# Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials

R Graham Barr, Brian H Rowe, Carlos A Camargo Jr


## Abstract

**Objective** To evaluate the addition of methylxanthines to standard treatments in patients presenting with acute exacerbations of chronic obstructive pulmonary disease (COPD).

**Design** Meta-analysis of randomised controlled trials.

**Data source** The Cochrane airways review group's COPD register. Two reviewers independently selected articles for inclusion, assessed methodological quality, and extracted data.

**Selection of studies** Four trials met the inclusion criteria, with 169 patients.

**Main outcome measures** Mean change in spirometry, clinical end points, symptom scores, and adverse events.

**Results** Mean change in forced expiratory volume at one second at two hours was similar in methylxanthine and placebo groups but transiently increased with methylxanthines at three days. Non-significant reductions in admissions to hospital and length of stay were offset by a non-significant increase in relapses at one week. Changes in symptom scores did not reach significance. Methylxanthines caused more nausea and vomiting than placebo (odds ratio 4.6, 95% confidence interval 1.7 to 12.6), and non-significant increases in tremor, palpitations, and arrhythmias were also observed.

**Conclusions** The available data do not support the use of methylxanthines for the treatment of exacerbations of chronic obstructive pulmonary disease. Potential benefits of methylxanthines for lung function and symptoms were generally not confirmed at standard levels of significance, whereas the potentially important adverse events of nausea and vomiting were significantly increased in patients receiving methylxanthines.


## Introduction

The guidelines of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) currently recommend consideration of the addition of an oral or intravenous methylxanthine to aerosolised bronchodilators for severe exacerbations of chronic obstructive pulmonary disease (COPD).[1] This recommendation follows prior guidelines of the British, European, and American thoracic societies that recommended methylxanthines for patients with severe exacerbations[2] or incomplete response to bronchodilators.[3 4]

Methylxanthines produce several effects that may be beneficial to patients with stable COPD,[5] including bronchodilation, immunomodulation, and bronchoprotection.[6] They may also influence the course of exacerbations of COPD through actions to decrease diaphragmatic muscle fatigue, increase mucociliary clearance, block centrally mediated hypoventilation, and decrease capillary leakage.[7]

Some studies have implied that the clinical impact of methylxanthines is larger than their modest bronchodilator effects.[8] Randomised controlled trials of methylxanthines for exacerbations of COPD, however, have been small and have produced conflicting results. We therefore conducted a meta-analysis of randomised controlled trials to determine the effect of methylxanthines on the course of exacerbations of COPD.

## Methods

We included randomised trials that compared methylxanthines (oral theophylline, intravenous aminophylline, or intravenous doxofylline) with placebo for exacerbations of COPD. Treatment was required to occur in the emergency department or immediately on admission to hospital. Co-interventions were permitted and included $\beta_2$ agonists, ipratropium, antibiotics, corticosteroids, and oxygen. We required participants in the studies to have known COPD with an exacerbation that necessitated presentation to an emergency department or other acute care setting, or admission to hospital. Patients with a diagnosis of asthma, cystic fibrosis, bronchiectasis, or other lung diseases were excluded. Patients with partial reversibility on pulmonary function testing were included.

### Outcome measures

We defined outcomes of lung function testing as change in forced expiratory volume at one second ($FEV_1$) at two hours and at three days. Clinical outcomes included admission to hospital, relapse within seven days (for patients in emergency departments), length of stay (for patients admitted to hospital), and change in self rated symptom scores within hours and at three days. Adverse events were recorded and included nausea and vomiting, hypokalaemia, hyperglycaemia, headache, confusion, tremor,


Division of General Medicine, PH-9 East Room 105, Columbia-Presbyterian Medical Centre, 622 West 168th Street, New York, NY 10032, USA

R Graham Barr *assistant professor of medicine and epidemiology*

Division of Emergency Medicine, University of Alberta, Edmonton, AB, Canada T6G 2B7

Brian H Rowe *professor*

Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA021143, USA

Carlos A Camargo Jr *assistant professor of medicine and epidemiology*

Correspondence to: R Graham Barr rgb9@columbia.edu


bmj.com 2003;327:643

seizures, palpitations or arrhythmias, myocardial infarction, and sudden death.

**Search strategy for identification of studies**

The COPD register of the Cochrane airways review group is a compilation of controlled clinical trials assembled from systematic searches of Medline, Embase, and CINAHL and supplemented by hand searches of 20 leading respiratory journals. It is not limited by language of publication. We used the following terms to search the database:

methylxanthine* *or* theophylline *or* aminophylline *or* doxofylline *and*

acute *or* emerg* *or* exacerbation* *or* sudden

We checked reference lists of all primary studies and review articles and contacted authors of identified trials. Two reviewers independently identified trials that seemed potentially relevant from title and abstracts. By using the abstract or the full text of each study as necessary two reviewers independently decided if trials fulfilled inclusion criteria for the review. Differences were resolved by discussion.

**Assessment of methodological quality**

We used the Cochrane approach and Jadad criteria to assess methodological quality.[9] Two reviewers extracted data independently. Authors of trials were contacted to provide missing data and intention to treat results, when necessary. Two reviewers independently estimated some information regarding outcomes from graphs.

**Statistical analysis**

We used Review Manager (version 4.1; MetaView version 4.1) to combine trials and analysed them by intention to treat. For continuous variables we calculated mean difference and 95% confidence intervals for each study. We pooled similar studies by using weighted mean difference or standardised mean difference and 95% confidence intervals. For dichotomous variables we calculated an odds ratio with 95% confidence intervals for individual studies and pooled results. We tested heterogeneity among pooled estimates; $P<0.10$ was considered statistically significant heterogeneity. Where we found significant heterogeneity we used a random effects model.

All studies provided measures of standard deviation or standard error of the mean for $FEV_1$; the method of reporting, however, differed between studies. We calculated standard deviations from the standard error of the mean by multiplying the standard error by the square root of the number of subjects in each group. All studies provided the standard deviation or standard error of the $FEV_1$ before treatment. One study provided the standard deviation for relative change in $FEV_1$ at two hours,[10] one provided the SD for $FEV_1$ at two hours after treatment,[8] and two provided an estimate of the variance for the absolute change in $FEV_1$ at three days.[11 12] The two former studies were therefore not directly comparable, whereas the latter two were. For the former two studies we report individual study results in this paper and made estimates of the combined effect under various assumptions of the covariance. We calculated the variance before and after the intervention from the standard deviation at each time point and combined variances ($\sigma^2$) by using the formula

$$\sigma^2_{1,2}=\sigma^2_2+\sigma^2_1-2\times\text{covariance}_{1,2}$$

Since the covariance between time points was not reported, we performed analyses with, firstly, a conservative estimate of no covariance, and secondly, with the covariance estimated as

$$\text{covariance}_{1,2}=\rho\times\sqrt{[\sigma^2_2\times\sigma^2_1]}$$

where $\rho$ is the correlation coefficient between $\sigma^2_2$ and $\sigma^2_1$ among all the included trials. We converted the variance of the mean difference ($\sigma^2_{1,2}$) to the standard deviation of the mean difference.

**Table 1** Studies of methylxanthines for the treatment of exacerbations of chronic obstructive pulmonary disease that were identified but did not meet all inclusion criteria, and reason for exclusion

| Study | Reasons for exclusion |
|---|---|
| Brantingham 1970[13] | Stable COPD |
| Tedders et al 1976[14] | Stable COPD |
| Dorow 1978[15] | Stable COPD |
| Bone 1980[16] | Not randomised |
| Donner et al 1980[17] | Stable COPD |
| Perret et al 1980[18] | Stable COPD |
| Jenkins et al 1982[19] | Stable COPD |
| Tanser 1982[20] | Stable COPD |
| Vozeh et al 1982[21] | No placebo group |
| Chin et al 1983[22] | Not randomised |
| Dolcetti et al 1988[23] | Crossover design not appropriate for assessment of treatment of exacerbations |
| Light 1983[24] | Not randomised |
| Sahay et al 1983[25] | Stable COPD |
| Reinecke et al 1986[26] | No intervention |
| Sahay et al 1986[27] | Stable COPD |
| Furukawa 1988[28] | Asthma |
| Jonsson et al 1988[29] | Asthma |
| Lloberes 1988[30] | Unclear if randomised; stabilised exacerbation |
| Musil et al 1988[31] | Not randomised |
| Schmidt et al 1988[32] | Stable COPD |
| Morandini et al 1989[33] | Stable COPD |
| Chiappini et al 1990[34] | Relevant end points not reported |
| Thomas et al 1992[35] | Stable COPD |
| Holford et al 1993[36] | No placebo group |
| Holford et al 1993[37] | No placebo group |

COPD=chronic obstructive pulmonary disease.

## Results

We identified 1299 articles in the COPD register of the Cochrane airways review group. The review of titles and abstracts yielded 29 articles that possibly fulfilled inclusion criteria. Among these, four[8 10–12] met criteria and were included in the analysis. Excluded studies and reason for exclusion are listed in table 1.

Three studies were published in the peer reviewed literature, and the fourth[12] has been published in abstract form. Table 2 shows the characteristics of the studies. The included trials yielded results for 169 patients. Two studies recruited patients presenting to emergency departments,[8 10] and the other two recruited patients admitted to hospital. Three tested intravenous aminophylline,[8 10 11] and the fourth tested oral theophylline.[12] All evaluated the incremental effectiveness of aminophylline added to standard treatment (generally inhaled $\beta_2$ agonists, anticholinergics, supplemental oxygen, steroids, and antibiotics).

Three of the four studies made substantial efforts to restrict asthmatic patients from the analysis. One study enrolled patients with asthma and COPD and reported both combined and stratified results.[8] Whenever

**Table 2** Characteristics of randomised clinical trials of methylxanthines for acute exacerbations of chronic obstructive pulmonary disease that were included in the meta-analysis

| Study | Methods | Participants | Interventions | Outcomes |
|---|---|---|---|---|
| Seidenfield 1984[10] | Type: parallel group study<br>Duration: 2 hours<br>Randomisation: random number generator<br>Outcome blinding: double blind<br>Co-interventions: metaproterenol sulfate 0.3 ml/2.5 ml nebuliser saline<br>Confounders: none noted<br>Assessment score: 4 | Setting: emergency department<br>Inclusion criteria: American Thoracic Society defined bronchitis (1962) with COPD exacerbation<br>Exclusion criteria: febrile (>37.5°C), direct admission, arrhythmia, pneumonia, congestive heart failure<br>Number recruited: 52<br>Mean age: 63 years<br>Sex: 100% men<br>Baseline $FEV_1$: 0.8 l<br>Likelihood of COPD: clinical diagnosis of chronic bronchitis, baseline FEV1 0.8 l | Experimental: intravenous aminophylline 2.8-5.6 mg/kg over 1 hour, based on prior theophylline use<br>Control: dextrose 5% water | Analysed: change in $FEV_1$ at 2 hours, returns to emergency department in one week<br>Reported: change in FVC, symptom scores<br>Mortality: experimental group (3); control group (5) at 6 months<br>Morbidity: "No significant side effects observed" |
| Rice 1987[11] | Type: parallel group study<br>Duration: 72 hours<br>Randomisation: block<br>Outcome blinding: double blind (except for one investigator who adjusted theophylline and placebo infusion rates)<br>Co-interventions: metaproterenol sulfate 0.3 ml/2.5 ml of normal saline every 4 hours; methylprednisolone 0.5 mg/kg every 6 hours, ampicillin 500 mg/kg every 6 hours<br>Confounders: none noted<br>Assessment score: 5 | Setting: emergency department/medical walk in<br>Inclusion criteria: prior diagnosis of COPD, prior spirometry: $FEV_1$<2 standard deviations from the mean predicted and $FEV_1$/FVC <60%, COPD exacerbation requiring admission to hospital<br>Exclusion criteria: concurrent left heart failure, pneumonia, intubation; prior diagnosis of asthma, readily reversible exacerbations, bronchodilator response of >30% in $FEV_1$<br>Number recruited: 30<br>Mean age: 65 years<br>Sex: 96% (29) men<br>Baseline $FEV_1$: 0.6 l<br>Likelihood of COPD: stringent spirometry criteria | Experimental: intravenous aminophylline 0-6 mg/kg load, based on prior theophylline use 0.5 mg/kg maintenance infusion for level of 72-94 μmol/l (abstract lists 72-83 μmol/l)<br>Control: placebo | Analysed: change in $FEV_1$ at 2 hours, symptom score, adverse effects<br>Reported: change in FVC, $Po_2$ and $Pco2$<br>Mortality: none<br>Morbidity: experimental group—intubation (1); control group—intubation (1) |
| Wrenn 1991[8] | Type: parallel group study<br>Duration: until discharge from emergency department<br>Randomisation: method not specified<br>Outcome blinding: double blind<br>Co-interventions: metaproterenol 0.3 ml sulfate/2.5 ml saline nebuliser every 30 minutes as needed, intravenous methylprednisolone 80 mg once<br>Confounders: randomisation not stratified by type of obstructive airways disease<br>Assessment score: 4 | Setting: emergency department<br>Inclusion criteria: asthma exacerbation or wheeze, age >45, smoked ≥20 pack years, duration of disease >20 years or onset of disease after age 45 years.<br>Exclusion criteria: concurrent pulmonary oedema, myocardial infarction; theophylline use in prior 24 hours; allergy to theophylline, corticosteroids, or β agonists; type 1 diabetes mellitus<br>Number recruited: 39<br>Mean age: 62 years<br>Sex: 64% (25) men<br>Baseline $FEV_1$: 0.7 l<br>Likelihood of COPD: misclassification with asthma since asthma and COPD subgroups established post hoc; no prior testing of pulmonary function data | Experimental: intravenous aminophylline 5.6 mg/kg over 20 minutes, 0.9 mg/kg maintenance infusion<br>Control: placebo | Analysed: change in $FEV_1$ at 3 days, symptoms, admissions to hospital, return to emergency department in 3 days, adverse effects<br>Reported: change in peak expiratory flow rate and FVC at 2 hours, approximate costs, emergency department length of stay<br>Mortality: none reported<br>Morbidity: experimental group—new T wave inversions on electrocardiogram+hyperglycaemia (1); control group—none |
| Ram 2000[12] | Type: parallel group study<br>Duration: 7 days or duration of hospitalisation (lesser of)<br>Randomisation: blocks of 4, computer generated<br>Outcome blinding: double blind<br>Co-interventions: salbutamol 5 mg four times a day, ipatropium 0.5 mg four times a day, prednisone 40 mg four times a day, oral antibiotic (if purulent sputum)<br>Confounders: none noted<br>Assessment score: 5 | Setting: medical ward<br>Inclusion criteria: admission for COPD exacerbation; age ≥50; smoked ≥20 pack years; admission $FEV_1$ ≤1.5 l.<br>Exclusion criteria: theophylline use in prior week; need for intravenous aminophylline; concurrent pneumonia or congestive heart failure; prior diagnosis of asthma, bronchiectasis, carcinoma, interstitial lung disease, paroxysmal atrial fibrillation; theophylline allergy<br>Number recruited: 50<br>Mean age: 71 years<br>Sex: 46% (23) men<br>Baseline $FEV_1$: 0.6 l<br>Likelihood of COPD: stringent spirometry criteria | Experimental: long acting oral theophylline 200 mg or greater, titrated to serum concentration of 10-20 mg/l<br>Control: placebo | Analysed: change in $FEV_1$ at 3 days, symptom scores, length of stay, adverse effects<br>Reported: change in FVC, $Sao_2$<br>Mortality: none<br>Morbidity: experimental group—myocardial infarction (1), non-malignant tachycardia (2); control group—none |

COPD=chronic obstructive pulmonary disease.
$FEV_1$=forced expiratory volume in one second.
FVC=forced vital capacity.

possible, data were extracted for patients with COPD only.The authors of two studies[8 12] provided supplemental, unpublished data. Overall, the methodological quality of the studies was moderate, as listed in table 2.

### Pulmonary function

Two trials reported baseline $FEV_1$ and change at two hours. One study reported a small, non-significant benefit with methylxanthines (relative change in $FEV_1$

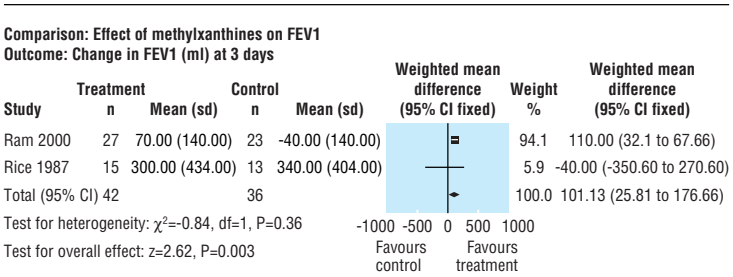


**Fig 1** Weighted mean difference in change in $FEV_1$ at three days (in ml) and 95% confidence intervals between methylxanthines and placebo. Please note that the right side of the scale in figures 1 and 3 favours treatment (methylxanthines) whereas the right side of the scale in figures 2 and 4 favours control. This visual inconsistency is required for numerical consistency

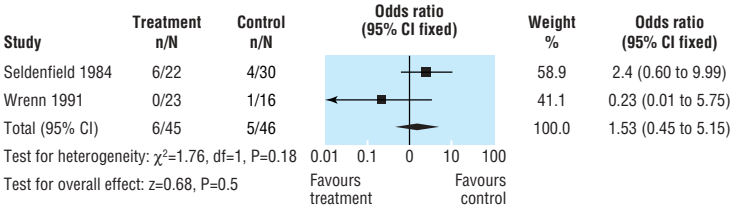


**Fig 2** Odds ratios and 95% confidence intervals of relapses within seven days that required return to the emergency department for methylxanthines compared with placebo use

for methylxanthines: 27% (95% confidence interval 3% to 51%) *v* 22% (13% to 31%) for placebo),[10] whereas the other showed a non-significant worsening with methylxanthines (relative change in $FEV_1$ for methylxanthines: 28% *v* 37% for placebo (95% confidence interval could not be estimated from available data)).[8] Owing to variation in reporting, these trials could not be combined without additional assumptions. We made estimates of the combined effect under various assumptions. All estimates of the combined effect showed a smaller improvement in $FEV_1$ at two hours with methylxanthines than with placebo; in no case did the difference reach significance, and for most estimates the 95% confidence interval excluded any clinically meaningful benefit (for example, weighted mean difference −36 ml, 95% confidence interval −134 ml to 63 ml).

Two trials provided data on change in $FEV_1$ at three days of hospitalisation. The pooled results of the trials for $FEV_1$ were homogenous (P=0.36), and the combined weighted mean difference was 101 ml (26 ml to 177 ml) in favour of methylxanthines (fig 1). Only one of the two trials, however, showed a benefit of methylxanthines.[12] In that trial baseline $FEV_1$ was considerably lower in intervention group than the placebo group (0.59 l and 0.68 l, respectively; a difference of 90 ml). The improvement in $FEV_1$ in methylxanthine compared with placebo arms in that trial was only observed at days 3 and 4 over seven days of follow up.[12] Severity of COPD, as measured by baseline $FEV_1$, was similar in the two trials.

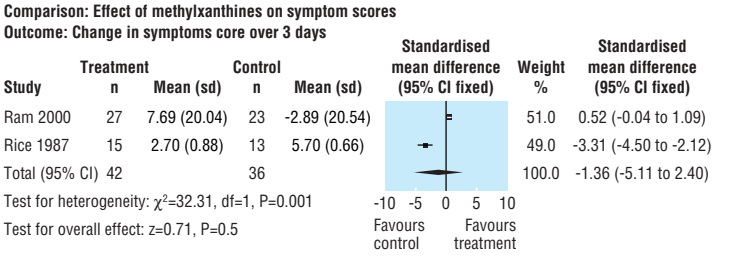


**Fig 3** Standardised mean difference in symptom score (0-100) at three days and 95% confidence intervals between methylxanthines compared with placebo use

### Clinical end points

Data on admissions were available from only one trial.[8] This trial showed a non-significant reduction in admissions to hospital with methylxanthine use (odds ratio 0.3, 0.1 to 1.8). Data on relapses within seven days that necessitated a return to the emergency department were reported in two trials.[8 10] These showed a non-significant increase in relapses in the methylxanthine group (1.5, 0.4 to 5.2) (fig 2). Among patients admitted to hospital one trial showed a non-significant reduction in length of stay in the methylxanthine group (absolute difference −1.4 (95% confidence interval −2.9 to 0.1) days).[12]

### Symptom scores

We extracted data for change in any symptom. One study reported changes in symptoms over several hours as a dichotomised result.[8] Another reported mean differences in four symptom scores over the same time interval[10]; these were, however, not interpretable as dichotomous outcomes.

The two studies that examined symptom scores over three days in patients admitted to hospital reported similar, continuous outcomes, which were comparable as improvement in a 100 point (overall) symptom score.[11 12] Results at three days were heterogeneous (P<0.001), with one study reporting a non-significant benefit and the other reporting a statistically significant harm. The combined estimate indicated a small, non-significant worsening of symptom score with methylxanthines (standardised mean difference −1.4, 95% confidence interval −5.1 to 2.4) (fig 3). The extracted three day symptom score for the intervention group in one trial was unrepresentative of the overall trend for symptom scores in that trial.[11] Re-extraction of the closest, more representative score (at 2.5 days) and re-analysis by using this measure removed the heterogeneity in the analysis (P=0.69) and showed an even smaller, non-significant improvement with methylxanthines (standardised mean difference 0.45, 0.0 to 0.9, P=0.05).

### Adverse effects

Three trials reported adverse effects of methylxanthines.[8 11 12] The trials were homogeneous for all adverse event outcomes (fig 4). The odds of nausea or vomiting were significantly higher for patients receiving a methylxanthine (odds ratio 4.6, 95% confidence interval 1.7 to 12.6) than for patients receiving placebo. More frequent tremor (1.8, 0.7 to 4.6) and palpitations and arrhythmias (4.1, 0.9 to 19.6) were observed among patients receiving methylxanthines, although these associations did not reach significance. Other adverse effects were reported infrequently and could not be combined. One definite myocardial infarction and one patient with acute T wave inversion and hyperglycaemia suggestive of a myocardial infarction were reported among the 97 patients receiving

methylxanthines; no similar events were reported in the placebo group. One intubation was reported in both the methylxanthine and placebo groups, and no deaths were reported during treatment.

## Discussion

Methylxanthines do not confer statistically significant benefit for lung function, clinical outcomes, and symptoms in patients with exacerbations of COPD, but significantly increase nausea and vomiting. This meta-analysis examined the available evidence from randomised controlled trials on methylxanthines in exacerbations of COPD and did not show a consistent benefit of methylxanthines. Whereas a variety of potential benefits of methylxanthines on clinical outcomes were not confirmed at standard levels of statistical significance, nausea and vomiting were significantly increased compared with placebo and other adverse events were non-significantly increased.

Methylxanthines had no consistent effect on $FEV_1$ at two hours. At three days the change in $FEV_1$ was greater in the methylxanthine group, a finding that is based heavily on the results from one study.[12] However, this finding may have been biased by an imbalance in baseline $FEV_1$ in that study. The difference in baseline $FEV_1$ between the theophylline and placebo groups was approximately as large as the difference in change in $FEV_1$ between two groups, such that the $FEV_1$ at the end of follow up three days was the same in treatment and placebo groups. In the original report the differential improvement observed in $FEV_1$ at three days was not sustained with greater follow up.[12]

Our intention was to examine clinical outcomes and symptom scores, but this was constrained by sparse data and reporting vagaries. A non-significant reduction in admissions to hospital among emergency department patients in one study was offset by a non-significant increase in the number of treatment relapses among patients sent home from the emergency department. Length of stay in hospital was shorter among patients receiving theophylline than among those receiving placebo, although this result was not statistically significant. In the original study length of stay was significantly reduced only in an analysis that was not by intention to treat.[12] The magnitude of changes in symptom scores was clinically unimportant and the direction inconsistent.

In contrast to findings for lung function and clinical end points, the pattern of higher risk of adverse events was consistent and, for nausea and vomiting, reached significance. Nausea and vomiting may not be trivial side effects in patients with severe respiratory distress—more than a third of patients in the methylxanthine group developed nausea or vomiting.

Most international recommendations currently recommend methylxanthines for severe exacerbations of chronic obstructive pulmonary disease or exacerbations that are not responding aerosolised bronchodilator treatment.[1–4] We had limited power to examine differences by subgroup of severity of exacerbations; however, no greater benefit was apparent for more severe exacerbations. All four studies evaluated the addition of a methylxanthine to aerosol treatment and enrolled patients with moderately severe exacerbations (pre-treatment $FEV_1$ range 0.6-0.8 l). Our results therefore apply to the target population of these recommendations. Our findings concur with the recommendations of the joint panel of the American College of Physicians-American Society of Internal Medicine and the American College of Chest Physicians, which recommended against use of methylxanthines for exacerbations of chronic obstructive pulmonary disease.[38]

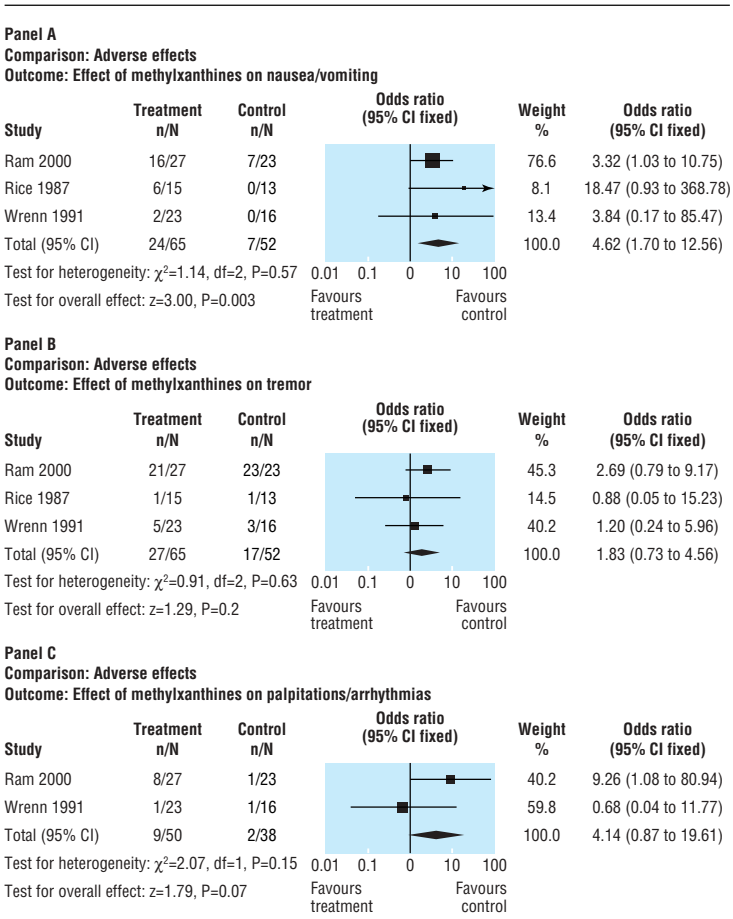


**Fig 4** Odds ratio and 95% confidence intervals of nausea/vomiting (panel A), tremor (panel B), and palpitations/arrhythmias (panel C) for methylxanthines compared with placebo use

### Limitations

The major limitation of this meta-analysis was the paucity of randomised trial data. The sparseness of the data prevented the assignment of definitive conclusions regarding benefits of methylxanthines but allowed firmer conclusions regarding their effect on adverse events. There is a possibility of publication and selection bias in any meta-analysis; but publication bias is unlikely to affect this analysis since the published trials were predominantly negative. The data were not evaluated for the presence of publication bias since too few trials were available to perform a meaningful evaluation. To avoid selection bias, a systematic and comprehensive search was conducted and two reviewers independently evaluated trials for inclusion.

The available data do not support the use of methylxanthines to treat exacerbations of chronic obstructive pulmonary disease. Potential benefits of methylxanthines on lung function and symptoms were generally not confirmed at standard levels of

## What is already known on this topic

Methylxanthines are thought to have modest beneficial effects for the management of stable chronic obstructive pulmonary disease

Randomised trials of methylxanthines for exacerbations of chronic obstructive pulmonary disease have been small and have produced conflicting results

## What this study adds

Potential benefits of methylxanthines on lung function, clinical outcomes, and symptoms were generally not confirmed at standard levels of significance

The important adverse events of nausea and vomiting were significantly increased in patients receiving methylxanthines

significance, whereas the potentially important adverse events of nausea and vomiting was significantly increased in patients receiving methylxanthines.

The authors wish to acknowledge the help of Stephen Milan, Karen Blackwell, and Toby Lasserson of the Cochrane Airways Review Group. We thank Gary M Strauss for assistance with article selection, Keith Wrenn and Felix Ram for providing unpublished data, and Brenda Taveras for help with manuscript preparation. Finally, the assistance of Paul Jones (the Cochrane Airways Review Group's coordinating editor) was greatly appreciated.

Contributors: RGB oversaw the planning of the study, evaluated studies for inclusion, assessed methodological quality, extracted data, performed the statistical analysis, and prepared the manuscript. BHR assisted in planning, execution and manuscript preparation. CAC assisted in planning, evaluated studies for inclusion, assessed methodological quality, extracted data, and assisted in manuscript preparation. All authors approved the final version of the paper. RGB will act as guarantor.

Funding: Supported by grants PE-11001, HL-07427, and HL-63841 from the National Institutes of Health. RGB is funded by a Robert Wood Johnson Generalist Physician Faculty Scholar Award and BHR by the Canadian Institute of Health Research.

Competing interests: None declared.

1 Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Respir Crit Care Med* 2001;163:1256-76.
2 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;8:1398-420.
3 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152(suppl):S77-S121.
4 British Thoracic Society guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the British Thoracic Society. *Thorax* 1997;52(suppl 5):S1-S28.
5 Ram FSF, 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
6 Peleman RA, Kips JC, Pauwels RA. Therapeutic activities of theophylline in chronic obstructive pulmonary disease. *Clin Exp Allergy* 1998;28(suppl 3):53-6.
7 Weinberger M, Hendeles L. Theophylline in asthma. *N Engl J Med* 1996;334:1380-8.
8 Wrenn K, Slovis C, Murphy F, Greenberg AS. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med* 1991;115:241-7.
9 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
10 Seidenfeld JJ, Jones WN, Moss RE, Tremper J. Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease. *Ann Emerg Med* 1984;13:248-52.
11 Rice KL, Leatherman JW, Duane PG, Snyder LS, Harmon KR, Abel J, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease: a controlled trial. *Ann Intern Med* 1987;305-9.
12 Ram FSF, Poole PJ, Bagg W, Stewart, Black PN. Randomized, controlled trial of oral theophylline for the treatment of acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161(suppl):A489.
13 Brantingham P. Clinical trial of theograd. *Br J Clin Pract* 1970;24:165-70.
14 Tedders JG, Thomas AK, Edwards G. A double-blind comparison of a microcrystalline theophylline tablet and salbutamol in reversible airways obstruction. *Br J Clin Prac* 1976;30:212-6.
15 Dorow P. The effect of oral aminophylline compound with protracted activity on respiratory resistance and blood gases in obstructive respiratory diseases. *Arzneimittel-Forschung* 1978;28:853-6.
16 Bone RC. Treatment of respiratory failure due to advanced chronic obstructive pulmonary disease. *Arch Intern Med* 1980;140:1018-1021.
17 Donner C, Fracchia C, Ioli F. Bronchospasm management by means of ipratropium, beclomethasone, and their combination. *G Ital Mal Torace* 1980;34:307-10.
18 Perret L, Laitinen LA. Aspects of chronic bronchitis and emphysema. *Finska Lakaresallskapets Handlingar* 1980;124:101-3.
19 Jenkins PF, White JP, Jariwalla A, Anderson G, Campbell IA. A controlled study of slow-release theophylline and aminophylline in patients with chronic bronchitis. *Br J Dis Chest* 1982;76:57-60.
20 Tanser AR. Maintenance of bronchodilation in chronic reversible airways obstruction. Comparison between choline theophylline and salbutamol. *Practitioner* 1982;226:569-71.
21 Vozeh S, Kewitz G, Perruchoud A, Tschan M, Kopp C, Heitz M, et al. Theophylline serum concentration and therapeutic effect in severe bronchial obstruction: the optimal use of intravenously administered aminophylline. *Am Rev Resp Dis* 1982;125:181-4.
22 Chin R, Pescoe R. Practical aspects in management of respiratory failure in chronic obstructive pulmonary disease. *Crit Care Q* 1983;6:1-21.
23 Dolcetti A, Osella D, DeFilippis G, Carnuccio C, Grossi E. Comparison of intravenously administered doxofylline and placebo for the treatment of severe acute airways obstruction. *J Intl Med Res* 1988;16:264-9.
24 Light RW. Conservative treatment of hypercapnic acute respiratory failure. *Respir Care* 1983;28:561-6.
25 Sahay JN, Bell R, Chatterjee SS, Jayaswal R. Comparative study of the effects of intravenous aminophylline, salbutamol and terbutaline in patients suffering from reversible airways obstruction. *Curr Med Res Opin* 1984;9:1-6.
26 Reinecke T, Seger D, Wears R. Rapid assay of serum theophylline levels. *Annal Emerg Med* 1986;15:147-51.
27 Sahay JN, Chatterjee SS, Summerfield PJ. A comparative trial of ipratropium bromide, controlled release theophylline, and a combination of these in patients with reversible airflow obstruction. *Br J Clin Pract* 1986;40:198-202.
28 Furukawa CT. Comparative trials including a $\beta_2$ adrenergic agonist, a methylxanthine, and a mast cell stabilizer. *Ann Allergy* 1988;60:472-6.
29 Jonsson S, Kjartansson G, Gislason D, Helgason H. Comparison of the oral and intravenous routes for treating asthma with methylprednisone and theophylline. *Chest* 1988;94:723-6.
30 Lloberes P, Ramis L, Montserrat JM, Serra J, Campistol J, Picado C, et al. Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 1988;1:536-9.
31 Musil J, Hirsch V, Votroubkova O. The role of theophylline in treatment of exacerbations of chronic obstructive pulmonary disease. *Prakt Lek* 1998;78:319-20.
32 Schmidt EW, Ulmer WT. Anstieg des arteriellen Sauerstoffdruckes unter Therapie mit Theophyllin bei Patienten mit obstruktiver Ventilationsstörung und respiratorischer Partialinsuffizienz. *Prax Klin Pneumol* 1988;42:600-2.
33 Morandini G. Treatment of chronic bronchitis: combined therapy with sustained-release theophylline and a mucoactive drug sobrerol. *Clin Trials J* 1989;26:163-74.
34 Chiappini F, Bevignani G, Fresu R. Effects of theophylline on the course of hypercapnic respiratory insufficiency. *Clinica Terapeutica* 1990;135:121-7.
35 Thomas P, Pugsley JA, Stewart JH. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. *Chest* 1992;101:160-5.
36 Holford N, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction—10 or 20 mg/L? A randomised concentration-controlled trial. *Clin Pharmacokinet* 1993;25:495-505.
37 Holford N, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial. *Clin Pharmacokinet* 1993;25:506-15.
38 Snow V, Lascher S, Mottur-Pilson C, Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians–American Society of Internal Medicine. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2001;134:595-9.

*(Accepted 11 July)*