

# Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT

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**Declared competing interests of authors:** Graham Burns reports personal fees from Boehringer Ingelheim GmbH (Ingelheim am Rhein, Germany), Teva Pharmaceutical Industries Ltd (Petah Tikva, Israel), Chiesi Farmaceutici SpA (Parma, Italy), Pfizer Inc. (New York City, NY, USA) and AstraZeneca plc (Cambridge, UK), and non-financial support from Chiesi and Boehringer Ingelheim, outside the submitted work. Rekha Chaudhuri reports personal fees from AstraZeneca, GlaxoSmithKline (GSK) plc (London, UK), Teva and Novartis International AG (Basel, Switzerland) for advisory board meetings, outside the submitted work. Anthony De Soyza reports grants and non-financial support from AstraZeneca and Chiesi, non-financial support from Boehringer Ingelheim, grants and personal fees from GSK, Bayer AG (Leverkusen, Germany) and Pfizer, and grants from Forest Laboratories (New York City, NY, USA)/Teva, outside the submitted work. He is also a member of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Elective and Emergency Specialist Care (EESC) Panel. Simon Gompertz reports personal fees from Pfizer and GSK, outside the submitted work. John Norrie reports grants from the NIHR HTA programme during the conduct of the study, was a member of the NIHR HTA Commissioning Board (2010–16) and is currently Deputy Chairperson of the NIHR HTA General Board (2016–present) and a NIHR Journals Library Editor (2014–present). Andrew Wilson reports grants from F. Hoffmann-La Roche (Basel, Switzerland), outside the submitted work. David Price reports grants and personal fees from Aerocrine AB (Stockholm, Sweden), AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan NV (Canonsburg, PA, USA), Mundipharma International Ltd (Cambridge, UK), Napp Pharmaceuticals Ltd (Cambridge, UK), Novartis, Pfizer, Teva, Theravance Biopharma (San Francisco, CA, USA) and Zentiva Group a.s. (Prague, Czech Republic); personal fees from Amgen Inc. (Newbury Park, CA, USA), Cipla Ltd (Mumbai, India), GSK, Kyorin Pharmaceutical Co. Ltd (Tokyo, Japan), Merck Sharp & Dohme (Kenilworth, NJ, USA), Skyepharma Production SAS (Saint-Quentin-Fallavier, France); grants from AKL Research and Development Ltd (Stevenage, UK), the British Lung Foundation, the Respiratory Effectiveness Group and the UK NHS; and non-financial support from the NIHR Efficacy and Mechanism Evaluation and HTA programmes, outside the submitted work. He also reports stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals and owns 74% of the social enterprise Optimum Patient Care Ltd (Cambridge, UK, and Australia and Singapore) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore).

**Published July 2019**

DOI: 10.3310/hta23370

## Scientific summary

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Health Technology Assessment 2019; Vol. 23: No. 37

DOI: 10.3310/hta23370

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# Scientific summary

## Background

Chronic obstructive pulmonary disease (COPD) is an incurable lung disease characterised by airway inflammation and progressive airflow limitation; typical symptoms include slowly worsening shortness of breath on exertion, productive cough and wheeze. The progressive airflow limitation of COPD is associated with symptoms becoming increasingly worse, ill health, work absence, disability and premature mortality. In the UK, there are 1.2 million people with diagnosed COPD. It is the fifth leading cause of death, is also a leading cause of emergency hospital admission and costs the NHS in excess of £1B per year.

Acute deteriorations in symptoms, known as exacerbations, are an important clinical feature of COPD; many patients require treatment with antibiotics and/or corticosteroids and the severest exacerbations necessitate hospital admission. Exacerbations are associated with increased ill health and a poorer prognosis and are the most costly aspect of COPD for the NHS. Recent studies have identified a frequent COPD exacerbator (defined as two or more exacerbations in a year) phenotype. Such patients can be reliably identified by patient recall and are highly likely to exacerbate in subsequent years. Despite advances in management, there is still an unmet need for improved pharmacological treatment of COPD, particularly the prevention of exacerbations.

Oral theophylline has been used in the treatment of COPD for > 70 years. Conventionally, theophylline has been used as a bronchodilator; however, in order to achieve modest clinical effects, relatively high blood concentrations (of 10–20 mg/l) are required, which are also associated with a wide range of well-recognised side effects. The availability of more effective inhaled therapies as well as theophylline's narrow therapeutic index, its modest clinical effect and its side effect profile have resulted in current COPD guidelines relegating high-dose theophylline to third-line therapy, although in low- to middle-income countries it is often used earlier in clinical practice.

In recent years, molecular mechanisms contributing to the reduced corticosteroid sensitivity of the airway inflammation of COPD have been elucidated. In vitro and animal models have demonstrated that, at low plasma concentrations (of 1–5 mg/l), there is a marked synergistic effect between theophylline and corticosteroids, with theophylline inducing a 100- to 10,000-fold increase in the suppressive effect of corticosteroids on the release of pro-inflammatory mediators. A number of small exploratory studies of short duration have confirmed that, at low dose, theophylline increases the anti-inflammatory properties of inhaled corticosteroids (ICSs), as evidenced by molecular signatures. Two small, year-long, hospital-based placebo-controlled trials of low-dose theophylline in COPD have reported conflicting results. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy guideline [GOLD. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. 2017. URL: <https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd> (accessed March 2018)] highlights that the clinical relevance of low-dose theophylline has not been fully established and that clinical evidence on low-dose theophylline, particularly on exacerbations, is limited and contradictory.

The Theophylline With Inhaled CorticoSteroid (TWICS) trial was a pragmatic, double-blind, randomised, placebo-controlled clinical trial built on emerging evidence that low-dose (plasma concentration of 1–5 mg/l) theophylline may produce a beneficial synergistic effect in COPD by increasing the corticosteroid sensitivity of the airway inflammation underlying COPD and, as a consequence, reduce the rate of COPD exacerbation when used in conjunction with ICSs.

## Objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to ICS therapy in patients with COPD and a history of two or more exacerbations treated with antibiotic and/or oral corticosteroids (OCSs) in the previous year. The primary clinical outcome was the number of exacerbations in the 1-year treatment period that required treatment with antibiotics and/or OCSs. The primary economic outcome was cost per QALY gained during the 1-year treatment period.

The secondary objectives were to compare the following outcomes between participants treated with low-dose theophylline and those treated with placebo:

- hospital admissions with a primary diagnosis of exacerbation of COPD
- total number of episodes of pneumonia
- total number of emergency hospital admissions
- lung function
- all-cause and respiratory mortality
- drug reactions and serious adverse events (SAEs)
- health-related quality of life
- disease-specific health status
- total inhaled corticosteroid dose/usage
- health-care utilisation
- modelled lifetime incremental cost per quality-adjusted life-year (QALY)
- time to first exacerbation (an additional secondary objective).

## Methods

The TWICS trial was a pragmatic, double-blind randomised, placebo-controlled, UK multicentre clinical trial that compared the addition of low-dose theophylline to current COPD therapy that included ICS with the addition of placebo to current COPD therapy that included ICS for 52 weeks, in patients with COPD who had experienced two or more exacerbations in the previous year treated with OCSs and/or antibiotics. The aim was to recruit 1424 participants, with  $\geq 50\%$  being recruited from primary care.

## Inclusion criteria

Participants were people with COPD likely to experience an exacerbation during the 52-week treatment period. The key inclusion criteria were:

- aged  $\geq 40$  years
- smoking history of  $> 10$  pack-years
- predominant respiratory diagnosis of COPD [forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) of  $< 0.7$ ]
- current use of ICS therapy
- patient report of two or more exacerbations treated with antibiotics and/or OCSs in the previous year.

## Exclusion criteria

The key exclusion criteria are listed below. They include concomitant treatment with drugs with the potential to increase plasma theophylline concentration above the low-dose range of 1–5 mg/l:

- severe or unstable ischaemic heart disease
- a predominant respiratory disease other than COPD, including alpha-1-antitrypsin deficiency
- current use of drugs with the potential to increase plasma theophylline.

## Participant identification and recruitment

Participants were identified and recruited from both primary and secondary care sites across the UK. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

## Randomisation/treatment allocation

Participants were randomised using an internet-based computerised randomisation system created and administered by the Centre for Healthcare Randomised Trials (CHaRT) in the University of Aberdeen. Participants were stratified by trial centre/area and recruitment setting (primary and secondary) and then randomised with equal probability to the intervention (low-dose theophylline) or control (placebo) arm.

## Intervention

The treatment period was 52 weeks with either 200-mg tablets of Uniphyllin modified release (MR) (Napp Pharmaceuticals Ltd, Cambridge, UK) or a visually identical placebo. Dosing was based on pharmacokinetic modelling incorporating the major determinants of theophylline steady-state concentration, designed to achieve a steady-state plasma theophylline of 1–5 mg/l. The dosing of both the active and placebo drugs was determined by a participant's ideal body weight (IBW) and smoking status:

- 200 mg of Uniphyllin MR once daily (or one placebo once daily) for non-smoking participants, or participants who smoked but had an IBW of  $\leq 60$  kg
- 200 mg of Uniphyllin MR twice daily (or one placebo twice daily) for participants who smoked and had an IBW of  $> 60$  kg.

All supplies of trial tablets were delivered to participants' homes, except for participants recruited in secondary care sites who received their initial 4-week supply from their local clinical trials pharmacy.

## Data collection

Outcome data were collected by face-to-face assessments conducted at recruitment/baseline (week 0), 6 months (week 26) and 12 months (week 52). Participants unable to attend the 6- and 12-month assessments were followed up by telephone or home visit, or were sent the questionnaires to complete at home. The key data collected were:

- number of COPD exacerbations requiring antibiotics/OCSs (i.e. moderate/severe exacerbations)
- number of unscheduled hospital admissions
- health-related quality of life [measured using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L)]
- disease-related health status [measured using the COPD Assessment Test (CAT)]

- modified Medical Research Council (mMRC) dyspnoea score
- post-bronchodilator spirometry (FEV<sub>1</sub>, FVC)
- health-care utilisation
- adverse reactions and SAEs
- adherence, persistence with trial medication.

## Sample size

The sample size was based on the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, which indicated that, in our trial population, the expected mean number of COPD exacerbations within 1 year would be 2.22 [standard deviation (SD) 1.86]. An estimated 669 participants were needed in each trial arm to detect a 15% reduction in COPD exacerbations (i.e. from a mean of 2.22 to 1.89) with 90% power at the 5% significance level. Allowing for 6% loss to follow-up, this was inflated to 712 participants in each trial arm, giving 1424 in total.

## Statistical analysis

All analyses were prespecified in the statistical and health economic analysis plan approved in advance of analysis. All analyses were in accordance with the intention-to-treat (ITT) principle, with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking  $\geq 70\%$  of their expected doses of trial medication.

## Results

Recruitment to the trial took place between 6 February 2014 and 31 August 2016. A total of 1578 people were randomised: 791 to theophylline and 787 to placebo. Participants were recruited in 121 trial sites (88 primary care and 33 secondary care); 941 (60%) participants were identified in primary care. There were 11 post-randomisation exclusions (theophylline,  $n = 3$ ; placebo,  $n = 8$ ). A total of 1567 participants were prescribed trial medication: 788 in the theophylline arm and 779 in the placebo arm. A higher proportion (26%) of participants than the expected 6% ceased their trial medication. To counteract this, recruitment continued beyond 1424 participants in the time available; therefore, the total number recruited was 1578.

The baseline characteristics of the participants allocated to theophylline and placebo were balanced: the mean age was 68.4 (SD 8.4) years, 54% were male, the mean body mass index (BMI) was 27.2 kg/m<sup>2</sup> (SD 6.1 kg/m<sup>2</sup>), 31.7% smoked, 80% were using inhaled corticosteroids (ICSs)/long-acting  $\beta_2$ -agonists (LABAs)/long-acting muscarinic antagonists (LAMAs), the mean FEV<sub>1</sub> was 51.7% (SD 20.0%) predicted, 13.6% had very severe airflow obstruction (i.e. FEV<sub>1</sub> of  $< 30\%$  predicted), 37.7% had severe airflow obstruction (i.e. FEV<sub>1</sub> of 30–50% predicted), 39.6% had moderate airflow obstruction (i.e. FEV<sub>1</sub> of 50–80% predicted) and 9.2% had mild airflow obstruction (FEV<sub>1</sub> of  $> 80\%$  predicted). The mean number of participants reporting exacerbations in the previous year was 3.6 (SD 2.2). CAT scores indicated that COPD had a high impact on participants' lives: the mean CAT score was 22.6 (SD 7.7)] and the mean EQ-5D-3L utility score was 0.63 (SD 0.28).

## Intention-to-treat analysis

### Primary outcomes

For the ITT analysis, primary outcome data were available for 98% of participants: 772 in the theophylline arm and 764 in the placebo arm. There were 1489 person-years of follow-up data. In total, there were 3430 exacerbations (theophylline;  $n = 1727$ ; placebo,  $n = 1703$ ), the mean number of exacerbations in

participants allocated to theophylline was 2.24 (SD 1.99) and for participants allocated to placebo it was 2.23 (SD 1.97) [unadjusted incidence rate ratio (IRR) 1.00, 95% confidence interval (CI) 0.92 to 1.09; adjusted IRR 0.99, 95% CI 0.91 to 1.08].

As there was no statistically significant difference in the exacerbation rate between treatment arms, the economic analysis was limited to a within-trial analysis. There was a significant difference in unadjusted mean total costs (£452, 95% CI £133 to £771), which were higher in the placebo arm than in the theophylline arm. This was driven by a significant difference in exacerbation costs between arms of £447 (95% CI £186 to £709). This difference was a result of higher costs in the placebo arm for hospitalisations. After adjusting mean costs for baseline characteristics, there was no significant difference between arms in either exacerbation or total costs, although total costs were £222 (95% CI –£27 to £472) higher in the placebo arm.

Adjusted mean QALYs were 0.621 [standard error (SE) 0.006] in the theophylline arm and 0.616 (SE 0.007) in the placebo arm; there was no significant difference between arms. Overall, theophylline dominates placebo, with lower costs and higher QALYs. However, this result is not significant and care should be taken when interpreting it.

### Secondary outcomes

There were 319 severe COPD exacerbations treated in hospital: 134 in the theophylline arm and 185 in the placebo arm. The mean number of severe COPD exacerbations treated in hospital was 0.17 (SD 0.49) in the theophylline arm and 0.24 (SD 0.66) in the placebo arm (unadjusted IRR 0.72, 95% CI 0.55 to 0.95; adjusted IRR 0.72, 95% CI 0.55 to 0.94). However, 39 of the 51 excess hospital admissions in the placebo group were accounted for by 10 participants having three or more exacerbations. Low-dose theophylline had no significant effect on non-COPD-related hospital admissions (adjusted IRR 0.99, 95% CI 0.71 to 1.38), episodes of pneumonia (incidence 1.5%, unadjusted IRR 1.55, 95% CI 0.67 to 3.62), FEV<sub>1</sub>% predicted (adjusted mean difference –0.56, 95% CI –2.42 to 1.30), CAT score (adjusted marginal mean difference 0.01, 95% CI –0.65 to 0.68), mMRC dyspnoea score [adjusted odds ratio (OR) 1.20, 95% CI 0.88 to 1.63], total mortality (which was 2.5% in the theophylline arm and 1.8% in the placebo arm;  $p = 0.400$ ) or COPD-/respiratory-related mortality (which was 0.9% in the theophylline arm and 1.1% in the placebo arm;  $p = 0.762$ ).

Low-dose theophylline was not associated with a significant increase in adverse reactions (ARs) or SAEs: the percentage of participants reporting ARs was 48.1% in the theophylline arm and 43.9% in the placebo arm ( $p = 0.116$ ), the total number of ARs was 883 in the theophylline arm and 818 in the placebo arm and the percentage of participants reporting SAEs was 13.2% in the theophylline arm and 14.0% in the placebo arm ( $p = 0.616$ ). There were no differences in the profiles of ARs or SAEs between the theophylline and placebo arms.

### Per-protocol analysis

#### Primary outcome

Of the 1578 participants randomised, 1567 were prescribed trial medication, of whom 31 were missing some primary outcome data: 16 in the theophylline arm and 15 in the placebo arm. Adherence/compliance was < 70% for 356 participants: 181 (23.4%) in the theophylline arm and 175 (22.9%) in the placebo arm ( $p = 0.802$ ). The reasons given by participants for ceasing trial medication and the numbers reporting each reason were the same in the theophylline and placebo arms.

For the per-protocol analysis, primary outcome data were available for 1180 (75%) participants, 591 in the theophylline arm and 589 in the placebo arm; there were 1146 person-years of follow-up data. There were 2556 exacerbations: 1298 in the theophylline arm and 1258 in the placebo arm. The mean number of exacerbations in participants allocated to theophylline was 2.20 (SD 1.96), and in participants allocated to placebo it was 2.14 (SD 1.92) (unadjusted IRR 1.02, 95% CI 0.92 to 1.13; adjusted IRR 1.00, 95% CI 0.91 to 1.10).

### Secondary outcomes

There were 218 severe COPD exacerbations treated in hospital: 92 in the theophylline arm and 126 in the placebo arm. The mean number of severe COPD exacerbations treated in hospital was 0.16 (SD 0.45) in the theophylline arm and 0.21 (SD 0.61) in the placebo arm (adjusted IRR 0.70, 95% CI 0.50 to 0.97). For the other secondary outcomes, the per-protocol analysis did not differ significantly from the results of the ITT analysis.

### Conclusions

This is the first pragmatic, double-blind, randomised, placebo-controlled trial to assess the effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD at high risk of exacerbation. The analyses demonstrated that, overall, low-dose theophylline has no clinical or health economic benefit.

### Implications for health care

This is the largest trial of low-dose theophylline in COPD to date. National and international COPD guidelines will need to consider the findings of this trial when making recommendations on the treatment of COPD and the prevention of COPD exacerbations.

### Recommendations for research

A further study investigating the clinical effectiveness and cost-effectiveness of low-dose theophylline in reducing severe COPD exacerbations requiring admission to hospital needs careful consideration. Such a study would necessarily be very large.

### Trial registration

This trial is registered as ISRCTN27066620.

### Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.



ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/58/15. The contractual start date was in July 2013. The draft report began editorial review in April 2018 and was accepted for publication in November 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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