**Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with chronic obstructive pulmonary disease: a randomized clinical trial.**

Subtitle: Theophylline in COPD

Graham Devereux PhD1,2,10

Seonaidh Cotton PhD3

Shona Fielding PhD4

Nicola McMeekin MSc5

Peter J Barnes DSc6

Andrew Briggs PhD5

Graham Burns PhD7

Rekha Chaudhuri MD8

Henry Chrystyn PhD9

Lisa Davies FRCP10

Anthony De Soyza PhD11

Simon Gompertz MD12

John Haughney FRCGP13

Karen Innes MSc3

Joanna Kaniewska PhD3

Amanda Lee PhD4

Alyn Morice FRCP14

John Norrie MSc3

Anita Sullivan PhD12

Andrew Wilson PhD15

David Price FRCGP13,16 \*

1. University of Aberdeen, Respiratory Medicine, Aberdeen Royal Infirmary, Aberdeen. AB25 2ZN. UK.

2. Liverpool School of Tropical Medicine, Liverpool. L3 5QA. UK

3. University of Aberdeen, Centre for Healthcare Randomised Trials (CHaRT), Aberdeen. AB25 2ZD. UK.

4. University of Aberdeen, Medical Statistics Team, Division of Applied Health Sciences, Aberdeen. AB25 2ZD. UK.

5. University of Glasgow, Institute of Health & Wellbeing, 1 Lilybank Gardens, Glasgow. G12 8RZ. UK.

6. Imperial College, National Heart & Lung Institute, Dovehouse St, London. SW3 6LY. UK.

7. Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle. NE1 4LP

8. University of Glasgow, Gartnavel General Hospital, Glasgow. G12 0YN. UK.

9. Inhalation Consultancy Ltd, Tarn House, 77 High Street, Yeadon, Leeds, LS19 7SP

10. Aintree Chest Centre, University Hospital Aintree, Liverpool, L9 7AL. UK.

11. Newcastle University, Medical School, Newcastle Upon Tyne. NE2 4HH. UK.

12. Queen Elizabeth Hospital Birmingham, Birmingham. B15 2WB. UK.

13. University of Aberdeen, Academic Primary Care, Aberdeen. AB25 2ZD. UK.

14. Cardiovascular and Respiratory Studies, Castle Hill Hospital, Hull. HU16 5JQ. UK.

15. Department of Medicine, Norwich Medical School, University of East Anglia, Norwich. NR4 7TJ. UK.

16. Observational and Pragmatic Research Institute, 60 Paya Lebar Road, Paya Lebar Square, Singapore, 409051.

\*corresponding author:

Professor David Price,

Academic Primary Care,

Division of Applied Health Sciences,

University of Aberdeen,

Polwarth Building,

Foresterhill,

Aberdeen,

AB25 2ZD;

UK

Email: dprice@opri.sg

Tel: +65 6802 9724;

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**Key Points**

Question: Does low dose theophylline reduce the risk of exacerbation in patients with chronic obstructive pulmonary disease (COPD) when added to inhaled corticosteroids?

Findings: In this pragmatic randomized clinical trial that included 1567 participants with COPD treated with inhaled corticosteroids, the addition of low dose theophylline did not significantly reduce the mean number of exacerbations compared with placebo over a one year period (2.24 vs 2.23).

Meaning: The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the treatment of COPD.**Abstract**

*Importance:* Chronic obstructive pulmonary disease (COPD) is a major global health issue and theophylline is used extensively. Pre-clinical investigations demonstrate low plasma concentrations (1-5mg/l) of theophylline enhance anti-inflammatory effects of corticosteroids in COPD.

*Objective:* To investigate the effectiveness of adding low-dose theophylline to inhaled corticosteroids in COPD.

*Design, Setting, and Participants:* The theophylline with inhaled corticosteroids (TWICS) trialwas a pragmatic double-blind placebo-controlled randomized clinical trial which enrolled between 6th February 2014 and 31st August 2016. Final follow-up was 31st August 2017. Participants had COPD (FEV1/FVC<0.7), with ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year and were using an inhaled corticosteroid. 1567 participants were randomized in 121 UK primary and secondary care sites.

*Interventions:* 788 participants were randomized to low-dose theophylline (200mg once or twice a day) to provide plasma concentrations 1-5mg/l, determined by ideal body weight and smoking status. 779 participants were randomized to placebo.

*Main outcomes and Measures:* The number of participant reported exacerbations treated with antibiotics and/or oral corticosteroids, i.e. moderate-severe exacerbations, over the one-year treatment period.

*Results:* 1567 participants were randomized, mean (SD) age 68.4 (8.4) years, 54% male. 1536 (98%) had data available for evaluation of the primary outcome (772 theophylline, 764 placebo). In total there were 3430 exacerbations, 1727 theophylline, 1703 placebo, the mean (95% CI) number of exacerbations in participants allocated to theophylline was 2.24/year (2.10, 2.38) and for participants allocated to placebo 2.23/year (2.09, 2.37), unadjusted mean difference (95% CI) 0.01 (-0.19, 0.21) and adjusted incident rate ratio 0.99 (0.91, 1.08). There were no differences in serious adverse events between theophylline and placebo groups (cardiac, 2.4% vs 3.4%; gastrointestinal, 2.7% vs 1.3%) or adverse reactions (nausea, 10.9% vs 7.9%; headaches, 9.0% vs 7.9%).

*Conclusions and relevance:* Among adults with COPD at high risk of exacerbation treated with inhaled corticosteroids, the addition of low-dose theophylline, compared with placebo, did not reduce the number COPD exacerbations over a one year period. The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the treatment of COPD.

*Registration:* ISRCTN27066620 registered 19th September 2013. <http://www.isrctn.com/ISRCTN27066620>

**Introduction**

Chronic obstructive pulmonary disease (COPD) is well recognised as a major growing global health concern1,2. An important clinical feature of COPD are acute exacerbations that are adversely associated with morbidity3 and mortality4 and are the most costly aspect of COPD for healthcare systems2.

Oral theophylline has been used as a bronchodilator to treat COPD for decades, however to achieve modest bronchodilatation through phosphodiesterase inhibition, blood concentrations (10-20mg/l) are required that are associated with side effects5. Recently there has been interest in using theophylline at low dose in COPD with plasma levels 1-5mg/l. Pre-clinical investigations have demonstrated, that at low plasma concentrations (1-5mg/l) there is marked synergism between theophylline and corticosteroids, with theophylline inducing a 100-10,000 fold increase in anti-inflammatory effects of corticosteroids6-9. Small exploratory clinical studies have reported that low-dose theophylline increases the anti-inflammatory properties of inhaled corticosteroids (ICS) as evidenced by biomarkers10,11. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy guideline does not recommend the use of theophylline unless other long-term treatment bronchodilators are unavailable or unaffordable. The issue of affordability and availability are important determinants of theophylline use globally and in resource limited countries, with high burdens of COPD, theophylline continues to be used extensively12-15.

The GOLD management strategy guideline does not dismiss the use of low-dose theophylline, highlighting 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 contradictory5. The theophylline with inhaled corticosteroids (TWICS) trial addressed this area of clinical uncertainty by investigating the clinical effectiveness of adding low-dose theophylline to ICS therapy in people with COPD and frequent exacerbations, with the rate of moderate and severe exacerbations as the primary outcome.

**Methods**

This trial was reviewed and approved by Scotland A Research Ethics Committee (13/SS/0081) and the Medicines and Healthcare products Regulatory Agency (EudraCT 2013-001490-25). The trial was registered on 19th September 2013, and the protocol published (online supplement 1)16. All participants provided written informed consent.

*Study design and oversight*

A pragmatic UK based multicentre double-blind randomized clinical trial comparing addition of low-dose theophylline or placebo for 52 weeks to current therapy that included ICS, in patients with COPD and ≥2 exacerbations in the previous year. The trial aimed to recruit 1424 participants with at least 50% being recruited in primary care.

*Participants*

Participants were identified and recruited from primary and secondary care sites across the UK. In primary care, General Practice staff conducted searches of their patients’ electronic patient records (based on inclusion/exclusion criteria) to identify potential participants. Potential participants were also identified from community COPD services such as Pulmonary Rehabilitation, COPD Community Matrons, smoking cessation services and COPD Integrated/Intermediate Care Services. Potentially suitable patients were sent study information packs and contact details to be seen in their local primary care research site by primary care staff, if interested. In secondary care, potential participants were identified from patients attending (or who had previously attended) Respiratory Out-Patient Clinics or who had been in-patients. Potentially suitable patients were sent study information and contact details to be seen in their local secondary care research site by secondary care staff, if interested.

Participants were aged ≥40 years with a predominant respiratory diagnosis of COPD (FEV1/FVC<0.7), >10 pack year smoking history, currently using ICS and ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year. The diagnosis of COPD was established from clinical records during screening and spirometry conducted at recruitment. Smoking and exacerbation history was ascertained by participant recall. Potential participants were excluded if they had a predominant respiratory disease other than COPD, severe/unstable ischaemic heart disease or were using drugs with the potential to increase plasma theophylline concentration above 1-5mg/l17.

*Randomisation/treatment allocation.*

Participants were stratified by region and recruitment setting (primary/secondary care) and allocated with equal probability (1:1) to low-dose theophylline or placebo groups. The random allocation sequence was generated using randomly generated blocks of entries of varying sizes (two or four) permuted for each combination of region and recruitment setting (primary or secondary care). The internet based computerised randomisation system was created and administered by the Centre for Healthcare Randomised Trials, University of Aberdeen.

*Intervention*

The treatment period was 52 weeks with either theophylline (Uniphyllin MR) 200mg tablets or visually identical placebo (Napp Pharmaceuticals, Cambridge, UK). Dosing was based upon pharmacokinetic modelling incorporating the major determinants of theophylline plasma concentration and designed to achieve a steady state plasma theophylline concentration of 1-5 mg/l16. Dosing was determined by participant’s ideal body weight (IBW) and smoking status: non-smokers, or smokers with IBW≤60kg took one theophylline MR 200mg (or one placebo) daily; smokers with IBW>60kg took one theophylline MR 200mg (or one placebo) twice daily. No other changes were made to participants care, they continued to be managed in the usual way by their primary and secondary care teams.

*Outcomes*

The primary outcome was the number of COPD exacerbations requiring antibiotics and/or oral corticosteroids during the 52 week treatment period as reported by the participant18. Patient recall of this outcome is highly reliable over a year19. A validation exercise was conducted at two of the largest recruiting sites. At these two sites a care/encounter summary from the GPs of a random 20% sample of participants was requested and compared against participant report of exacerbation. A minimum of two weeks between exacerbations was necessary to be considered as separate events18.

Outcome data were collected by face-to-face assessments conducted at recruitment/baseline (week 0), 26 weeks and 52 weeks. In addition to exacerbation data, secondary outcomes collected were: participant reported unscheduled hospital admissions because of exacerbations of COPD (severe exacerbations), and unscheduled hospital admissions not related to COPD; health related quality of life (EQ-5D-3L, scale -0.59 to 1, where 1 is full health, no generally accepted meaningful MCID)20; COPD related health status (COPD Assessment Test CAT, scale 0-40, with ≤5 being the norm for healthy non-smokers and >30 indicative of very high COPD effect on quality of life, MCID is 2 units)21; modified MRC dyspnoea score (a 0 to 4 scale with 0 being ‘Not troubled by breathlessness except on strenuous exercise’ and 4 being ‘Too breathless to leave the house, or breathless when dressing or undressing’)22; post-bronchodilator spirometry (FEV1,FVC as percent predicted, for regulatory purposes a change of less than 3% from baseline is considered as not clinically important)23,24; adverse reactions/serious adverse events; episodes of pneumonia; mortality. Adherence was assessed by pill counting of study drug returns at the 26 and 52 week assessments. In some self-selected recruitment centres, the Hull Airway Reflux Questionnaire (HARQ) was completed by participants at recruitment, 6 and 12 months to assess symptoms not elucidated by the CAT or mMRC dyspnoea scale25. Health care utilisation data were also collected at recruitment, 6 and 12 months for use in a health economic analysis that will be reported separately.

Participants ceasing study medication were encouraged to attend the 26 and 52 week assessments to capture outcome data. For those who did not wish to attend, consent was obtained to contact their GPs who were sent a questionnaire to complete enquiring about exacerbations, alternatively GPs could send an encounter summary from which exacerbation data was extracted. The minimum information requested from GPs was the number of exacerbations in the specified treatment period, this was often provided without dates of individual exacerbations.

*Sample Size*

Data from a previous study indicated that for a trial population with ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year the mean (SD) number of exacerbations in the subsequent year would be 2.22 (1.86)26. An estimated 669 participants were needed in each trial group to detect a clinically important 15% reduction in COPD exacerbations (i.e., from a mean of 2.22 to 1.89) with 90% power at 5% significance level. There is no validated MCID for COPD exacerbation frequency24,27. The 15% reduction in COPD exacerbations was decided upon after consultation with primary and secondary care colleagues who considered a 15% reduction to be small but clinically important. A 6% loss to follow-up was anticipated based on a systematic review that noted very few participants withdrew from COPD theophylline trials28. This inflated each study group to 712 participants, giving 1424 in total.

*Statistical methods*

All analyses were governed by a Statistical Analysis Plan (online supplement 2). Analysis was in accordance with the intention to treat principle. A per-protocol analysis, excluding non-adherent (<70% of doses taken) participants was performed as a sensitivity analysis. Adherence was defined as participants having taken ≥ 70% of expected doses of study tablets as determined by pill counting.

Baseline characteristics were described for both treatment groups. The primary clinical outcome of number of COPD exacerbations was compared between randomized groups using a negative binomial model with an appropriate dispersion parameter (to adjust for between participant variability) and length of time in the study as an offset. Estimates were adjusted for baseline covariates known to be related to outcome: age, gender, pack years, number of exacerbations in previous 12 months, COPD treatment, recruitment setting, centre as a random effect. For those covariates used in the model, any missing data was replaced by the value required (and confirmed) for inclusion in the study (number of exacerbations in previous year = 2, pack years = 10, treatment = ICS only). Given the small amount of missing data for the primary outcome, multiple imputation was not carried out.

The secondary outcomes of number of exacerbations requiring hospitalisation, and, non-COPD hospital admissions were analysed using the same methods as that used for the primary outcome. Further exploration of the outcome, exacerbations requiring hospitalisation in a post-hoc analysis included inspection of the frequency distribution to ascertain if any differences were limited to those with few or many exacerbations. Episodes of pneumonia, all cause (and respiratory related) mortality, mMRC score were analysed with chi-squared tests. Lung function and continuous CAT score were compared between groups using mixed effects models. As there is a potential for type I error due to multiple comparisons, secondary outcomes should be interpreted as exploratory.

The analysis for the primary outcome was repeated for a number of prespecified subgroups: age, gender, body mass index, smoking status at recruitment (ex/current), baseline treatment for COPD, GOLD stage, exacerbations in 12 months prior to recruitment, oral corticosteroid use at recruitment, dose of ICS at recruitment. The subgroup analyses were undertaken by adding a treatment\*variable interaction term to the model using for the primary outcome.

Analyses were performed using Stata v14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX). A 5% two-sided significance level was used throughout.

**Results**

Participant involvement in the trial is outlined in figure 1. Participants were recruited between 6th February 2014 and 31st August 2016, the final follow-up was in August 2017. A total of 1578 participants were randomized: 791 theophylline, 787 placebo. There were 11 post-randomisation exclusions (3 theophylline, 8 placebo), 1567 participants commenced study medication: 788 theophylline, 779 placebo. Table e1 in supplement 3 details the reasons for post-randomisation exclusion. Participants were recruited in 121 study sites (88 primary care, 33 secondary care), 941 (60%) participants were identified in primary care. A higher proportion (26%) of participants than anticipated (6%) failed to initiate treatment (3 theophylline, 6 placebo) or ceased study medication (203 theophylline, 193 placebo). The proportion of participants ceasing study medication was balanced between the theophylline and placebo groups. To counteract this, recruitment continued within allocated recruitment period beyond the original target of 1424. The decision to continue recruitment was made by the Trial Steering Committee (TSC) and approved by the funding organisation based on aggregated recruitment and study medication cessation data, the investigators, the TSC and funder remained blinded to outcome data throughout the trial.

The baseline characteristics of the participants allocated to theophylline and placebo were well balanced (table 1). The mean (SD) age of participants was 68.4 (8.4) years, 54% were male, and 31.7% were current smokers. Eighty percent of participants were using ‘triple therapy’ of ICS, long-acting-beta2-agonists (LABA) and long-acting muscarinic antagonists (LAMA). Although mean FEV1 (51.7%) was indicative of moderate to severe COPD, 13.5% of participants had very severe COPD and 9.2% mild. Participants fulfilled the definition of frequent exacerbators27 with a mean (SD) number of self-reported exacerbations in previous year of 3.59 (2.15). CAT scores indicated that COPD was severely affecting participants’ lives, (mean (SD) 22.5 (7.7) with 65% high/very high).

*Primary outcome: intention to treat.*

Primary outcome (exacerbation) data were available for 98% of participants: 772 in the theophylline group and 764 in the placebo group, there were 1489 person years of follow up data. In total there were 3430 exacerbations: 1727 theophylline, 1703 placebo; mean (95% CI) number of exacerbations in participants allocated to theophylline was 2.24 (2.10, 2.38) and for participants allocated to placebo 2.23 (2.09, 2.37), giving unadjusted mean difference (95% CI) 0.01 (-0.19, 0.21), unadjusted incident rate ratio (95% CI) 1.00 (0.92, 1.09), adjusted IRR 0.99 (0.91, 1.08). The incidence of exacerbations by the month of treatment by GOLD stage (at baseline) for the two groups is presented in figure 2. Missing data for primary outcome was minimal (2%) so no multiple imputation was carried out.

*Secondary outcomes: intention to treat.*

The analysis of the secondary outcomes is detailed in table 2. There were 319 severe COPD exacerbations treated in hospital, i.e. severe exacerbations: 134 theophylline, 185 placebo. The mean number of severe COPD exacerbations treated in hospital was: 0.17 (0.49) theophylline, 0.24 (0.66) placebo, (mean difference and 95% CI -0.07 (-0.13, -0.01), unadjusted IRR 0.72 (0.55, 0.95), adjusted IRR 0.72 (0.55, 0.94), p = 0.017.

There were no significant differences in non-COPD hospital admissions, episodes of pneumonia, FEV1, CAT score, mMRC dyspnoea score, or mortality (COPD related and overall) between the two groups. Low-dose theophylline was not associated with a increase in adverse reactions (ARs) or serious adverse events (SAEs) (table e4 supplement 3). There were no differences in the symptom profiles of SAEs between theophylline and placebo groups (cardiac, 2.4% vs 3.4%; gastrointestinal, 2.7% vs 1.3%; neurological, 1.4% vs 0.9%) or for ARs (tachycardia, 1.9% vs 3.5%; nausea, 10.9% vs 7.9%; insomnia, 10.9% vs 7.9%; headaches, 9.0% vs 7.9%).

For the two centre validation exercise the GP records of 67 participants were examined and in 53 (79%) there was complete agreement between participant and GP records.

*Primary outcome: per protocol.*

The per-protocol analysis excluded 356 (23%) participants with <70% adherence: 181 (23.0%) theophylline, 175 (22.9%) placebo, p=0.80. The reasons for ceasing study medication were equally distributed between theophylline and placebo groups (Table e2 in supplement 3). The most common reason for stopping medication was for gastrointestinal disorders (46 theophylline, 32 placebo), 46 participants discontinued study medication because they felt no benefit (25 theophylline, 21 placebo) and in 64 cases no reason was given (28 theophylline, 36 placebo), and 29 ceased for social circumstances (15 theophylline, 14 placebo).

For the per-protocol analysis primary outcome data were available for 1180 (75%) participants: 591 theophylline, 589 placebo, there were 1146 person years of follow up data. There were 2557 exacerbations: 1298 theophylline, 1258 placebo, mean (95% CI) number of exacerbations in participants allocated to theophylline was 2.20 (2.04, 2.35) and for participants allocated to placebo 2.14 (1.98, 2.29), providing mean difference (95% CI) 0.06 (-0.16, 0.28), unadjusted IRR 1.02 (0.92, 1.13), adjusted IRR 1.00 (0.91, 1.10).

*Secondary outcomes: per protocol.*

The per-protocol analysis of the secondary outcomes demonstrated that low-dose theophylline reduced the rate of severe COPD exacerbations treated in hospital, mean difference (95% CI) -0.05 (-0.12,-0.003) and adjusted IRR 0.70 (0.50, 0.97), p = 0.031. There were no other statistically significant differences between the groups (table 3).

*Pre-specified sub group analysis*

There was no evidence that the treatment effect differed in any of the pre-specified sub groups (all interaction p values >0.05) : age, gender, body mass index, smoking status at recruitment (Ex vs current), baseline COPD treatment, GOLD staging, exacerbations in 12 months prior to recruitment, oral corticosteroid use at recruitment and ICS dose at recruitment.

*Post-hoc analyses*

The analysis of secondary outcome number of exacerbations requiring hospital admission showed a significant difference between theophylline and placebo. On further investigation the placebo group had 51 more COPD related hospital admissions than the theophylline group. Inspection of the frequency distribution (Table e3 in supplement 3) indicated that a small number (n=10) of participants in the placebo group with frequent (≥3 /year) COPD related hospital admissions accounted for 39 of the extra 51 hospital admissions in the placebo group.

**Discussion**

This trial showed that among adults with COPD at high risk of exacerbation treated with inhaled corticosteroids, the addition of low-dose theophylline, compared with placebo, did not reduce the number COPD exacerbations over a one year period. . The primary outcome was COPD exacerbations treated with oral corticosteroids and/or antibiotics during one year of treatment. Exploratory analyses of 11 pre-specified secondary outcomes, indicated that low-dose theophylline had no clinical effect in 10, including ARs and SAEs.

Pre-clinical studies have demonstrated that addition of low-dose theophylline to corticosteroid has a synergistic anti-inflammatory effect29. The few randomized clinical trials of low-dose theophylline have been small (n=58-110), reported contradictory results and have major limitations30-32. The current pragmatic trial recruited 1578 participants with 98% ascertainment of the primary outcome, achieved by participants who ceased study medication attending scheduled study assessments, requesting exacerbation data from GPs or inspecting primary care records. The current study attempted to replicate the use of low-dose theophylline in routine clinical practice with 121 geographically dispersed study centres, minimal inclusion criteria, infrequent study assessments, no changes to routine care, usual care settings and use of participant reported exacerbations. A formal assessment of the pragmatic features of this trial is provided in online supplement 4.

The inclusion criterion of ≥2 exacerbations in the previous year was a pragmatic trade-off between clinical relevance, size of eligible population and sample size. Sample size requirement was based on a mean (SD) exacerbation rate of 2.22 (1.86) reported for people with COPD with ≥2 exacerbations in the previous year26, this was very similar to the exacerbation rate (2.23-2.24) observed in the current trial. The exacerbation rate in this trial is somewhat higher than recent explanatory trials33,34, however it is consistent with the recent pragmatic UK Salford Lung Study that used an inclusion criterion of ≥1 exacerbation and reported exacerbation rates of 1.74-1.90/year35. Previous low-dose theophylline studies used a single dose for all participants10,11,30 however in the current study theophylline dosing was personalised, being determined by IBW and smoking status, being designed to achieve plasma theophylline concentrations of 1-5 mg/l. The use of IBW avoided the potential for inappropriately high doses of theophylline in overweight participants. The dosing regimen avoided the need for blood sampling to measure plasma theophylline concentrations and the attendant risk of unblinding, and participants in the low-dose theophylline group did not report an excess of adverse reactions typical of theophylline toxicity.

In the current trial low-dose theophylline did reduce the number of severe COPD exacerbations requiring hospital admission with most benefit being evident in a small (1-2%) sub-group of patients frequently hospitalised with COPD. Given that adjustments for multiple comparisons were not performed, it is possible that this finding could be due to type I error. However, in light of a recent report that another phosphodiesterase inhibitor (roflumilast), is most beneficial in people with prior COPD hospitalization for exacerbation and greater exacerbation frequency36 this finding warrants further investigation.

*Limitations*

This study has several limitations. First, more participants than anticipated (26%) ceased taking study drug, however this was offset by 10% over-recruitment and 98% follow-up rate. When compared with the current trial most effectiveness trials of theophylline are relatively short and exclude people with significant co-morbidities28. This may explain why the current yearlong trial in ‘real life’ people with COPD with co-morbidities witnessed a 26% rate of ceasing study medication, similar to that reported in a recent yearlong low-dose theophylline trial31. Second, because the study was powered to detect a 15% reduction in COPD exacerbations it was unlikely to detect smaller effects. Although there is no established MCID for COPD exacerbations the literature suggests that the majority of trials consider a reduction in exacerbations of between 11% and 20% to be clinically important24,27. The 15% reduction chosen for this trial was decided upon after consultation with primary and secondary care colleagues who considered a 15% reduction to be small but clinically important. Third, the primary outcome was participant reported rather than documented exacerbations. Patient recall of COPD exacerbations has been shown to be highly reliable over a year19, and people with COPD do not report all their exacerbations to healthcare professionals3,19,37. Participant recall of exacerbations in the current study appeared to be reliable with a two centre validation exercise demonstrating 79% concordance between participant and GP clinical records. Fourth, the definition of exacerbation used in the current study of requiring treatment with antibiotics/corticosteroids, underestimates the frequency of symptom-defined mild exacerbations that are short lived and treated with a temporary increase in bronchodilator38. Although these mild exacerbations were not quantified, there were no differences between groups in quality of life or health status, suggesting either, that low-dose theophylline had no effect on mild exacerbations or if there was an effect, it did not affect health status

*Conclusion*

Among adults with COPD at high risk of exacerbation treated with inhaled corticosteroids, the addition of low-dose theophylline, compared with placebo, did not reduce the number COPD exacerbations over a one year period. The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the treatment of COPD.

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*Conflicts of interest*

Dr. Barnes reports grants and personal fees from AstraZeneca, grants and personal fees from Novartis, personal fees from Teva, grants and personal fees from Boehringer Ingelheim, personal fees from Chiesi, during the conduct of the study.

Dr Briggs reports grants from UK National Institute for Health Research during the conduct of the study, and personal fees from GSK outside the submitted work.

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Prof. De Soyza reports meeting support from AstraZeneca, non-financial support from Novartis and Forest labs, personal fees from Bayer and Novartis, travel bursaries from Chiesi, Almirall, and Boehringer Ingelheim, personal fees from AstraZeneca, and grants from AstraZeneca, GlaxoSmithKline. Dr De Soyza has received medical education grant support for a UK bronchiectasis network from GlaxoSmithKline, Gilead Chiesi and Forest labs. Dr De Soyza's employing institution receives fees for his work as Coordinating investigator in a phase III trial in Bronchiectasis sponsored by Bayer.

Professor Price has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva (Sanofi Generics); payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Skyepharma, Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, Zentiva (Sanofi Generics); stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.

Dr. Haughney reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, Cipla, Chiesi, Mundipharma, Novartis, Pfizer, Sanofi, and Teva, outside the submitted work; .

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Graham Devereux, Seonaidh Cotton, Shona Fielding, Nicola McMeekin, Henry Chrystyn, Lisa Davies, Simon Gompertz, Karen Innes, Joanna Kaniewska, Amanda Lee, Anita Sullivan, Andrew Wilson have no conflicts of interest to declare.

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*Role of sponsor*

The study was co-sponsored by the University of Aberdeen and NHS Grampian who had no input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

*Access to Data and Data Analysis*

Graham Devereux (Co chief investigator) and Prof Amanda Lee (Study statistician) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Shona Fielding (University of Aberdeen), Ms Nicola McMeekin (University of Glasgow) and Prof Amanda Lee (University of Aberdeen) conducted and are responsible for the data analysis.

*Data sharing*

All available data can be obtained by contacting Graham Devereux c/o Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen, Aberdeen. AB25 2ZD. UK.

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FIGURE 1: Diagram illustrating enrolment, randomisation and follow up of participants.

Footnote

\*Adherence as assessed by pill counting indicated that participant non-adherent because <70% of total doses not taken

\*\*The number of potential participants identified by screening of records and sent invitations was not recorded. The participants physically seen for screening is provided.

a Reasons for ineligibility were as follows: 16 did not meet inclusion criteria for established COPD diagnosis or had predominant respiratory disease other than COPD, 10 had not had 2 exacerbations in previous year, 7 did not meet the smoking history criteria, 7 contraindicated medication, drug interaction 3 were not currently using ICS, 1 was not clinically stable, 2 were participating in another clinical trial, 1 was currently taking theophylline, 1 had known or suspected hypersensitivity to theophylline, 1 pregnancy, 2 with severe heart disease, 11 did not meet two or more of the inclusion criteria.



FIGURE 2: Exacerbations for each treatment month by baseline GOLD stage\* for low-dose theophylline and placebo groups\*\*.

Footnote

\*GOLD6 stage: I mild, FEV1 ≥80% predicted; II moderate, FEV1 50-80% predicted; III severe, FEV1 30-50% predicted; IV very severe, FEV1 0-30% predicted;

\*\*Total exacerbations 3420, missing data points 41.



TABLE 1: Baseline characteristics of all participants and those allocated to theophylline and placebo

|  |  |  |
| --- | --- | --- |
|  | Allocated theophylline(n=788)~ | Allocated placebo(n=779)~ |
| Age (years), mean (SD) [N] | 68.3 (8.2) [788] | 68.5 (8.6) [779] |
| Male, n (%)[N] | 425 (53.9) [788] | 418 (53.7) [779] |
| BMI (kg/m2), mean (SD) [N] | 27.1 (6.2) [788] | 27.3 (6.0) [779] |
| Current smoker, n (%)[N]) | 247 (31.4%)[788] | 249 (32.0%) [779] |
| Pack years smoking, median (IQR) [N] | 43.0(28.5, 57.0) [788] | 41.0(27.0, 55.0) [779] |
| COPD treatment\*, [N] | [788] | [779] |
|  *ICS only,* n (%) | 13 (1.6%) | 17 (2.2%) |
|  *ICS/LABA,* n (%) | 136 (17.3%) | 125 (16.0%) |
|  *ICS/LAMA,* n (%) | 13 (1.6%) | 10 (1.3%) |
|  *ICS/LABA/LAMA,* n (%) | 625 (79.3%) | 627 (80.5%) |
| Long term antibiotics, n(%) [N] | 51 (6.5%) [784] | 48 (6.2%) [771] |
| FEV1, % predicted, mean (SD) [N] | 51.3% (20.1) [785] | 52.2% (19.8) [771] |
| FEV1, % predicted, GOLD6 stage\*\*  |  |  |
|  Very severe*,* n (%) | 116 (14.8%) | 95 (12.2%) |
|  Severe*,* n (%) | 291 (37.1%) | 295 (38.4%) |
|  Moderate*,* n (%) | 308 (39.2%) | 308 (40.0%) |
|  Mild*,* n (%) | 70 (8.9%) | 73 (9.5%) |
| FEV1/FVC, % ratio, median (IQR)[(N] | 47.4 (37.6, 59.0) [783]  | 47.8 (37.5,59.3) [770] |
| Exacerbations^ (last 12 months), median (IQR) [N] |  |  |
|  *Any exacerbation*  | 3 (2, 4) [785] | 3 (2, 4) [773] |
|  *Resulting in hospitalisation*  | 0 (0, 1) [784] | 0 (0, 0) [773] |
| Exacerbations (last 12 months), mean (SD) [N] | 3.63 (2.21) [785] | 3.54 (2.09) [773] |
| Co-morbidities |  |  |
| Hypertension, n (%) [N] | 317 (40.2%) [782] | 277 (35.6%) [772] |
| Treated anxiety/depression last 5 years, n (%) [N] | 222 (28.2%) [782] | 213 (27.3%) [772] |
| Asthma, n (%) [N] | 138 (17.5%) [782] | 147 (18.9%) [772] |
| Ischaemic heart disease, n (%) [N] | 111 (14.1%) [781] | 96 (12.3%) [771] |
| Osteoporosis, n (%) [N] | 109 (13.8%) [783] | 90 (11.6%) [771] |
| Diabetes Mellitus, n (%) [N] | 83 (10.5%) [782] | 93 (11.9%) [772] |
| Cerebrovascular event, n (%) [N] | 46 (5.8%) [783] | 58 (7.4%) [772] |
| Bronchiectasis, n (%) [N] | 41 (5.2%) [782] | 27 (3.5%) [770] |
| mMRC dyspnoea score , n (%) [N] | [783] | [772] |
| 0: *(breathless strenuous exercise)* | 35 (4.5%) | 50 (6.5%) |
| 1: *(breathless hurrying ……)* | 216 (27.6%) | 224 (28.9%) |
| 2: *(slower than contemporaries…)* | 251 (32.1%) | 239 (31.0%) |
| 3: *(stop after 100m …..)* | 225 (28.7%) | 204 (26.5%) |
| 4: *(breathless leaving house ….)* | 56 (7.2%) | 55 (7.2%) |
| COPD assessment test (CAT), mean (SD) [N]  | 22.8 (7.5) [780] | 22.3 (7.9) [771] |
| CAT#, [N] | [780] | [771] |
|  *Low effect (0-9),* n (%) | 37 (4.7%) | 45 (5.8%) |
|  *Medium effect (10-19),* n (%) | 219 (28.1%) | 244 (31.7%) |
|  *High effect (20-29),* n (%) | 361 (46.3%) | 328 (42.5%) |
|  *Very high effect (30-40), n (%)* | 163 (20.9%) | 154 (20.0%) |
| EQ-5D## utility, mean (SD) [N] | 0.62 (0.28) [785] | 0.63 (0.28) [770] |

\*ICS-inhaled corticosteroid, LAMA Long acting muscarinic antagonists, LABA, long acting beta2 agonist.

\*\*GOLD6 stage: very severe, FEV1 0-30% predicted; severe, FEV1 30-50% predicted; moderate, FEV1 50-80% predicted; mild, FEV1 ≥80% predicted.

^Exacerbation defined as symptomatic deterioration in COPD requiring treatment with antibiotics and/or oral corticosteroids

# EQ-5D-3L: Euroqol 5D health outcome instrument, has a scale of -0.59 to 1, where 1 is full health.

##CAT: COPD Assessment Test CAT, range 0-40, ≤5 being the norm for healthy non-smokers and >30 indicative of very high COPD effect on quality of life.

TABLE 2: Secondary outcomes for participants allocated to theophylline and placebo, intention to treat population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   | **Allocated theophylline** | **Allocated placebo** |   |
|   |   | Baseline to week 52 | Baseline to week 52 |   |
| COPD hospital admissions | N participants | 772 | 764 |   |
| Total admissions | 134 | 185 | Adj IRR (95% CI)1 0.72 (0.55-0.94); p = 0.02 |
| Mean (SD) per participant | 0.17 (0.49) | 0.24 (0.66) | Mean difference (95% CI)2: -0.07 (-0.13, -0.01) |
| Non-COPD hospital admissions | N participants | 762 | 755 |   |
| Total admissions | 116 | 119 | Adj IRR (95% CI)1 0.99 (0.71, 1.38) |
| Mean (SD) per participant | 0.15 (0.56) | 0.16 (0,47) | Mean difference (95% CI)2: -0.01 (-0.06, 0.05) |
|   |   | Week 0 | Week 26 | Week 52 | Week 0 | Week 26 | Week 52 |   |
| FEV1% predicted | N Participants | 769 | 553 | 533 | 757 | 539 | 489 | Marginal mean difference3 (95% CI) |
| Mean (SD) | 51.2% (20.1) | 52.2% (20.5) | 51.5% (20.4) | 52.3% (19.8) | 53.2% (20.9) | 52.1 (21.7%) | -0.57 (-2.51, 1.36) |
|   |
| CAT score | N Participants | 764 | 675 | 633 | 756 | 657 | 615 | Marginal mean difference3 (95% CI) |
| Mean (SD) | 22.7 (7.5) | 21.3 (8.1) | 21.4 (8.2) | 22.3 (7.9) | 21.1 (8.3) | 21.4 (8.6) | 0.01 (-0.65, 0.68) |
| mMRC dyspnoea score  | N Participants | 767 | 676 | 631 | 757 | 655 | 615 | Comparison between groups4 |
| 0 (breathless strenuous exercise) | n (%) | 35 (4.6%) | 42 (6.2%) | 38 (6%) | 50 (6.6%) | 51 (7.8%) | 52 (8.5%) | 6 months p = 0.63 |
| 1 (breathless hurrying) | n (%) | 211 (27.5%) | 209 (30.9%) | 186 (29.5%) | 218 (28.8%) | 189 (28.9%) | 158 (25.7%) | 12 months p = 0.31 |
| 2: (slower than contemporaries) | n (%) | 248 (32.3%) | 197 (29.1%) | 174 (27.6%) | 235 (31.0%) | 179 (27.3%) | 182 (29.6%) |   |
| 3: (stop after 100m) | n (%) | 219 (28.6%) | 178 (26.3%) | 178 (28.2%) | 201 (26.6%) | 186 (28.4%) | 167 (27.2%) |   |
| 4: (breathless leaving house) | n (%) | 54 (7.0%) | 50 (7.4%) | 55 (8.7%) | 53 (7.0%) | 50 (7.6%) | 56 (9.1%) |   |
|   |   | Baseline to week 52 | Baseline to week 52 |   |
| Pneumonia during 12 months | n/N (%) | 14/772 (1.8%) | 9/764 (1.2%) | Unadj OR5 1.55 (0.67, 3.62) p=0.31 |
| All cause mortality  | n/N (%) | 19/772 (2.5%) | 14/764 (1.8%) | Unadj HR6 1.35 (0.68, 2.69) p=0.40 |
| COPD related mortality  | n/N (%) | 7/772 (0.9%) | 9/764 (1.2%) | Unadj HR6 0.77 (0.29, 2.07) p=0.61 |
| Adverse reactions | n/N (%) | 341/709 (48.0) | 308/699 (43.9%) | p=0.124 |
|   | Total adverse reactions | 883 | 818 |   |
| SAEs  | n/N (%) | 103/783 (13.2%) | 108/770 14.0%) | p=0.604 |
|   | Total number SAEs | 141 | 135 |   |

 1 Adjusted incidence rate ratio (IRR) calculated with negative binomial model adjusting for baseline characteristics of age, gender, pack years smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting and centre as a random effect.

2 Unadjusted mean difference in exacerbations per participant

3 Marginal mean difference calculated from mixed effect models adjusting for baseline characteristics of age, gender, pack years smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting and centre as a random effect.

4 Calculated using a chi-squared test

5 From mixed effects logistic model

6 From Cox regression model

CAT: COPD Assessment Test CAT, range 0-40, ≤5 being the norm for healthy non-smokers and >30 indicative of very high COPD effect on quality of life.

TABLE 3: Secondary outcomes for participants allocated to theophylline and placebo, per-protocol population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   | **Allocated theophylline** | **Allocated placebo** |   |
|   |   | Baseline to week 52 | Baseline to week 52 |   |
| COPD hospital admissions | N participants | 591 | 589 |   |
| Total admissions | 92 | 126 | Adj IRR (95% CI)1 0.70 (0.50-0.97); p = 0.03 |
| Mean (SD) per participant | 0.16 (0.45) | 0.21 (0.61) | Mean difference (95% CI)2: -0.05 (-0.12, -0.003) |
| Non-COPD hospital admissions | N participants | 587 | 589 |   |
| Total admissions | 66 | 85 | Adj IRR (95% CI)1 0.82 (0.54, 1.24); p = 0.35 |
| Mean (SD) per participant | 0.11 (0.49) | 0.14 (0.45) | Mean difference (95% CI)2: -0.03 (-0.08, 0.02) |
|   |   | Week 0 | Week 26 | Week 52 | Week 0 | Week 26 | Week 52 |   |
| FEV1% predicted | N Participants | 588 | 471 | 455 | 583 | 471 | 432 | Marginal mean difference3 (95% CI) |
| Mean (SD) | 50.7% (20.5) | 52.0% (20.8) | 51.3% (20.3) | 52.8% (20.0) | 53.7% (20.9) | 52.6% (21.8) | -1.33 (-3.47, 0.80) |
|   |
| CAT score | N Participants | 584 | 560 | 534 | 583 | 555 | 527 | Marginal mean difference3 (95% CI) |
| Mean (SD) | 22.7 (7.5) | 21.0 (8.2) | 21.0 (8.2) | 21.8 (7.9) | 20.5 (8.2) | 20.9 (8.7) | 0.29 (-0.45, 1.04) |
| mMRC dyspnoea score  | N Participants | 585 | 560 | 534 | 583 | 550 | 527 | Comparison between groups4 |
| 0 (breathless strenuous exercise) | n (%) | 26 (4.4%) | 34 (6.1%) | 32 (6.0%) | 44 (7.5%) | 46 (8.3%) | 47 (8.9%) | 6 months p = 0.43 |
| 1 (breathless hurrying ……) | n (%) | 160 (27.3%) | 182 (32.5%) | 167 (31.3%) | 176 (30.1%) | 160 (29.0%) | 149 (28.3%) | 12 months p = 0.34 |
| 2: (slower than contemporaries…) | n (%) | 198 (33.8%) | 161 (28.8%) | 146 (27.3%) | 181 (31.0%) | 155 (28.1%) | 153 (29.0%) |   |
| 3: (stop after 100m …..) | n (%) | 157 (26.8%) | 142 (25.4%) | 147 (27.5%) | 149 (25.5%) | 153 (27.7%) | 135 (25.6%) |   |
| 4: (breathless leaving house ….) | n (%) | 45 (7.7%) | 41 (7.3%) | 43 (8.0%) | 34 (5.8%) | 38 (6.9%) | 43 (8.2%) |   |
|   |   | Baseline to week 52 | Baseline to week 52 |   |
| Pneumonia during 12 months | n/N (%) | 9/591 (1.5%) | 5/589 (0.8%) | Unadj OR5 1.81 (0.60, 5.44) p=0.29 |
| All cause mortality  | n/N (%) | 13/591 (2.2%) | 9/589 (1.5%) | Unadj HR6 1.45 (0.62, 3.38) p=0.39 |
| COPD related mortality | n/N (%) | 5/591 (0.8%) | 5/589 (0.8%) | Unadj HR6 1.00 (0.29, 3.46) p=0.99 |

1 Adjusted incidence rate ratio (IRR) calculated with negative binomial model adjusting for baseline characteristics of age, gender, pack years smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting and centre as a random effect.

2 Unadjusted mean difference in exacerbations per participant

3 Marginal mean difference calculated from mixed effect models adjusting for baseline characteristics of age, gender, pack years smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting and centre as a random effect.

4 Calculated using a chi-squared test

5 From mixed effects logistic model

6 From Cox regression model

CAT: COPD Assessment Test CAT, range 0-40, ≤5 being the norm for healthy non-smokers and >30 indicative of very high COPD effect on quality of life.