Pharmacological Management of Chronic Obstructive Pulmonary Disease by Low-Dose Theophylline: A Prospective Hospital-based Study in East Godavari of Andhra Pradesh

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Abstract

Background: High therapeutic dose of theophylline is not tolerated well by some patients. As it is an effective and affordable drug, the effectiveness of low-dose theophylline in pharmacological management of chronic obstructive pulmonary disease (COPD) was assessed.

Aim: The aim of this study was to detect the efficacy of low-dose theophylline in COPD patients.

Patients and Methods: Patients with stable COPD were enrolled. The complete blood picture (CBP), pulmonary function tests (PFTs), and St. George’s Respiratory Questionnaire (SGRQ) were performed at enrolment. Patients were categorized into two groups: subjects and controls. All the participants were given medication for COPD as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. However, subjects were kept on low-dose sustained-release oral drug theophylline (150 mg twice daily) as an add-on. At every follow-up, once every 10 days up to 30 days, their parameters were recorded. The difference between the prognostic biomarkers was analyzed using the Student’s “t”-test.

Results: The CBP, SGRQ, and PFTs showed improvement in COPD patients treated with low-dose theophylline, i.e., subject group. Even though the PFTs improved in subjects, evidence of COPD remained. Low-dose theophylline may help to improve the quality of life in COPD patients.

Conclusion: As a Cost-effective medication, low-dose theophylline can be used as an add-on drug to GOLD guidelines for the treatment of COPD. The subjects may feel better and can lead their normal life even with COPD.

Keywords: Complete blood picture, pulmonary disease, pulmonary function tests theophylline

INTRODUCTION

Theophylline, a xanthine derivative bronchodilator, has been used to treat chronic obstructive pulmonary disease (COPD) for over seven decades. Currently, it has lost popularity because of the introduction of more effective bronchodilators; theophylline is needed in relatively high concentrations (10–20 mg/L). At this high dose, theophylline can relax the human airway smooth muscle by elevating the cyclic adenosine monophosphate levels. Unfortunately, many patients are not able to tolerate high-dose therapeutic concentrations of theophylline. Current studies bring a new insight into the molecular action of low-dose sustained-release theophylline; it can reverse the steroid resistance in COPD and can act as an anti-inflammatory drug. Theophylline is recommended when other long-term bronchodilators are not available or patient cannot afford it.

A clinical diagnosis of COPD should be considered in patients having chronic cough, sputum production, and dyspnea and having a history of exposure to risk factors such as smoking or biomass fuel. The presence of postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV₁/FVC) ratio <0.7 confirms the diagnosis of COPD which remains a clinical diagnosis, confirmed by measurement of airflow limitation using spirometry, a postbronchodilator FEV₁ <80% (predicted). Although theophylline has effects when used in bronchodilator doses,
increasing evidence shows that at low plasma concentrations, it has significant anti-inflammatory effects in COPD.\[3\]

Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. The aim of this study was to assess the effects of low-dose theophylline at 150 mg/day twice, added to long acting β2 agonist (LABA) + long-acting muscarinic antagonists (LAMAs) + inhaled corticosteroids (ICSs) rotahalers. This study was done in accordance with the provisions of the Declaration of Helsinki.

The primary goal of treatment was to improve exercise capacity, lung function, and to reduce symptoms of dyspnea. Secondary aims were to evaluate self-reported COPD symptoms and intake of relief medications and lung function variables such as Forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC).

**Patients and Methods**

We enrolled 472 COPD patients above 65 years of age, among 620 patients who presented to the pulmonology department of our hospital during the year 2016–2018. One hundred and forty-eight patients were excluded from this study due to a history of right heart failure, severe diabetes, hypertension, and not willing to continue in this study. After explaining the protocol and benefits of this in their own language, written informed consent was obtained from all the participants for participation in the study as well as presentation of the data for research purposes.

All the consenting patients were investigated for COPD through routine tests (1) chest X-ray, (2) complete blood picture (CBP), (3) sputum bacterial culture sensitivity, and (4) pulmonary function tests (PFTs). The diagnosis of COPD was obtained by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: The presence of a post-bronchodilator FEV1/FVC <0.70 confirms the presence of persistant airflow limitation. Most of the participants had at least one exacerbation in the past 6 months before screening. Mild-to-moderate COPD cases with exacerbations were enrolled in this study.

For the clinical and prognostic assessment of the patients, St. George’s Respiratory Questionnaire (SGRQ) was used. This included assessment of the frequency of cough episodes, quantity of sputum/per day, baseline dyspnea index grading improvement, frequency of rotahalers use, and 6-min walk test (6MWD test).\[3\] CBP of the patients such as white cell count, neutrophils, eosinophils, monocytes, basophils, and erythrocyte sedimentation rate (ESR) was assessed. All the participants were from poor and lower middle-class background and most of them were daily Agricultural labourers and farmers. They were habituated to smoking cigars from a young age of 15 years.

Two hundred forty COPD patients were treated with 150 mg of theophylline, twice daily along with standard medication as per the GOLD guidelines, i.e., long-acting beta-2 agonists (LABA) + LAMA and ICSs rotahalers as the study group. Two hundred thirty-two participants were treated with only LABA + LAMA + ICSs rotahalers and were considered as the control group.\[5\] Two hundred micrograms of budesonide, 6 µg of formoterol fumarate, and 80 µg of ipratropium bromide dry powder inhalers were used due to their cheap availability. Their effect lasted up to 24 h. Single-blind method was used in this study because the use of placebo was not acceptable to the institutional ethical committee.

During the 30 days of the study period, all the participants were followed up every 10 days, i.e., three times in a month. At every follow-up, CBP, SGRQ, and PFTs were obtained again. In each visit, the patients were examined with respect to the correctness of inhalation technique and were advised as appropriate. Cigar smoking was completely banned.

DxH 800 (Beckman Cell Counter, Inc., Brea, CA, USA) blood analyzer was used for CBP. Jaeger Master Screen spirometer (Jaeger, Inc., Bodnegg, Germany) was used for PFTs.

The data are presented as a mean ± standard deviation. Comparison of continuous variables between two groups was done using unpaired “t”-test. Statistical significance was accepted if \( P < 0.05 \). All the statistical analysis was done by GraphPad Insat 3 software.

**Results**

A total of 472 stable and eligible COPD patients underwent screening and enrolment to the study. The demographic and anthropometric characteristics of the patients and the use of respiratory medications were similar in both the study and control groups. The main characteristics of the subjects at the baseline are shown in Tables 1 and 2.

| Variable | Subjects (\( n=240 \)) | Control (\( n=232 \)) | \( P \) |
|----------|------------------------|------------------------|-------|
| Age (years) | 66.5±5.6 | 65.5±5.8 | 0.2334 |
| Gender (male/female) | 169/71 | 152/80 | - |
| Smoking (male/female) | Yes | | |
| No | 33/56 | 24/63 | - |
| BMI (kg/m²) | 26.70±4.23 | 25.9±4.5 | 0.0766 |
| RBC (1×10⁶/µL) | 5.13±1.32 | 5.11±0.98 | 0.8524 |
| WBC (1×10³/µL) | 6.33±1.98 | 6.13±1.24 | 0.1908 |
| Neutrophils (1×10³/µL) | 5.42±1.09 | 5.63±1.98 | 0.1523 |
| Lymphocyte (1×10³/µL) | 3.01±0.21 | 3.04±0.25 | 0.1582 |
| Basophils (1×10³/µL) | 1.01±0.11 | 1.05±0.40 | 0.1364 |
| Platelets (1×10³/µL) | 243.23±103.45 | 251.23±123.5 | 0.44449 |
| Hb (g/dL) | 14.43±5.12 | 14.83±4.22 | 0.3557 |
| ESR (mm/h) | 62.78±2.87 | 64.23±4.09 | <0.0001 |

BMI: Body mass index, CBP: Complete blood picture, RBC: Red blood cell, WBC: While blood cell, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate
After all the three follow-ups, the overall comparison of variables between both the groups throughout the whole study was performed. In the study group, on the 10th day of posttreatment, the prognostic factors such as CBP, indices of SGRQ, and PFTs were significantly improved as compared to the control group except FVC% \((P = 0.0815)\) [Tables 3 and 4].

On the 20th day of the examination, significant improvement from the baseline characteristics was seen among the subjects who were treated with theophylline along with the routine treatment. A significant decrease in sputum volume and increase of 6MWD were also seen. In CBP, we observed a significant decrease in neutrophils, eosinophils, and ESR. PFTs (FEV\(_1\) and FEV\(_1\)/FVC ratio) showed significant improvement in the study group than control, while there was no significant difference with respect of FVC% \((P = 0.2164)\).

All the subjects were instructed to come for follow-up on the 30th day of treatment and were assessed as before. All the parameters in CBP were significantly improved in the study group than in the control group. The study group showed subjective improvement as assessed by St. George’s respiratory criteria. Sputum volume was lower in the study group with minimal cough episodes. Pulmonary functions also improved significantly in the study group [Figures 1 and 2].

### Discussion

According to the GOLD guidelines 2019, controversy remains about the exact effects of xanthine derivatives. Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome p450 mixed-function oxidases. There is evidence for a modest bronchodilator effect compared with placebo in stable COPD. The addition of theophylline to salmeterol produces a greater improvement in FEV\(_1\), and breathlessness than salmeterol alone.\(^7\) The addition of theophylline to salmeterol produces a greater improvement in FEV\(_1\), and breathlessness than salmeterol alone.\(^3\) The GOLD 2018 and 2019 has recommended using the ABCD assessment tool for the treatment of COPD. However, GOLD 2019 has not included

### Table 2: St. George’s Respiratory Questionnaire and pulmonary function tests of the study participants

| Variable SGRQ and PFT | Study group | Control group | \(P\) | Significant |
|------------------------|-------------|---------------|------|------------|
| Sputum volume (ml/day) | 158.01±2.67 | 158.04±2.10   | 0.8924 | Yes        |
| MMRC dyspnea score     | 2.48±0.19   | 2.49±0.34   | 0.6646 | Yes        |
| 6 MWD (m)              | 122.80±10.76| 128.8±8.76   | 0.001  | Yes        |
| Number of cough episodes/day | 15          | 14          | -      |            |
| PFTs                   |             |              |       |            |
| FVC % predicted        | 63.51±11.30 | 63.14±11.90  | 0.7296 | Yes        |
| FEV\(_1\)% predicted   | 60.42±8.10  | 60.97±7.41   | 0.4506 | Yes        |
| FEV\(_1\)/FVC % predicted | 69.36±6.20 | 69.98±6.24  | 0.2798 | Yes        |

SGRQ: St. George’s Respiratory Questionnaire, PFTs: Pulmonary function tests, FEV\(_1\): Forced expiratory volume in 1 s, FVC: Forced vital capacity, 6 MWD: 6-min walk distance, MMRC: Modified medical research council

### Table 3: Overall comparison of complete blood picture between the control group and study group

| CBP \((1\times10^8)\) cells/µL | Study versus/ control group | Pretreatment \((P)\) | 10th day treatment \((P)\) | 20th day treatment \((P)\) | 30th day treatment \((P)\) |
|-------------------------------|----------------------------|---------------------|--------------------------|--------------------------|--------------------------|
| RBC                           | Study group/ control group | 5.3±1.32/5.76±0.45 (\(<0.001\)*) | 5.3±1.02/5.56±0.12 (\(<0.001\)*) | 5.12±2.25/5.12±1.21 (0.9991*) | 5.21±0.24/5.62±0.34 (\(<0.0001\)*) |
| WBC                           | Study group/ control group | 6.33±1.98/6.24±1.23 (0.5549) | 5.12±1.01/6.33±0.15 (\(<0.001\)*) | 5.02±1.43/6.12±0.34 (\(<0.001\)*) | 4.12±1.65/6.01±3.12 (\(<0.0001\)*) |
| Neutrophils \((1\times10^7)\) cells/µL | Study group/ control group | 5.42±1.09/5.45±0.12 (0.6770) | 5.12±0.98/5.55±0.12 (\(<0.001\)*) | 4.01±1.09/5.34±0.23 (\(<0.001\)*) | 3.01±1.41/6.01±0.54 (\(<0.001\)*) |
| Lymphocytes \((1\times10^7)\) cells/µL | Study group/ control group | 3.01±0.21/2.96±0.54 (0.1829) | 2.67±0.45/2.96±0.12 (\(<0.001\)*) | 2.61±0.21/3.01±0.02 (\(<0.001\)*) | 2.11±0.44/3.98±0.34 (\(<0.001\)*) |
| Basophils \((1\times10^5)\) cells/µL | Study group/ control group | 0.19±0.11/0.14±0.10 (\(<0.001\)*) | 0.06±0.02/0.15±0.04 (\(<0.001\)*) | 0.02±0.01/0.15±0.02 (\(<0.001\)*) | 0.02±0.01/0.15±0.01 (\(<0.001\)*) |
| Eosinophils \((1\times10^6)\) cells/µL | Study group/ control group | 0.34±0.05/0.34±0.02 (0.9991) | 0.29±0.03/0.32±0.11 (\(<0.001\)*) | 0.28±0.05/0.34±0.10 (0.0001*) | 0.11±0.01/0.34±0.05 (\(<0.0001\)*) |
| Platelets \((1\times10^9)\) cells/µL | Study group/ control group | 243.2±103.22/254.22±100.5 (0.2464) | 216.98±13.24/125.12±95.12 (0.0024*) | 218.44±121.23/212.09±114.23 (0.5586) | 215.50±91.56/219.22±102.23 (0.6771) |
| Hb (g/dL)                     | Study group/ control group | 14.43±5.12/14.83±4.22 (0.3357) | 14.42±1.65/14.55±2.65 (0.5211) | 13.89±2.09/13.22±2.98 (0.0048*) | 13.98±0.89/14.00±1.09 (0.8270) |
| ESR (mm/h)                    | Study group/ control group | 62.78±2.00/59.22±6.22 (0.0001*) | 26.12±12.33/59.12±2.12 (\(<0.0001\)*) | 25.54±11.23/64.94±1.33 (\(<0.0001\)*) | 15.98±1.33/62.12±0.54 (\(<0.0001\)*) |

*\(P\) value. CBP: Complete blood picture, RBC: Red blood cell, WBC: White blood cell, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate.
The preferred treatment algorithm. The initial treatment was streamlined, i.e., Group A: bronchodilator; Group B: LABA or LAMA; Group C: LAMA; and Group D: LAMA, LABA + LAMA or ICS + LABA. Single-inhaler triple therapy versus ICS plus LABA for COPD (TRILOGY) has been tried effectively.\[9\]

In this study, the primary effect of low-dose theophylline on CBP (white blood cell [WBC], eosinophil, neutrophils, monocytes, platelet count, and hemoglobin), St. George’s respiratory indices, and PFTs (FVC, FEV\(_1\), and FEV\(_1\)/FVC) of COPD patients was compared with patients treated without theophylline and the results were analyzed.

Table 4: Overall comparison of St. George’s Respiratory Questionnaire and Pulmonary function tests between study group and control group

| Days   | Variable          | Subject | Control | Subject | Control | P     |
|--------|-------------------|---------|---------|---------|---------|-------|
| 10°    | Sputum volume (ml/day) | 105.12±2.67 | 121.23±3.11 | 0.0001  |
|        | Dyspnea           | 2.08±0.98  | 1.39±1.01  | 0.0008  |
|        | 6 MWD test (m)    | 150.30±15.26 | 128.20±10.36 | <0.0001 |
|        | Cough episodes/day| 10       | 12       | -       |         |
| PFT    | FVC % predicted   | 64.74±10.23 | 63.24±8.30  | 0.0815  |
|        | FEV\(_1\) % predicted | 62.42±8.10 | 60.97±7.41  | 0.0432  |
|        | FEV\(_1\)/FVC % predicted | 69.67±6.40 | 68.23±3.90  | 0.0034  |
| 20°    | Sputum volume (ml/day) | 27.32±0.67  | 89.13±3.0  | 0.001   |
|        | Dyspnea           | 2.98±0.98  | 1.79±0.34  | 0.1862  |
|        | 6 MWD test (m)    | 160.22±10.12 | 158.00±2.67 | <0.0013 |
|        | Cough episodes/day| 5        | 8        | -       |         |
| PFT    | FVC % predicted   | 64.92±7.32  | 63.98±0.911 | 0.2164  |
|        | FEV\(_1\) % predicted | 63.13±9.32  | 58.34±6.19  | <0.0001 |
|        | FEV\(_1\)/FVC predicted | 72.08±5.90 | 64.86±6.20  | 0.0001  |
| 30°    | Sputum volume (ml/day) | Nil       | 39.33±1.0  | -       |         |
|        | Dyspnea           | 3.58±0.02  | 2.87±0.24  | 0.0001  |
|        | 6 MWD test (m)    | 280.00±10.34 | 189.76±3.36 | <0.0001 |
|        | Cough episodes/day| 1        | 5        | -       |         |
| PFT    | FVC % predicted   | 66.12±6.45  | 62.02±4.43 | <0.0001 |
|        | FEV\(_1\) % predicted | 63.05±5.92  | 59.13±6.24  | <0.0001 |
|        | FEV\(_1\)/FVC predicted | 72.12±3.60 | 64.12±3.80  | <0.0001 |

SGRQ: St. George’s Respiratory Questionnaire, PFT: Pulmonary function test, 6 MWD: 6-min walk distance, FEV\(_1\): Forced expiratory volume in 1 s, FVC: Forced vital capacity

Figure 1: Comparison of pulmonary function tests between pre- and post-treatment among study group after a period of 30 days

Figure 2: Comparison of pulmonary function tests between pre- and post-treatment among control group after a period of 30 days

No significant improvement in PFTs of the participants was observed. However, blood parameters such as CBP, St. George’s respiratory criteria, and daily life were significantly improved in the study group compared to the control group. Theophylline has an anti-inflammatory role in COPD. It inhibits cigarette smoke-induced inflammation in skeletal muscle by upregulating histone deacetylase 2 (HDAC2) expression and decreases NF-KB activation.\[10\] This can be explained by decreases in dyspnea, air trapping, and breathing

\[10\]
difficulties and increases in diaphragmatic muscle contraction force with theophylline. It decreases the cough episodes as well as improvement in 6MWD. Markham and Faulds\(^\text{(10)}\) reported that theophylline can reduce the eosinophil accumulation in bronchial tissue in the patients with asthma. Hirano et al.\(^\text{(11)}\) confirmed that low-dose theophylline reduces the sputum neutrophils. Koo et al.\(^\text{(12)}\) in Korea found a significant association between WBC and PFTs among COPD patients, especially noncurrently smoking COPD patients. A decrease in neutrophils was observed in the subjects who were treated with theophylline in this study. This suggests an anti-inflammatory effect of theophylline.

The fall in PFTs in the control group suggests that low-dose theophylline may not improve the PFTs, but it can decelerate the reduction in PFTs. Kirsten et al. found worsening of COPD control when theophylline was withdrawn.\(^\text{(13)}\) Similar results were seen by Panahi et al., who assessed the effect of low-dose theophylline on the improvement of PFTs of sulfur mustard-exposed patients.\(^\text{(14)}\)

The cumulative results of this study showed that a low-dose of theophylline can improve the COPD patients’ symptoms, but it has minimal effect on the reversal of PFTs into normal. This can be explained by the findings of Gibson et al.\(^\text{(15)}\) Theophylline shows its effect by restoring reduced HDAC activity to normal levels, thus suppressing inflammation and potentially making the COPD patients responsive to corticosteroids. Devereux et al.\(^\text{(16)}\) demonstrated that low-dose theophylline increases the efficacy of corticosteroids in COPD by reducing the incidence of exacerbations.

In summary, despite an overall lack of benefit, approximately one-third of the patients were subjective responders in both dyspnea and FEV\(_1\) improvement. Selective phosphodiesterase –type 4 inhibitors (PDE-4) inhibitors have potential to improve the beneficial effects of theophylline and reduce its adverse effects, although the existing inhibitors appear to be limited by the same side effects as theophylline. In the present study, slight FEV\(_1\) improvement was observed in the study group, but moderate obstruction was persisting with no change in peak expiratory flow rate. Cough episodes were reduced in the study group in 30 days. In the study group, 6 MWD test was improved up to 300 m compared to the control group. Dyspnea subsided in 30 days of treatment with theophylline in compared with control group, and sputum production was reduced significantly. In contrast to our results, other studies\(^\text{(16-18)}\) found no beneficial effect. Further large-scale, long-duration study on a larger population is needed.

**Conclusion**

Add-on therapy with theophylline improves the clinical condition and spirometric measurements of patients with COPD without an effect on peak expiratory flow rate. Quality of life improvement can be achieved by add-on therapy with theophylline along with ICS, long-acting beta agonists, and LAMA.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Cosio BG, Tsaprouni L, Ito K, Jazrawi E, Adcock IM, Barnes PJ. Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. J Exp Med 2004;200:689-95.

2. To Y, Ito K, Kizawa Y, Failla M, Ito M, Kusama T, et al. Targeting phosphoinositide-3-kinase-delta with theophylline reversing corticosteroid insensitivity in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:897-904.

3. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease; 2019. Available from: https://goldcopd.org/wp-content/uploads/2019/04/GOLD_Spirometry_2019.pdf. [Last accessed on 2019 Aug 24].

4. Jones PW, Quirk FH, Baveystock CM. The St. George’s Respiratory Questionnaire. Respir Med 1991;85 Suppl B: 25-31.

5. Rennard SI. Treatment of stable chronic obstructive pulmonary disease. Lancet 2004;364:791-802.

6. Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. N Engl J Med 2004;350:2689-97.

7. Ram FS, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y, et al. Oral theophylline for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2002;4:CD003902.

8. ZWallaack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 2001;119:166-70.

9. Singh D, Papi A, Corrada M, Pavlouva I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): A double-blind, parallel group, randomised controlled trial. Lancet 2016;388:963-73.

10. Markham A, Faulds D. Theophylline. A review of its potential steroid sparing effects in asthma. Drugs 1998;56:1081-91.

11. Hirano T, Yamagata T, Gohda M, Yamagata Y, Ichikawa T, Yanagisawa S, et al. Inhibition of reactive nitrogen species production in COPD airways: Comparison of inhaled corticosteroid and oral theophylline. Thorax 2006;61:761-6.

12. Koo HK, Kang HK, Song P, Park HK, Lee SS, Jung H, et al. Systemic white blood cell count as a biomarker associated with severity of chronic obstructive lung disease. Tuberc Respir Dis (Seoul) 2017;80:304-10.

13. Kirsten DK, Wegner RE, Jörres RA, Magnussen H. Effects of theophylline withdrawal in severe chronic obstructive pulmonary disease. Chest 1993;104:1101-7.

14. Panahi Y, Pourazal E, Amini-Harandi A, Powel H, Walters EH. Study on effectiveness of low dose theophylline as add-on to inhaled corticosteroid for patients with sulfur mustard induced bronchiolitis. Asia Pac J Med Toxicol 2013;2:126-30.

15. Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev 2000;(2):CD001117.

16. Devereux G, Cotton S, Barnes P, Briggs A, Burns G, Chaudhuri R, et al. Use of low-dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease: Study protocol for a randomised controlled trial. Trials 2015;16:267.

17. Waterhouse JC, Pritchard SM, Howard P. Hyperinflation, trapped gas and theophylline in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis 1993;48:126-9.

18. McKay SE, Howie CA, Thomson AH, Whiting B, Addis GJ. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. Thorax 1993;48:227-32.