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Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD
A Randomized Clinical Trial

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IMPORTANCE Chronic obstructive pulmonary disease (COPD) is a major global health issue and theophylline is used extensively. Preclinical investigations have demonstrated that low plasma concentrations (1-5 mg/L) of theophylline enhance antiinflammatory 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 TWICS (theophylline with inhaled corticosteroids) trial was a pragmatic, double-blind, placebo-controlled, randomized clinical trial that enrolled patients with COPD between February 6, 2014, and August 31, 2016. Final follow-up ended on August 31, 2017. Participants had a ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) of less than 0.7 with at least 2 exacerbations (treated with antibiotics, oral corticosteroids, or both) in the previous year and were using an inhaled corticosteroid. This study included 1578 participants in 121 UK primary and secondary care sites.

INTERVENTIONS Participants were randomized to receive low-dose theophylline (200 mg once or twice per day) to provide plasma concentrations of 1 to 5 mg/L (determined by ideal body weight and smoking status) (n = 791) or placebo (n = 787).

MAIN OUTCOMES AND MEASURES The number of participant-reported moderate or severe exacerbations treated with antibiotics, oral corticosteroids, or both over the 1-year treatment period.

RESULTS Of the 1567 participants analyzed, mean (SD) age was 68.4 (8.4) years and 54% (843) were men. Data for evaluation of the primary outcome were available for 1536 participants (98%) (772 in the theophylline group; 764 in the placebo group). In total, there were 3430 exacerbations: 1727 in the theophylline group (mean, 2.24 [95% CI, 2.10-2.38] exacerbations per year) vs 1703 in the placebo group (mean, 2.23 [95% CI, 2.09-2.37] exacerbations per year); unadjusted mean difference, 0.01 (95% CI, −0.19 to 0.21) and adjusted incidence rate ratio, 0.99 (95% CI, 0.91-1.08). Serious adverse events in the theophylline and placebo groups included cardiac, 2.4% vs 3.4%; gastrointestinal, 2.7% vs 1.3%; and adverse reactions such as nausea (10.9% vs 7.9%) and 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 1-year period. The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the prevention of COPD exacerbations.

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Supplemental content

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Chronic obstructive pulmonary disease (COPD) is well recognized as a major growing global health concern.[1,2] An important clinical feature of COPD is acute exacerbations, which are adversely associated with morbidity[3] and mortality[4] and are the most costly aspect of COPD for health care systems.[2]

Oral theophylline has been used as a bronchodilator to treat COPD for decades; however, to achieve modest bronchodilatation through phosphodiesterase inhibition, blood concentrations (10-20 mg/L) are required that are associated with adverse effects.[5] Recently there has been interest in using theophylline at a low dose in COPD to achieve plasma levels of 1 to 5 mg/L. Preclinical investigations have demonstrated that at low plasma concentrations (1-5 mg/L), there is marked synergism between theophylline and corticosteroids, with theophylline inducing a 100- to 10 000-fold increase in antiinflammatory effects of corticosteroids.[6-9] Small exploratory clinical studies have reported that low-dose theophylline increases the antiinflammatory properties of inhaled corticosteroids (ICS) as evidenced by biomarkers.[10,11] 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 extensively.[12-15]

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 contradictory.[5] The TWICS (theophylline with inhaled corticosteroids) trial addressed this area of clinical uncertainty by investigating the clinical effectiveness of adding low-dose theophylline to inhaled corticosteroid (ICS) therapy in people with COPD and frequent exacerbations, with the rate of moderate and severe exacerbations as the primary outcome.

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 1-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 prevention of COPD exacerbations.

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 September 19, 2013, and the protocol appears in Supplement 1 and Supplement 2.[16] All participants provided written informed consent.

Study Design and Oversight

A pragmatic, UK-based, multicenter, double-blind, randomized clinical trial compared addition of low-dose theophylline or placebo for 52 weeks to current therapy that included ICS in patients with COPD and at least 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 (hospital) care sites across the United Kingdom. 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 departments, COPD community matrons, smoking cessation services, and COPD integrated and 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 outpatient clinics or who had been inpatients. 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 or older with a predominant respiratory diagnosis of COPD (ratio of forced expiratory volume in the first second to forced vital capacity [FEV_1/FVC] of <0.7); a smoking history of more than 10 pack-years; current use of ICS; and 2 or more exacerbations treated with antibiotics, oral corticosteroids, or both in the previous year. The diagnosis of COPD was established from clinical records during screening and spirometry conducted at study 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 or unstable ischemic heart disease, or were using drugs with the potential to increase plasma theophylline concentration to greater than 1 to 5 mg/L.[17]

Randomization/Treatment Allocation

Participants were stratified by region and recruitment setting (primary or secondary care) and randomized with equal probability (1:1) to receive low-dose theophylline or placebo. The random allocation sequence was generated using randomly generated blocks of entries of varying sizes (2 or 4) permuted for each combination of region and recruitment setting (primary or secondary care). The internet-based computerized randomization system was created and

administered by the Centre for Healthcare Randomized Trials, University of Aberdeen.

Intervention

The treatment period was 52 weeks with either theophylline (Uniphyllin MR), 200 mg-tablets, or visually identical placebo (Napp Pharmaceuticals). Dosing was based on pharmacokinetic modeling incorporating the major determinants of theophylline plasma concentration and designed to achieve a steady-state plasma theophylline concentration of 1 to 5 mg/L.[16] Dosing was determined by the participant's ideal body weight (IBW) and smoking status (nonsmokers or smokers with IBW ≤60 kg took 1 theophylline MR [200 mg] or 1 placebo daily; smokers with IBW >60 kg took 1 theophylline MR [200 mg] or 1 placebo twice daily). No other changes were made to participants' care, which 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, oral corticosteroids, or both during the 52-week treatment period as reported by the participant.[18] Patient recall of this outcome is highly reliable over a year.[19] A validation exercise was conducted at 2 of the largest recruiting sites. At these 2 sites, a care/encounter summary (prepared by the general practice staff) of a random 20% sample of participants was requested and compared against participant report of exacerbation. A minimum of 2 weeks between exacerbations was necessary to be considered as separate events.[18]

Outcome data were collected by face-to-face assessments conducted at week 0 (recruitment baseline), 26 weeks, and 52 weeks. In addition to exacerbation data, the following secondary outcomes were collected: participant-reported unscheduled hospital admissions because of severe exacerbations of COPD; unscheduled hospital admissions not related to COPD; health-related quality-of-life score (EQ-5D-3L [EuroQol 5 Dimension 3 Level] scale, −0.59 to 1 with 1 indicating full health, no generally accepted meaningful minimal clinically important difference [MCID])[20]; COPD-related health status (COPD Assessment Test [CAT] scale, 0 to 40 with ≤5 being the norm for healthy nonsmokers and >30 indicating a very high COPD effect on quality of life, MCID is 2 units)[21]; modified Medical Research Council (mMRC) dyspnea score (range, 0 [not troubled by breathlessness except on strenuous exercise] to 4 [too breathless to leave the house or breathless when dressing or undressing])[22]; post bronchodilator spirometry (FEV_1/FVC as percent predicted; for regulatory purposes a change <3% from baseline is considered as not clinically important)[23,24]; adverse reactions or serious adverse events; episodes of pneumonia; and mortality. Adherence was assessed by pill counting of study drug returns at the 26- and 52-week assessments. In some self-selected recruitment centers, the Hull Airway Reflux Questionnaire (HARQ) was completed by participants at recruitment, 6 months, and 12 months to assess symptoms not elucidated by the CAT or mMRC dyspnea scale.[25] Health care utilization data were also collected at recruitment, 6 months, 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 send a questionnaire to their general practice about exacerbations, or alternatively, general practice staff could send an encounter summary from which exacerbation data were extracted. The minimum information requested from general practice was the number of exacerbations in the specified treatment period, which was often provided without dates of individual exacerbations.

Sample Size

Data from a previous study indicated that for a trial population with 2 or more exacerbations treated with antibiotics, oral corticosteroids, or both during 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 (ie, from a mean of 2.22 to 1.89) with 90% power at 5% significance level. There is no validated MCID for COPD exacerbation frequency.[24,27] The 15% reduction in COPD exacerbations was based on consultation with primary and secondary care colleagues (general practitioners and pulmonologists) 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 trials.[28] This inflated each study group to 712 participants, giving 1424 in total.

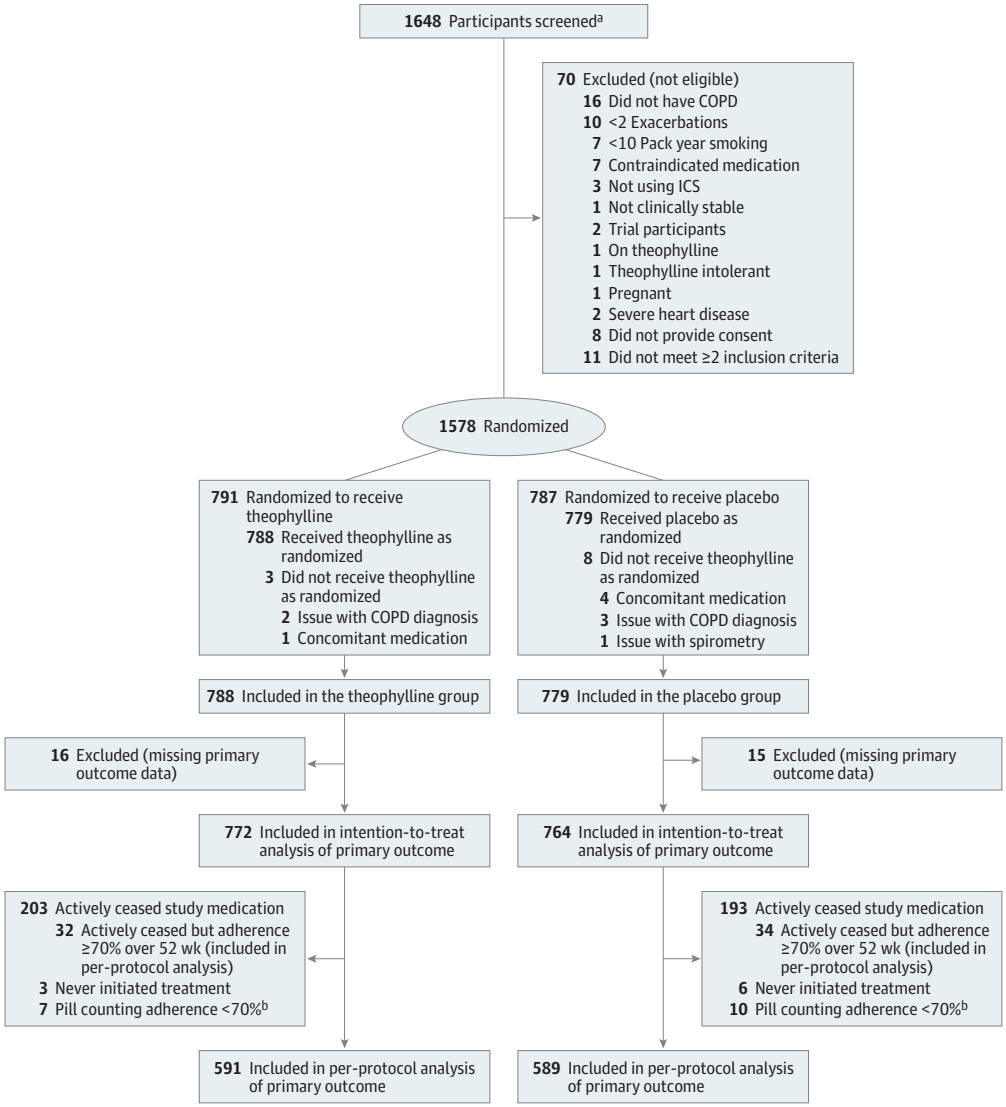
Statistical Methods

All analyses were governed by a statistical analysis plan (Supplement 3). Analysis was in accordance with the intention-to-treat principle. A per-protocol analysis, excluding nonadherent (<70% of doses taken) participants, was performed as a sensitivity analysis. Adherence was defined as participants having taken at least 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, sex, pack-years of smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting, and center as a random effect. For those covariates used in the model, any missing data were 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 implemented.

The secondary outcomes of number of exacerbations requiring hospitalization, as well as non-COPD hospital admissions, were analyzed using the same methods as that used for the primary outcome. Further exploration of the outcome, exacerbations requiring hospitalization in a post-hoc analysis, included inspection of the frequency distribution to ascertain

Figure 1. Enrollment, Randomization, and Follow-up of Participants Randomized to Theophylline as Adjunctive Therapy to Inhaled Corticosteroids vs Placebo for Prevention of COPD Exacerbations



COPD indicates chronic obstructive pulmonary disease.

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

[b] Adherence, as assessed by pill counting, indicated participant nonadherence because less than 70% of total doses were taken.

if any differences were limited to those with few or many exacerbations. Episodes of pneumonia, all-cause (and respiratory-related) mortality, and mMRC score were analyzed using χ^2 tests. Lung function and continuous CAT score were compared between groups using mixed-effects models. Because 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, sex, body mass index, smoking status at recruitment (former vs current), baseline treatment for COPD, GOLD stage, exacerbations in 12 months prior to recruitment, oral corticosteroid use at recruitment, and dose of ICS at recruitment. The subgroup analyses were undertaken by adding a treatment × variable interaction term to the model using the primary outcome.

Analyses were performed using Stata version 14 (StataCorp). A 5% 2-sided significance level was used throughout.

Results

Participant involvement in the trial is outlined in **Figure 1**. Participants were recruited between February 6, 2014, and August 31, 2016, and final follow-up was completed August 31, 2017. A total of 1578 participants were randomized: 791 to theophylline and 787 to placebo. There were 11

postrandomization exclusions (3 theophylline, 8 placebo), so 1567 participants were ultimately included: 788 theophylline and 779 placebo. eTable 1 in Supplement 4 details the reasons for postrandomization exclusion. Participants were recruited from 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%) did not 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 the allocated recruitment period beyond the original target of 1424. The decision to continue recruitment was made by the trial steering committee and approved by the funding organization based on aggregated recruitment and study medication cessation data. The investigators, the trial steering committee, and the 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% (843) were men, and 31.7% (496) were current smokers. Eighty percent of participants were using triple therapy of ICS, long-acting-β_2-agonists and long-acting muscarinic antagonists. Although mean FEV_1 (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 patients with frequent exacerbators[27] with a mean (SD) number of self-reported exacerbations in the 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 or very high).

Primary Outcome

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

Secondary Outcomes

The analysis of the secondary outcomes is detailed in **Table 2**. There were 319 severe COPD exacerbations treated in hospital (134 in the theophylline group; 185 in the placebo group). The mean (SD) number of severe COPD exacerbations treated in hospital was 0.17 (0.49) in the theophylline group vs 0.24 (0.66) in the placebo group (mean difference, −0.07 [95% CI, −0.13 to −0.01]; unadjusted IRR, 0.72 [95% CI, 0.55-0.95]; adjusted IRR, 0.72 [95% CI, 0.55-0.94]; P = .02).

There were no significant differences in non-COPD hospital admissions, episodes of pneumonia, FEV_1, CAT score, mMRC dyspnea score, or mortality (COPD-related and overall) between the 2 groups.

Only serious adverse events and adverse reaction data were collected during the 1-year treatment period. Low-dose theophylline was not associated with an increase in adverse reactions or serious adverse events (eTable 4 in Supplement 4). There were no significant differences in the symptom profiles of serious adverse events between the theophylline and placebo groups (cardiac, 2.4% vs 3.4%; gastrointestinal, 2.7% vs 1.3%; neurological, 1.4% vs 0.9%) or for adverse reactions (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 2-center validation exercise the general practice records of 67 participants were examined, and in 53 (79%), there was complete agreement between participant and general practice records.

Per-Protocol Analyses

The per-protocol analysis excluded 356 (23%) participants with less than 70% adherence (181 [23.0%] in the theophylline group; 175 [22.9%] in the placebo group; P = .80). The reasons for ceasing study medication were equally distributed between the theophylline and placebo groups (eTable 2 in Supplement 4). The most common reason for stopping medication was for gastrointestinal disorders (n=78 [46 in the theophylline group; 32 in the placebo group]), 46 participants discontinued study medication because they felt no benefit (25 in the theophylline group; 21 in the placebo group), 64 discontinued study medication without providing a reason (28 in the theophylline group; 36 in the placebo group), and 29 ceased for social circumstances (15 in the theophylline group; 14 in the placebo group).

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

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 −0.05 (95% CI, −0.12 to −0.003) and adjusted IRR 0.70 (95% CI, 0.50-0.97), P = .03. There were no other statistically significant differences between the groups (**Table 3**).

Prespecified Subgroup Analysis

There was no evidence that the treatment effect differed in any of the prespecified subgroups (all-interaction P values >.05): age, sex, body mass index, smoking status at recruitment (former vs current), baseline COPD treatment, GOLD staging, exacerbations in 12 months prior to recruitment, oral corticosteroid use at recruitment, and ICS dose at recruitment.

Table 1. Baseline Characteristics of Participants Randomized to Theophylline and Placebo

	Theophylline Group (n = 788)	Placebo Group (n = 779)
Age, mean (SD), y	68.3 (8.2)	68.5 (8.6)
Men, No. (%)	425 (53.9)	418 (53.7)
BMI, mean (SD)[a]	27.1 (6.2)	27.3 (6.0)
Current smoker, No. (%)	247 (31.4)	249 (32.0)
Smoking pack-years, median (IQR)	43.0 (28.5-57.0)	41.0 (27.0-55.0)
COPD treatment, No. (%)		
ICS only	13 (1.6)	17 (2.2)
ICS/LABA	136 (17.3)	125 (16.0)
ICS/LAMA	13 (1.6)	10 (1.3)
ICS/LABA/LAMA	625 (79.3)	627 (80.5)
Long-term antibiotics, No./total (%)	51/784 (6.5)	48/771 (6.2)
FEV_1 % predicted, No.	785	771
Mean (SD)	51.3 (20.1)	52.2 (19.8)
FEV_1 % predicted, GOLD[5] stage, No. (%)[b]		
Very severe	116 (14.8)	95 (12.2)
Severe	291 (37.1)	295 (38.4)
Moderate	308 (39.2)	308 (40.0)
Mild	70 (8.9)	73 (9.5)
FEV_1/FVC % ratio, No.	783	770
Median (IQR)	47.4 (37.6-59.0)	47.8 (37.5-59.3)
Exacerbations in last 12 mo[c]		
Any exacerbation, No.	785	773
Median (IQR)	3 (2-4)	3 (2-4)
Mean (SD)	3.63 (2.21)	3.54 (2.09)
Resulting in hospitalization, No.	784	773
Median (IQR)	0 (0-1)	0 (0-0)
Comorbidities, No./total (%)		
Hypertension	317/782 (40.2)	277/772 (35.6)
Treated anxiety or depression ≤last 5 y	222/782 (28.2)	213/772 (27.3)
Asthma	138/782 (17.5)	147/772 (18.9)
Ischemic heart disease	111/781 (14.1)	96/771 (12.3)
Osteoporosis	109/783 (13.8)	90/771 (11.6)
Diabetes mellitus	83/782 (10.5)	93/772 (11.9)
Cerebrovascular event	46/783 (5.8)	58/772 (7.4)
Bronchiectasis	41/782 (5.2)	27/770 (3.5)
mMRC dyspnea score, No. (%)	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 100 m	225 (28.7)	204 (26.5)
4: Breathless leaving house	56 (7.2)	55 (7.2)
COPD assessment test, No.	780	771
Mean (SD)	22.8 (7.5)	22.3 (7.9)
CAT, No. (%)[d]	780	771
Low effect (0-9)	37 (4.7)	45 (5.8)
Medium effect (10-19)	219 (28.1)	244 (31.7)
High effect (20-29)	361 (46.3)	328 (42.5)
Very high effect (30-40)	163 (20.9)	154 (20.0)
EQ-5D-3L utility, No.[e]	785	770
Mean (SD)	0.62 (0.28)	0.63 (0.28)

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol 5 dimension 3 level; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonists.

[a] BMI is calculated as weight in kilograms divided by height in meters squared.

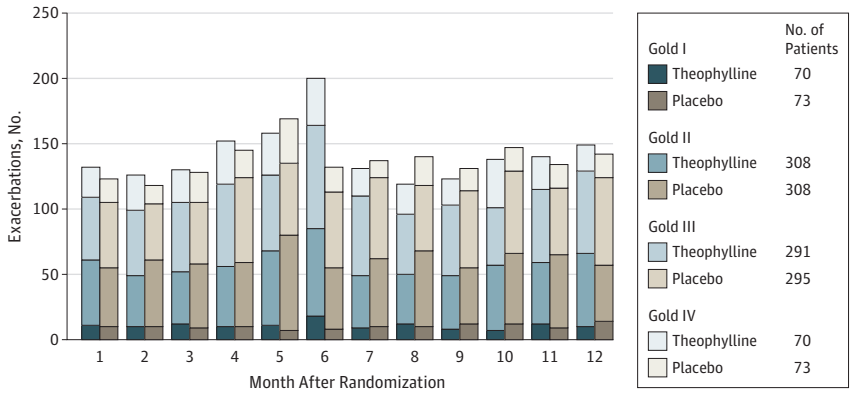
[b] GOLD[5] stage: very severe, FEV_1 <30% predicted; severe, FEV_1 30%-49% predicted; moderate, FEV_1 50%-79% predicted; mild, FEV_1 ≥80% predicted.

[c] Exacerbation is defined as symptomatic deterioration in COPD requiring treatment with antibiotics, oral corticosteroids, or both.

[d] CAT has a range of 0 to 40 (≤5 is the norm for healthy nonsmokers; >30 indicates a very high COPD effect on quality of life).

[e] EQ-5D-3L health outcome instrument has a scale range of −0.59 to 1, in which 1 indicates full health.

Figure 2. Exacerbations for Each Treatment Month by Baseline GOLD Stage[a] for Low-Dose Theophylline and Placebo Groups[b]



FEV_1 indicates forced expiratory volume in the first second.

[a] GOLD (global initiative for chronic obstructive lung disease)[6] stage: I mild, FEV_1 ≥80% predicted; II moderate, FEV_1 50%-79% predicted; III severe, FEV_1 30%-49% predicted; IV very severe, FEV_1 <30% predicted.

[b] Total exacerbations 3420; missing data points 41.

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 (eTable 3 in Supplement 3) indicated that a small number (n = 10) of participants in the placebo group with frequent (≥3 /y) 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 1-year period. The primary outcome was COPD exacerbations treated with oral corticosteroids, antibiotics, or both during 1 year of treatment. Exploratory analyses of 11 prespecified secondary outcomes indicated that low-dose theophylline had no clinical effect in 10, including adverse reactions and SAEs.

Preclinical studies have demonstrated that addition of low-dose theophylline to corticosteroid therapy has a synergistic anti-inflammatory effect.[29] The few randomized clinical trials of low-dose theophylline have been small (58-110 participants), reported contradictory results, and have had major limitations.[30-32] The current pragmatic trial recruited 1578 participants with 98% ascertainment of the primary outcome. This high ascertainment rate was achieved by participants who ceased study medication attending scheduled study assessments, the request for exacerbation data from general practice staff, or the inspection of primary care records. The current study attempted to replicate the use of low-dose theophylline in routine clinical practice with 121 geographically dispersed study centers, 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 Supplement 5.

The inclusion criterion of at least 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 or more exacerbations in the previous year[26]; 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 trials[33,34]; however, it is consistent with the recent pragmatic UK Salford Lung Study, which used an inclusion criterion of at least 1 exacerbation and reported exacerbation rates of 1.74 to 1.90 per year.[35] Previous low-dose theophylline studies used a single dose for all participants[10,11,30]; however, in the current study, theophylline dosing was personalized (determined by IBW and smoking status; designed to achieve plasma theophylline concentrations of 1 to 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%) subgroup of patients frequently hospitalized 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 frequency,[36] this finding warrants further investigation.

Limitations

This study has several limitations. First, more participants than anticipated (26%) ceased taking the study drug; however, this was offset by 10% overrecruitment and a 98% follow-up rate. When compared with the current trial, most effectiveness trials of theophylline are relatively short and

Table 2. Secondary Outcomes for Participants Randomized to Receive Theophylline and Placebo, Intention-to-Treat Population

	Baseline to Week 52							
	Theophylline Group (n=772)			Placebo Group (n=764)			Value (95% CI)	*P* Value
COPD hospital admissions								
Total admissions, No.	134			185			Adusted IRR, 0.72 (0.55 to 0.94)[a]	.02
Mean (SD) per participant	0.17 (0.49)			0.24 (0.66)			Mean difference, −0.07 (−0.13 to −0.01)[b]	
Non-COPD hospital admissions								
Participants, No.	762			755				
Total admissions, No.	116			119			Adjusted IRR, 0.99 (0.71 to 1.38)[a]	
Mean (SD) per participant	0.15 (0.56)			0.16 (0.47)			Mean difference, −0.01 (−0.06 to 0.05)[b]	
	Week 0	Week 26	Week 52	Week 0	Week 26	Week 52		
FEV_1 % predicted								
Participants, No.	769	553	533	757	539	489	Marginal mean difference, −0.57 (−2.51 to 1.36)[c]	
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)		
CAT score[d]								
Participants, No.	764	675	633	756	657	615	Marginal mean difference, 0.01 (−0.65 to 0.68)[c]	
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)		
mMRC dyspnea score								
Participants, No. (%)	767	676	631	757	655	615		
0: Breathless strenuous exercise	35 (4.6)	42 (6.2)	38 (6)	50 (6.6)	51 (7.8)	52 (8.5)		26 wk: .63[e]
1: Breathless hurrying	211 (27.5)	209 (30.9)	186 (29.5)	218 (28.8)	189 (28.9)	158 (25.7)		52 wk: .31[e]
2: Slower than contemporaries	248 (32.3)	197 (29.1)	174 (27.6)	235 (31.0)	179 (27.3)	182 (29.6)		
3: Stop after 100 m	219 (28.6)	178 (26.3)	178 (28.2)	201 (26.6)	186 (28.4)	167 (27.2)		
4: Breathless leaving house	54 (7.0)	50 (7.4)	55 (8.7)	53 (7.0)	50 (7.6)	56 (9.1)		
	Baseline to Week 52, No./Total (%)							
Pneumonia during first 12 mo	14 (1.8)			9 (1.2)			Unadjusted OR, 1.55 (0.67 to 3.62)[f]	.31
All-cause mortality	19 (2.5)			14 (1.8)			Unadjusted HR, 1.35 (0.68 to 2.69)[g]	.40
COPD-related mortality	7 (0.9)			9 (1.2)			Unadjusted HR, 0.77 (0.29 to 2.07)[g]	.61
Adverse reactions	341/709 (48.0)			308/699 (43.9)				.12[e]
Total adverse reactions, No.	883			818				
SAEs	103/783 (13.2)			108/770 (14.0)				.60[e]
Total SAEs, No.	141			135				

Abbreviations: CAT, COPD Assessment Test, COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; SAEs, serious adverse events.

[a] Adjusted incidence rate ratio calculated with negative binomial model adjusting for baseline characteristics of age, sex, pack-years of smoking, number of exacerbations in previous 12 months, COPD treatment, and recruitment setting and center as a random effect.

[b] Indicates unadjusted mean difference in exacerbations per participant.

[c] Marginal mean difference calculated from mixed-effect models adjusting for baseline characteristics of age, sex, pack-years of smoking, number of exacerbations in previous 12 months, COPD treatment, recruitment setting, and center as a random effect.

[d] CAT has a range of 0 to 40 (≤5 is the norm for healthy nonsmokers; >30 indicates a very high COPD effect on quality of life).

[e] Comparison between groups calculated using a χ^2 test.

[f] From a mixed-effects logistic model.

[g] From a Cox regression model.

exclude people with significant comorbidities.[28] This may explain why the current year-long trial in a population more representative of the population encountered in clinical practice witnessed a 26% rate of ceasing study medication, similar to that reported in a recent year-long low-dose theophylline trial.[31] 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

Table 3. Secondary Outcomes for Participants Randomized to Receive Theophylline and Placebo, Per-Protocol Population

	Baseline to Week 52							
	Theophylline Group (n=591)			Placebo Group (n=589)			Value (95% CI)	*P* Value
COPD hospital admissions								
Total admissions	92			126			Adjusted IRR, 0.70 (0.50 to 0.97)[a]	.03
Mean (SD) per participant	0.16 (0.45)			0.21 (0.61)			Mean difference, −0.05 (−0.12 to −0.003)[b]	
Non-COPD hospital admissions								
Participants, No.	587			589				
Total admissions	66			85			Adjusted IRR, 0.82 (0.54 to 1.24)[a]	.35
Mean (SD) per participant	0.11 (0.49)			0.14 (0.45)			Mean difference, −0.03 (−0.08 to 0.02)[b]	
	Week 0	Week 26	Week 52	Week 0	Week 26	Week 52		
FEV_1% predicted								
Participants, No.	588	471	455	583	471	432	Marginal mean difference, −1.33 (−3.47 to 0.80)[c]	
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)		
CAT score[d]								
Participants, No.	584	560	534	583	555	527	Marginal mean difference, 0.29 (−0.45 to 1.04)[c]	
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)		
mMRC dyspnea score								
Participants, No. (%)	585	560	534	583	550	527		
0: Breathless strenuous exercise	26 (4.4)	34 (6.1)	32 (6.0)	44 (7.5)	46 (8.3)	47 (8.9)		26 wk: .43[e]
1: Breathless hurrying	160 (27.3)	182 (32.5)	167 (31.3)	176 (30.1)	160 (29.0)	149 (28.3)		52 wk: .34[e]
2: Slower than contemporaries	198 (33.8)	161 (28.8)	146 (27.3)	181 (31.0)	155 (28.1)	153 (29.0)		
3: Stop after 100 m	157 (26.8)	142 (25.4)	147 (27.5)	149 (25.5)	153 (27.7)	135 (25.6)		
4: Breathless leaving house	45 (7.7)	41 (7.3)	43 (8.0)	34 (5.8)	38 (6.9)	43 (8.2)		
	Baseline to Week 52, No. (%)							
Pneumonia during first 12 mo	9 (1.5)			5 (0.8)			Unadjusted OR, 1.81 (0.60 to 5.44)[f]	.29
All-cause mortality	13 (2.2)			9 (1.5)			Unadjusted HR, 1.45 (0.62 to 3.38)[g]	.39
COPD-related mortality	5 (0.8)			5 (0.8)			Unadjusted HR, 1.00 (0.29 to 3.46)[g]	.99

Abbreviations: CAT, COPD Assessment Test, COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio.

[a] Adjusted incidence rate ratio calculated with negative binomial model adjusting for baseline characteristics of age, sex, pack-years of smoking, number of exacerbations in previous 12 months, COPD treatment, and recruitment setting and center as a random effect.

[b] Indicates unadjusted mean difference in exacerbations per participant.

[c] Marginal mean difference calculated from mixed-effect models adjusting for baseline characteristics of age, sex, pack-years of smoking, number of exacerbations in previous 12 months, COPD treatment, and recruitment setting and center as a random effect.

[d] CAT has a range of 0 to 40 (≤5 is the norm for healthy nonsmokers; >30 indicates a very high COPD effect on quality of life).

[e] Comparison between groups calculated using a χ^2 test.

[f] From mixed-effects logistic model.

[g] From Cox regression model.

between 11% and 20% to be clinically important.[24,27] The 15% reduction chosen for this trial was determined after consultation with primary and secondary care colleagues who considered a 15% reduction to be small but clinically important. Third, the primary outcome of exacerbations was participant-reported rather than documented. Patient recall of COPD exacerbations has been shown to be highly reliable over a year,[19] and people with COPD do not report all their exacerbations to health care professionals.[3,19,37] Participant recall of exacerbations in the current study appeared to be reliable with a 2-center validation exercise demonstrating 79% concordance between participant reporting and general practice clinical records. Fourth, the definition of exacerbation used in the current study of requiring treatment with antibiotics and corticosteroids underestimates the frequency of symptom-defined mild exacerbations that are short lived and treated with a temporary increase in bronchodilator use.[38] 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

Conclusions

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 1-year period. The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the prevention of COPD exacerbations.

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