic consumption, possibly mediated by reduced antibiotic prescribing. The study was not able to establish if reduced antibiotic consumption was achieved by a reduction in ear pain. Early study closure also prevented qualitative interview completion and the collection of 3-month follow-up data. Finally, there was lower than predicted antibiotic consumption in all study groups, perhaps suggesting that the participating GPs and parents were more motivated than the norm to reduce antibiotic use.

The premise of the study was the importance of tackling antibiotic resistance by reducing unnecessary antibiotic use in AOM. This study suggests that substantial reduction in antibiotic use might be achieved in AOM-affected children by combining a no or delayed prescribing strategy with anaesthetic–analgesic ear drops. There were no adverse events in the active treatment group. Importantly, the parents interviewed expressed their willingness to obtain the drops over the counter, with pharmacist guidance. Replication in a study with larger sample size would allow more confidence in informing clinical guidelines with these findings, would ensure the safety of the intervention over a longer follow-up period and, by establishing the mechanism by which antibiotic use is reduced, would allow refinements to the intervention.

## Trial registration

This trial is registered as ISRCTN09599764.

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