

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

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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 exacerbations² 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 broncho-protection.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 β_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 (FEV₁) 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,

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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 inter-

vals 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 FEV₁; 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 FEV₁ before treatment. One study provided the standard deviation for relative change in FEV₁ at two hours,¹⁰ one provided the SD for FEV₁ at two hours after treatment,⁸ and two provided an estimate of the variance for the absolute change in FEV₁ 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 (σ^2) by using the formula

$$\sigma_{1,2}^2 = \sigma_1^2 + \sigma_2^2 - 2 \times \text{covariance}_{1,2}$$

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

$$\text{covariance}_{1,2} = \rho \times \sqrt{[\sigma_1^2 \times \sigma_2^2]}$$

where ρ is the correlation coefficient between σ_1^2 and σ_2^2 among all the included trials. We converted the variance of the mean difference ($\sigma_{1,2}^2$) 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
Vozech 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 fourth¹² 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 β_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 Duration: 2 hours Randomisation: random number generator Outcome blinding: double blind Co-interventions: metaproterenol sulfate 0.3 ml/2.5 ml nebuliser saline Confounders: none noted Assessment score: 4	Setting: emergency department Inclusion criteria: American Thoracic Society defined bronchitis (1962) with COPD exacerbation Exclusion criteria: febrile (>37.5°C), direct admission, arrhythmia, pneumonia, congestive heart failure Number recruited: 52 Mean age: 63 years Sex: 100% men Baseline FEV ₁ : 0.8 l Likelihood of COPD: clinical diagnosis of chronic bronchitis, baseline FEV ₁ 0.8 l	Experimental: intravenous aminophylline 2.8-5.6 mg/kg over 1 hour, based on prior theophylline use Control: dextrose 5% water	Analysed: change in FEV ₁ at 2 hours, returns to emergency department in one week Reported: change in FVC, symptom scores Mortality: experimental group (3); control group (5) at 6 months Morbidity: "No significant side effects observed"
Rice 1987 ¹¹	Type: parallel group study Duration: 72 hours Randomisation: block Outcome blinding: double blind (except for one investigator who adjusted theophylline and placebo infusion rates) 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 Confounders: none noted Assessment score: 5	Setting: emergency department/medical walk in 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 Exclusion criteria: concurrent left heart failure, pneumonia, intubation; prior diagnosis of asthma, readily reversible exacerbations, bronchodilator response of >30% in FEV ₁ Number recruited: 30 Mean age: 65 years Sex: 96% (29) men Baseline FEV ₁ : 0.6 l 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) Control: placebo	Analysed: change in FEV ₁ at 2 hours, symptom score, adverse effects Reported: change in FVC, P _{O2} and P _{co2} Mortality: none Morbidity: experimental group—intubation (1); control group—intubation (1)
Wrenn 1991 ⁸	Type: parallel group study Duration: until discharge from emergency department Randomisation: method not specified Outcome blinding: double blind Co-interventions: metaproterenol 0.3 ml sulfate/2.5 ml saline nebuliser every 30 minutes as needed, intravenous methylprednisolone 80 mg once Confounders: randomisation not stratified by type of obstructive airways disease Assessment score: 4	Setting: emergency department 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. Exclusion criteria: concurrent pulmonary oedema, myocardial infarction; theophylline use in prior 24 hours; allergy to theophylline, corticosteroids, or β agonists; type 1 diabetes mellitus Number recruited: 39 Mean age: 62 years Sex: 64% (25) men Baseline FEV ₁ : 0.7 l 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 Control: placebo	Analysed: change in FEV ₁ at 3 days, symptoms, admissions to hospital, return to emergency department in 3 days, adverse effects Reported: change in peak expiratory flow rate and FVC at 2 hours, approximate costs, emergency department length of stay Mortality: none reported Morbidity: experimental group—new T wave inversions on electrocardiogram+hyperglycaemia (1); control group—none
Ram 2000 ¹²	Type: parallel group study Duration: 7 days or duration of hospitalisation (lesser of) Randomisation: blocks of 4, computer generated Outcome blinding: double blind 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) Confounders: none noted Assessment score: 5	Setting: medical ward Inclusion criteria: admission for COPD exacerbation; age ≥50; smoked ≥20 pack years; admission FEV ₁ ≤1.5 l. 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 Number recruited: 50 Mean age: 71 years Sex: 46% (23) men Baseline FEV ₁ : 0.6 l Likelihood of COPD: stringent spirometry criteria	Experimental: long acting oral theophylline 200 mg or greater, titrated to serum concentration of 10-20 mg/l Control: placebo	Analysed: change in FEV ₁ at 3 days, symptom scores, length of stay, adverse effects Reported: change in FVC, S _{ao2} Mortality: none Morbidity: experimental group—myocardial infarction (1), non-malignant tachycardia (2); control group—none

COPD=chronic obstructive pulmonary disease.

FEV₁=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 FEV₁ and change at two hours. One study reported a small, non-significant benefit with methylxanthines (relative change in FEV₁

Comparison: Effect of methylxanthines on FEV₁
Outcome: Change in FEV₁ (ml) at 3 days

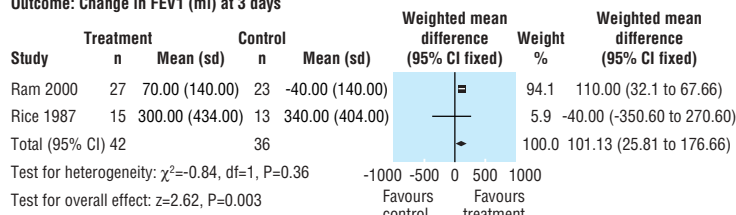


Fig 1 Weighted mean difference in change in FEV₁ at three days (in ml) and 95% confidence intervals between methylxanthines and placebo. Please note that the right side of the scale in figures 1 and 3 favours treatment (methylxanthines) whereas the right side of the scale in figures 2 and 4 favours control. This visual inconsistency is required for numerical consistency

Comparison: Effect of methylxanthines on clinical endpoints
Outcome: Emergency department returns within one week

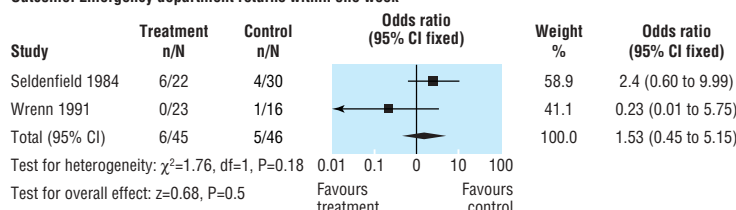


Fig 2 Odds ratios and 95% confidence intervals of relapses within seven days that required return to the emergency department for methylxanthines compared with placebo use

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 FEV₁ 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 FEV₁ 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 FEV₁ at three days of hospitalisation. The pooled results of the trials for FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁, was similar in the two trials.

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 interval¹⁰; 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

Comparison: Effect of methylxanthines on symptom scores
Outcome: Change in symptoms core over 3 days

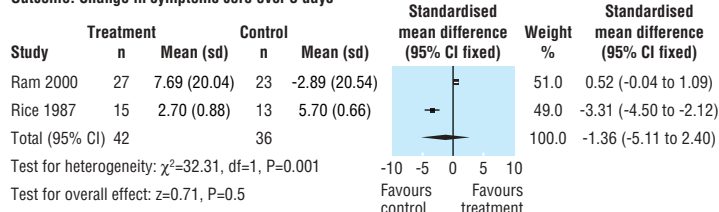


Fig 3 Standardised mean difference in symptom score (0-100) at three days and 95% confidence intervals between methylxanthines compared with placebo use

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 FEV₁ at two hours. At three days the change in FEV₁ 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 FEV₁ in that study. The difference in baseline FEV₁ between the theophylline and placebo groups was approximately as large as the difference in change in FEV₁ between two groups, such that the FEV₁ 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 FEV₁ 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.

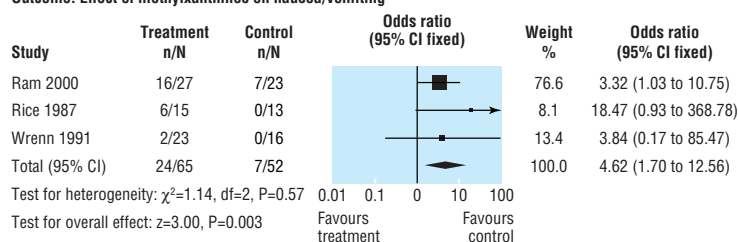
In contrast to findings for lung function and clinical end points, the pattern of higher risk of adverse events was consistent and, for nausea and vomiting, reached significance. Nausea and vomiting may not be trivial side effects in patients with severe respiratory distress—more than a third of patients 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 FEV₁ range 0.6-0.8 l). Our results there-

Panel A

Comparison: Adverse effects

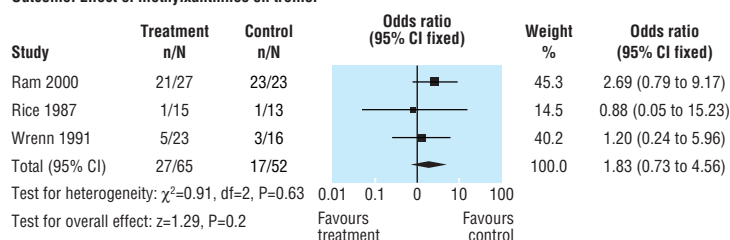
Outcome: Effect of methylxanthines on nausea/vomiting



Panel B

Comparison: Adverse effects

Outcome: Effect of methylxanthines on tremor



Panel C

Comparison: Adverse effects

Outcome: Effect of methylxanthines on palpitations/arrhythmias

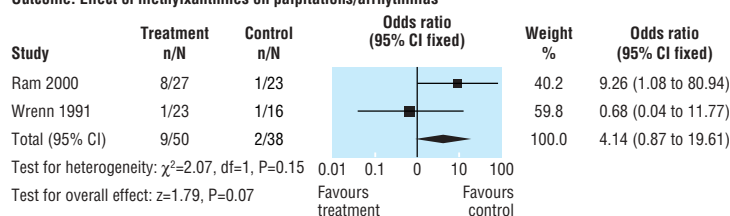


Fig 4 Odds ratio and 95% confidence intervals of nausea/vomiting (panel A), tremor (panel B), and palpitations/arrhythmias (panel C) for methylxanthines compared with placebo use

fore 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

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.

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(Accepted 11 July)