Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and side effects of intravenous theophylline in acute asthma: a systematic review and meta-analysis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Gulixian Mahemuti
Hui Zhang
Jing Li
Nueramina Tieliwaerdi
Lili Ren

Respiratory Department, The Second Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang Province, People's Republic of China

Background and objective: Theophylline has been used for decades to treat both acute and chronic asthma. Despite its longevity in the practitioner's formulary, no detailed meta-analysis has been performed to determine the conditions, including concomitant medications, under which theophylline should be used for acute exacerbations of asthma. We aimed to quantify the usefulness and side effects of theophylline with or without ethylene diamine (aminophylline) in acute asthma, with particular emphasis on patient subgroups, such as children, adults, and concomitant medications.
Methods: We searched PubMed, EMBASE, The Cochrane Library, ClinicalTrials.gov, and the WHO Clinical Trials Registry for randomized, controlled clinical trials. We planned a priori subgroup analyses by time post-medication, concomitant medication, control type, and age.
Results: We included 52 study arms from 42 individual trials. Of these, 29 study arms included an active control, such as adrenaline, beta-2 agonists, or leukotriene receptor antagonists, and 23 study arms compared theophylline (with or without ethylene diamine) with placebo or no drug. Theophylline significantly reduced heart rate when compared with active control (p=0.01) and overall duration of stay (p=0.002), but beta-2 agonists were superior to theophylline at improving forced expiratory volume in one second (FEV1) (p=0.002). Theophylline was not significantly different from other drugs in its effects on respiratory rate, forced vital capacity (FVC), peak expiratory flow rate, admission rate, use of rescue medication, oxygen saturation, or symptom score. Closer examination of the data revealed that the medications given in addition to theophylline or control significantly changed the effectiveness of theophylline (subgroup difference: $p<0.00001$).
Conclusion: Given the low cost of theophylline, and its similar efficacy and rate of side effects compared with other drugs, we suggest that theophylline, when given with bronchodilators with or without steroids, is a cost-effective and safe choice for acute asthma exacerbations.
Keywords: theophylline, theophylline with ethylene diamine, aminophylline, asthma, bronchodilators, beta-2 agonists, adrenaline, FEV, PEFR, affordable drugs

Introduction

Acute asthma exacerbations are a frequent and serious reason for presentation to hospital emergency departments. Asthma prevalence in adults globally is estimated at 4.3%, with Australia, the UK, Sweden, and the Netherlands all exceeding 15%.[1] In children, the prevalence is even higher, with many countries reporting asthma rates in children over 20%.[2] In many parts of the world, asthma prevalence in increasing, although in some countries with high rates of asthma, the prevalence may now be levelling off.[3]

Severe asthma exacerbations in children or adults are very serious and can be life-threatening. According to the World Health Organization, asthma causes ~250,000

Correspondence: Gulixian Mahemuti
Respiratory Department, The Second Affiliated Hospital of Xinjiang Medical University, No 38 Nanhu East Road, Urumqi 830063, Xinjiang Province, People's Republic of China
Email gulixianmahemuti@126.com

deaths worldwide each year.[4] Despite a range of drugs for the treatment of asthma,[5] systematic evidence for the efficacy of these drugs is not universal. Thus, especially in developing countries, it is essential that the comparative effectiveness of all asthma treatments, including older and more affordable drugs, be available to health practitioners.

Theophylline, a methylxanthine, is a bronchodilator. When combined with ethylene diamine as "aminophylline", it is more soluble and is thus the more common form of theophylline used for intravenous (IV) administration.[6,7] Available in generic form, theophylline with or without ethylene diamine is certainly affordable. However, its efficacy, especially in children, and the effective doses are a matter of dispute. We therefore undertook this study to compare the effectiveness of IV theophylline with all available comparators.

Methods

The current systematic review and meta-analysis was performed on the principles of the Cochrane Collaboration.[8]

Data sources and search strategy

We searched PubMed, EMBASE, the Cochrane Library, ClinicalTrials.gov, and the WHO international clinical trials registry for relevant articles. Our search strategy used the following keywords, as full-text and MESH terms (where appropriate): (Theophylline OR 1,3-dimethylxanthine OR Elixophyllin OR Norphyl OR Phyllocontin OR Quibron-TSR OR Theo-24 OR TheoCap OR Theochron OR Theo-Dur OR Theo-Time OR Truxophyllin OR Uniphyl OR aminophylline) AND ("Short-acting beta2 agonist" OR "short-acting beta agonist" OR "beta* adrenergic receptor agonist" OR SABA OR salbutamol OR formoterol OR eformoterol OR "long-acting beta agonist" OR LABA OR albuterol OR levalbuterol OR betamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR Ventolin OR Proventil OR Atock OR Atimos OR Foradil OR Oxis OR Perforomist OR salmeterol OR bambuterol OR fluticasone OR budesonide OR glucocorticoid OR Flixotide OR Flixonase OR Pulmicort OR Rhinocort OR anticholinergic OR ipratropium OR epinephrine OR beclamethasone OR montelukast OR zafirlukast OR "5-LOX inhibitor" OR cromolyn OR placebo OR no drug) AND Asthma AND (Intravenous OR IV OR iv) AND (RCT OR random OR randomised OR randomized OR groups OR "randomised controlled trial" OR "randomized controlled trial" OR "controlled clinical trial"). No date or language restrictions were applied. All citations were uploaded into EPPI-Reviewer 4[9] and were independently coded by two investigators. The date of the last search was 9 July 2017.

Inclusion criteria

Citations were included if they matched the following PICOTS: the population was children or adults presenting to an emergency department with an acute asthma exacerbation; the intervention was theophylline with or without ethylene diamine, administered intravenously; the control was placebo, no drug or active comparator; the outcomes were forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), symptom scores, admission rates, duration of stay, rescue medication use, oxygen saturation, pulse rate, respiratory rate, or adverse events; the time was between 15 minutes and 48 hours after administration of theophylline; the setting was acute, inpatient treatment in a hospital.

Study selection and study quality

Two authors independently assessed all citations at the title/abstract level in EPPI-Reviewer 4. Disagreements between the authors were resolved by consensus. Two authors then examined the full texts of all included abstracts in EPPI-Reviewer 4. In addition to the previously mentioned PICOTS criteria, studies were only included if they were randomized, controlled trials.

The Cochrane tool for assessing the risk of bias in RCTs[10] was used to assess study quality. Two investigators assessed the risk of bias according to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition, selective reporting, and other bias. We did not exclude studies if they were not blinded, but planned a sensitivity analysis to test the importance of blinding in assessing the outcomes.

Data extraction

One investigator extracted data from all included studies. A second investigator confirmed the data extraction. Data that were not given in the text or in tables were extracted using WebPlotDigitizer.[11] We extracted the data as given in the text. For the meta-analysis, we converted standard errors to standard deviations. Where more than one control was present, we extracted all study arms. If more than one study arm was used in an analysis, we avoided a unit of analysis error by dividing the number in the study arm by the number of study arms used in the analysis.

Statistical analysis

Meta-analysis was done using Review Manager (RevMan 5.3).[12] Mean differences and standardized mean differences with 95% confidence intervals (CIs) were calculated using an inverse variance model.[12] Odds ratios with 95% CI were calculated using the Mantel–Haenszel statistical method.[13] Because of differences in study design and participants, we used a random effects model for all analyses.

Results

All study results refer to "theophylline" whether or not it contained ethylene diamine. For a breakdown of which studies used which drug, please refer to the study characteristics given in the following section, as well as Table 1.

Study characteristics

A total of 52 study arms from 42 individual trials were included in the meta-analysis (Figure 1, Table 1). Adults were studied in 29 study arms,[14–36] with children the focus of 17 study arms.[37–53] One study did not restrict the age of participants,[54] and one study did not report the age of participants.[55] Twenty-five study arms compared theophylline with an active control such as adrenaline, beta-2 agonists, or leukotriene receptor antagonists, 21 compared theophylline with placebo, and two studies compared theophylline with no drug. Forty-eight study arms used theophylline with ethylene diamine; and four used theophylline without ethylene diamine. Only two studies were funded or partly funded by industry. All other studies were funded and carried out by university or hospital clinical teams. Blinding of some kind took place in 37 study arms, with blinding being unclear in 11 arms. All studies were carried out in both males and females.

Quality of included studies

The quality of included studies is given in Figure 2. In general, the risk of bias was unclear or low. Reporting of the method of randomization, allocation concealment, and study protocols was frequently missing. The lack of blinding in some studies led to an increase in the risk of bias to some degree.

FEV1/FVC

The FEV1 and FVC (after a full breath) are commonly measured outcomes for asthma studies. FEV1 can be measured in liters (L), or alternatively as a percent of the predicted value. In our analysis, the majority of the studies used liters to measure FEV1. We carried out a subgroup meta-analysis of FEV1 (L) by control type (Figure 3A). Intravenous (IV) theophylline was not significantly different from adrenaline (p=0.12), a leukotriene receptor antagonist (p=0.81), or placebo (p=0.07) in increasing FEV1, but was significantly worse than beta-2 agonists (mean difference [MD] =–0.20 L [95% CI: –0.34, –0.07], p=0.002). A pooled analysis of all active controls, however, also showed a small but significantly improved FEV1 in the control compared with theophylline (MD =–0.14L [95% CI: –0.25, –0.02], p=0.001; Figure 3B). Pooling of the six studies measuring FEV1 as a percent of predicted showed no difference between theophylline and control (MD =3.78 [95% CI: –1.08, 8.63], p=0.13, data not shown). Seven studies (nine study arms) reported on FVC (Figure 3C). There was no difference in FVC between theophylline and control groups (p=0.73).

PEFR

PEFR is another common measurement of lung function in asthmatics. As for FEV1, PEFR can be measured in L or as a percent of the predicted value. A subgroup meta-analysis of PEFR (L) was performed to determine if theophylline was effective at increasing PEFR in the short-term (30 minutes–2 hours) or the longer-term (5 hours–24 hours) (Figure 4A). There were no significant differences between theophylline and control at either time point. A sensitivity analysis removing the placebo-controlled trials from this analysis did not alter the results (data not shown). When measured as a percent of predicted PEFR value (Figure 4B), neither the short-term studies (30 minutes–2 hours; p=0.56) nor the longer-term studies (5 hours–48 hours; p=0.44) showed any significant differences between theophylline and control groups.

Heart rate

During an asthma exacerbation, the heart rate increases to compensate for a reduction in oxygenation in the blood. Therefore, a lower heart rate, both immediately after the administration of medication as well as over the longer term, indicates that the medication is relieving the bronchoconstriction. In order to compare the effect of IV theophylline on heart rate, we undertook a subgroup meta-analysis by time after infusion (Figure 5A). In the short-term (30 minutes–3 hours post-infusion), theophylline lowered the heart rate by 4.17 beats per minute (bpm) compared with control therapy, which was significant (p=0.02). At longer-term time points (24–36 hours post-infusion), the difference in heart rate between IV theophylline and control treatments was similar

Table 1 Characteristics of included studies

Study ID	Intervention (N)	Control (N)	Study type	Study length	Population	Age range, years	Average age, years	Inclusion (severity)	Intervention	Bolus dose
Anantharaman (1993/1)[14]	27	27	P	30 minutes	Adults	15–40	28	All	A	250 mg
Anantharaman (1993/2)[14]	27	17	P	30 minutes	Adults	15–40	27	All	A	250 mg
Appel and Shim (1981)[15]	12	12	P	60 minutes	Adults	No data	33	All	A	6 mg/kg
Coleridge et al (1993/1) (discharged)[16]	16	15	P	50 hours	Adults	No data	34	Not recovered at 30 minutes after salbutamol	A	Not stated
Coleridge et al (1993/2) (inpatients)[16]	14	14	P	50 hours	Adults	No data	34	Not recovered at 30 minutes after salbutamol	A	Not stated
Emerman et al (1986)[17]	20	20	P	90 minutes	Adults	18–45	31	All	A	5.6 mg/kg
Evans et al (1980)[18]	6	7	P	24 hours	Adults	No data	28	All	A	0.285 mg/kg/min
Fanta et al (1986/1)[19]	17	38	P	60 minutes	Adults	No data	30	All	A	5.6 mg/kg
Fanta et al (1986/2)[19]	17	41	P	60 minutes	Adults	No data	30	All	A	5.6 mg/kg
Femi-Pearse et al (1977/1)[20]	8	10	P	40 minutes	Adults	No data	No data	Not stated	A	250 mg over 15 minutes
Femi-Pearse et al (1977/2)[20]	15	17	P	40 minutes	Adults	No data	No data	Not stated	A	250 mg over 15 minutes
Greif et al (1985)[21]	10	11	P	120 minutes	Adults	15–68	38	All	A	6 mg/kg
Huang et al (1993)[22]	10	11	P	48 hours	Adults	22–48	33	Failed albuterol	A	To achieve 15 µg/mL
Johnson et al (1978)[23]	19	20	P	36 hours	Adults	16–65	39	Requiring treatment after 5 mg/kg theophylline and nebulized salbutamol	A	5 mg/kg
Lindholm and Helander (1966/1)[24]	29	21	P	30 minutes	Adults	22–73	48	Moderate severity	A	None
Lindholm and Helander (1966/2)[24]	29	23	P	30 minutes	Adults	15–73	49	Moderate severity	A	None
Lindholm and Helander (1966/3)[24]	29	19	P	30 minutes	Adults	15–73	49	Moderate severity	A	None
Montserrat et al (1995)[25]	6	6	P	51 hours	Adults	21–62	41	Failed bronchodilator therapy	A	6 mg/kg
Murphy et al (1993)[26]	22	22	P	5 hours	Adults	18–45	28	Failed metaproterenol sulfate	A	8 mg/kg
Nakano et al (2006)[27]	10	8	P	Unclear	Adults	22–70	47	Only mild to moderate asthmatics included	A	To achieve 18 µg/mL

Ongoing dose	Control	Bolus dose	Ongoing dose	Background medication	Gender	Country	Blinding	Funding
None	Adrenaline (sc)	1 mg	None	Oxygen	Mixed	Singapore	Unclear	Hospital
None	Salbutamol (nebulized)	10 mg	None	Oxygen	Mixed	Singapore	Unclear	Hospital
None	Epinephrine (sc)	0.3–0.5 mL	None	None	Mixed	USA	Double blind	University/hospital
0.5–0.75 mg/kg/h	Placebo	N/A	N/A	Hydrocortisone (IV), salbutamol (neb), ipratropium bromide (neb)	Mixed	Australia	Double blind	Hospital
0.5–0.75 mg/kg/h	Placebo	N/A	N/A	Hydrocortisone (IV), salbutamol (neb), ipratropium bromide (neb)	Mixed	Australia	Double blind	Hospital
None	Epinephrine (sc)	0.3 mL	None	None	Mixed	USA	Double blind	University/hospital
0.014 mg/kg/min	Salbutamol IV	0.285 μg/kg/min	0.057 μg/kg/min	Hydrocortisone (IV), potassium chloride (IV)	Mixed	UK	Single blind	University/hospital
0.9 mg/kg/h	Epinephrine (sc)	0.3 mg at 20 min ×3	None	Supplemental oxygen	Mixed	USA	Unclear	University/hospital
0.9 mg/kg/h	Isoproterenol (nebulized)	2.5 mg at 20 min ×3	None	Supplemental oxygen	Mixed	USA	Unclear	University/hospital
None	Salbutamol IV	200 μg bolus	None	Not stated	Not stated	Nigeria	Single blind	University
None	Salbutamol IV	200 μg over 15 minutes	None	Not stated	Not stated	Nigeria	Double blind	University
None	Salbutamol IV	4 μg/kg	None	Not stated	Mixed	Israel	Single blind	University/hospital
0.6 mg/kg/h	Placebo	N/A	N/A	Albuterol (neb), methylprednisone (IV)	Mixed	USA	Double blind	University
1 mg/min	Salbutamol IV	None	10 μg/min	Bolus aminophyllyine, salbutamol (neb), hydrocortisone IV, prednisone (oral)	Mixed	UK	Unclear	Hospital
250 mg	Adrenaline (sc)	None	0.5 mg	Not stated	Mixed	Sweden	Double blind	University
250 mg	Isoprenaline	None	0.06 mg inhaled three times	Not stated	Mixed	Sweden	Double blind	University
250 mg	Placebo	N/A	N/A	Not stated	Mixed	Sweden	Double blind	University
0.9 mg/kg/h	Placebo	N/A	N/A	Salbutamol, corticosteroids, oxygen	Mixed	Spain	Double blind	University
0.8 mg/kg/h	Placebo	N/A	N/A	Methylprednisolone (IV)		USA	Double blind	University/hospital
None	Salbutamol (nebulized)	2 mg	None	None	Mixed	Japan	Unclear	University/hospital

(*Continued*)

Table 1 (*Continued*)

Study ID	Intervention (N)	Control (N)	Study type	Study length	Population	Age range, years	Average age, years	Inclusion (severity)	Intervention	Bolus dose
NCT00442338 (2007)[28]	31	30	P	60 minutes	Adults	No data	56	All	A	None
Rodrigo and Rodrigo (1994)[29]	45	49	P	120 minutes	Adults	No data	36	All	A	5.6 mg/kg
Rossing et al (1980/1)[30]	17	16	P	60 minutes	Adults	18–45	30	All	A	5.6 mg/kg
Rossing et al (1980/2)[30]	17	15	P	60 minutes	Adults	18–45	31	All	A	5.6 mg/kg
Self et al (1990)[31]	21	18	P	32 hours	Adults	18–49	32	Failed albuterol and corticosteroids	A	To achieve 10–20 μg/mL
Sharma et al (1984/1)[32]	10	10	P	3 hours	Adults	No data	33	No broncho-dilators in previous 24 hours	A	250 mg
Sharma et al (1984/2)[32]	10	10	P	3 hours	Adults	No data	32	No broncho-dilators in previous 24 hours	A	250 mg
Siegel et al (1985)[33]	20	20	P	3 hours	Adults	18–45	30	None	A	5.6 mg/kg
Tribe et al (1976)[34]	12	11	P	3 hours	Adults	17–78	44	All	A	250 mg
Wrenn et al (1991)[35]	32	35	P	120 minutes	Adults	16 or older	34	All	A	5.6 mg/kg
Zainudin et al (1994)[36]	11	14	P	48 hours	Adults	18–60	No data	Severe asthma	A	No bolus
Bien et al (1995)[37]	19	20	P	24 hours	Children	2–10	6	Excluded: ICU admission, use of systemic corticosteroids	T	1.6 mg/mL
Carter et al (1993)[38]	12	9	P	36 hours	Children	5–18	12	Failed albuterol	A	To achieve 15 μg/mL
D'Avila et al (2008)[39]	30	30	P	60 minutes	Children	2–5	3	Failed albuterol and corticosteroids	A	5 mg/kg in two boluses 6 hours apart
DiGiulio et al (1993)[40]	16	13	P	35 hours	Children	2–16	7	Failed albuterol	T	4.8 mg/kg
Hambleton and Stone (1979)[41]	9	9	P	24 hours	Children	1.5–7	No data	Requiring intense hospital treatment	A	4 mg/kg
Ibrahim et al (1993/1)[42]	40	40	P	120 minutes	Children	No data	10	No broncho-dilators in previous 12 hours	A	5 mg/kg
Ibrahim et al (1993/2)[42]	40	40	P	120 minutes	Children	No data	10	No broncho-dilators in previous 12 hours	A	5 mg/kg
Needleman et al (1995)[43]	25	20	P	120 minutes	Children	2–18	8	Failed albuterol	T	6–8 mg/kg
Nuhoglu et al (1998)[44]	17	19	P	24 hours	Children	2–16	6	All	A	6 mg/kg

Ongoing dose	Control	Bolus dose	Ongoing dose	Background medication	Gender	Country	Blinding	Funding
250 mg	Montelukast	None	14 mg	Inhaled beta-agonist or oxygen	Mixed	Multicenter	Unclear	Industry
0.9 mg/kg/h	Placebo	N/A	N/A	Salbutamol (neb), hydrocortisone (IV)	Mixed	Uruguay	Double blind	University/ hospital
0.9 mg/kg/h	Epinephrine (sc)	0.3 mL ×3	None	Oxygen	Mixed	USA	Unclear	University/ hospital
0.9 mg/kg/h	Isoproterenol (neb)	2.5 mg ×3	None	Oxygen	Mixed	USA	Unclear	University/ hospital
To achieve 10–20 μg/mL	Placebo	N/A	N/A	Prednisone (oral), albuterol (neb), oxygen	Mixed	USA	Double blind	Industry/ university
None	Salbutamol	250 μg	None	None	Mixed	India	Unclear	Hospital
None	Terbutaline	250 μg	None	None	Mixed	India	Unclear	Hospital
0.7 mg/kg/h	Placebo	N/A	N/A	Meteproterenol	Mixed	USA	Double blind	University/ hospital
None	Salbutamol IV	100 μg	None	Hydrocortisone (IV)	Mixed	Australia	Double blind	Hospital
0.9 mg/kg/h	Placebo	N/A	N/A	Methylprednisolone (IV), metaproterenol (neb)	Mixed	USA	Double blind	University
0.6–0.9 mg/kg/h	No infusion	N/A	N/A	Salbutamol (neb), hydrocortisone (IV), oral prednisolone, oxygen	Mixed	Malaysia	Not blind	University
To achieve 10–20 μg/mL	Placebo	N/A	N/A	Albuterol (neb), methylprednisone (IV), oxygen	Mixed	USA	Double blind	Hospital
1 mg/kg	Placebo	N/A	N/A	Albuterol (neb), methylprednisone (IV), oxygen	Mixed	USA	Double blind	University/ hospital
None	Placebo	N/A	N/A	Prednisolone or prednisone 1 mg/kg, albuterol 150 μg/kg	Mixed	Brazil	Double blind	University/ hospital
To achieve 12–20 mg/L	Placebo	N/A	N/A	Methylprednisolone (IV), albuterol (neb)	Mixed	USA	Double blind	University/ hospital
0.6 mg/kg/h	Salbutamol IV	4 μg/kg	0.6 μg/kg/h	Hydrocortisone (IV)	Mixed	UK	Double blind	Hospital
None	Adrenaline	0.01 mg/kg	None	None	Mixed	Sudan	Unclear	University/ hospital
None	Salbutamol	0.15 mg/kg	None	None	Mixed	Sudan	Unclear	University/ hospital
0.8–1.0 mg/kg/h	Placebo	N/A	N/A	Methylprednisolone (IV), albuterol (neb)	Mixed	USA	Double blind	University/ hospital
1 mg/kg/h	Placebo	N/A	N/A	Methylprednisolone (IV), salbutamol	Mixed	Turkey	Double blind	University/ hospital

(*Continued*)

Table 1 (*Continued*)

Study ID	Intervention (N)	Control (N)	Study type	Study length	Population	Age range, years	Average age, years	Inclusion (severity)	Intervention	Bolus dose
Pierson et al (1971)[45]	11	12	P	24 hours	Children	5–17	12	Failed epinephrine	A	7 mg/kg
Ream et al (2001)[46]	23	24	P	48 hours	Children	No data	9	Severe asthma, failed repeated albuterol nebulizations	A	To achieve 12–17 μg·mL
Roberts et al (2003)[47]	26	18	P	120 minutes	Children	1.19–15.55 (IQR)	4	Failed salbutamol and ipratropium	A	5 mg/kg
Singhi et al (2014/1)[48]	33	34	P	60 minutes	Children	1–12	5	Failed salbutamol, budesonide, ipratropium bromide, and hydrocortisone	A	5 mg/kg
Singhi et al (2014/2)[48]	33	33	P	60 minutes	Children	1–12	4	Failed salbutamol, budesonide, ipratropium bromide, and hydrocortisone	A	5 mg/kg
Strauss et al (1994)[49]	14	17	P	48 hours	Children	5–18	11	Failed albuterol	A	7 mg/kg
Tiwari et al (2016)[50]	24	24	P	24 hours	Children	1–12	4	Moderate to severe asthma	A	5 mg/kg
Vieira et al (2000)[51]	24	19	P	24 hours	Children	1–7	6	Wood–Downes score 3–6 after three fenoterol nebulizations	A	6 mg/kg
Wheeler et al (2005)[52]	13	16	P	24 hours	Children	3–15	9	Severe asthma, CAS ≥7	T	6.4 mg/kg
Yung and South (1998)[53]	81	82	P	24 hours	Children	1–19	6	Failed salbutamol	A	10 mg/kg
Whig et al (2001)[54]	20	20	P	13 hours	Both	2–25	No data	Failed one dose of salbutamol plus hydrocortisone 4 mg/kg	A	6 mg/kg
Williams et al (1975)[55]	9	11	P	60 minutes	Unclear	No data	No data	Severe asthma	A	None

Abbreviations: A, theophylline with ethylene diamine (aminophylline); T, theophylline; P, parallel; sc, subcutaneous; N/A, not applicable; IV, intravenous; neb, nebulization; IQR, interquartile range; CAS, Clinical Asthma Score.

(−3.59 bpm), but failed to reach statistical significance (p=0.32). In order to determine if theophylline was superior to other active therapies, we undertook a subgroup meta-analysis by control type (Figure 5B). In the active control studies, theophylline lowered the heart rate by 5.17 bpm more than active controls, and this difference was significant (p=0.01). In the placebo-controlled trials, no significant difference was noted (p=0.79).

Ongoing dose	Control	Bolus dose	Ongoing dose	Background medication	Gender	Country	Blinding	Funding
9 mg/kg/24 h	Placebo	N/A	N/A	Epinephrine, hydrocortisone, oxygen, phenylephrine, isoproterenol	Mixed	USA	Double blind	Hospital
0.5–0.8 mg/kg/h	No infusion	N/A	N/A	Albuterol (neb), methylprednisone (IV), ipratropium	Mixed	USA	Partly blind	Hospital
0.9 mg/kg/h	Salbutamol IV	15 µg/kg	None	Salbutamol (neb), ipratropium (neb)	Mixed	UK	Double blind	Hospital
0.9 mg/kg/h	Magnesium sulfate	25 mg/kg	None	Salbutamol (neb), ipratropium (neb), budesonide, hydrocortisone	Mixed	India	Partly blind	University/ hospital
0.9 mg/kg/h	Terbutaline	10 µg/kg	0.1 µg/kg/min	Salbutamol (neb), ipratropium (neb), budesonide, hydrocortisone	Mixed	India	Partly blind	University/ hospital
25 mg/kg/h	Placebo	N/A	N/A	Albuterol (neb), methylprednisone (IV, oxygen)	Mixed	USA	Double blind	Hospital
0.9 mg/kg/h	Ketamine	0.5 mg/kg	0.6 mg/kg/h	Salbutamol (neb), ipratropium (neb), hydrocortisone	Mixed	India	Partly blind	Hospital
1.2 mg/kg/h	Placebo	N/A	N/A	Hydrocortisone (IV), fenoterol (neb)	Mixed	Brazil	Double blind	University/ hospital
0.6–1.0 mg/kg/h	Terbutaline	20 µg/kg	0.4 µg/kg/h	Methylprednisolone (IV), albuterol (neb)	Mixed	USA	Double blind	University/ hospital
0.7–1.1 mg/kg/h	Placebo	N/A	N/A	Methylprednisolone (IV), salbutamol (neb), ipratropium bromide (neb)	Mixed	Australia	Double blind	Hospital
0.5 mg/kg/h	Placebo	N/A	N/A	Hydrocortisone (IV), Salbutamol (neb)	Mixed	India	Unclear	University/ hospital
0.5 g over 1 h	Salbutamol IV	None	500 µg over 1 h	Hydrocortisone (IV), oxygen	Not stated	UK	Double blind	Hospital

Respiratory rate

An increased respiratory rate is, like heart rate, a sign of an ongoing asthma exacerbation.[56] Thus, a reduction in the respiratory rate should indicate an improvement in the status of a patient with acute asthma. We undertook a meta-analysis of the seven study arms measuring this outcome (Figure 6). Theophylline was slightly less effective at lower respiratory rate, although this was not significant (p=0.08).

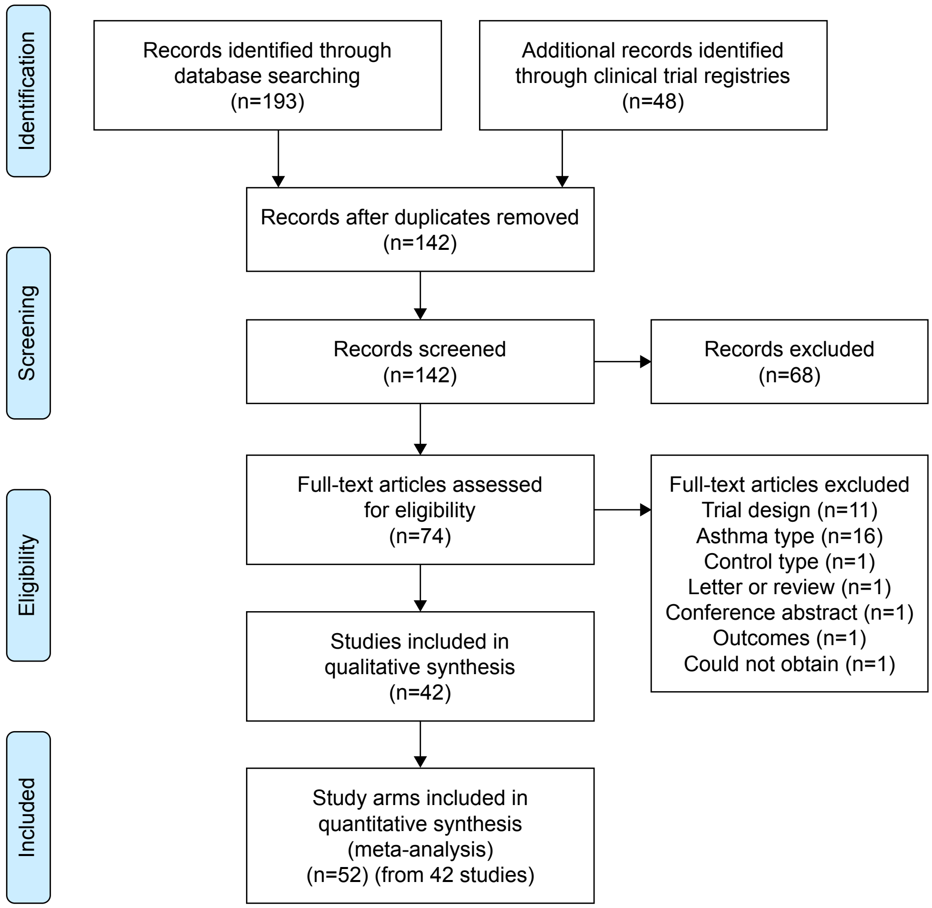


Figure 1 PRISMA flow diagram.

Notes: A total of 193 records were identified through database searching and other sources. After removal of duplicates, 142 records remained. Exclusion of 68 records at the title/abstract level resulted in 74 articles to be examined as full text. Of these, 32 full-text articles were excluded. Fifty-two study arms from 42 studies were included in the final analysis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Other outcomes

Other outcomes extracted were symptom scores, admission rate, duration of stay, use of rescue medication, and oxygen saturation (Figure 7). In almost every case, there were no significant differences between theophylline and control. The exception was the duration of hospital stay (Figure 7C), with theophylline reducing the duration of stay by 0.23 hours (14 minutes) (95% CI: –0.37, –0.08 hours, p=0.002).

Subgroup analysis: background medication

Theophylline was neither more nor less effective than control treatments for almost all outcomes. This was true whether the control was an active comparator like salbutamol, or a placebo. We questioned whether the regimen of medications given to patients before or during the studies (“background medication”) was responsible for the perceived lack of additional efficacy of theophylline over placebo.

In order to investigate this question, we undertook a subgroup analysis of FEV1 by background medication (Figure 8). In studies where the background medication was oxygen only or no additional medication other than the study drug, the control drugs performed better than theophylline (p<0.00001). Conversely, where patients were given bronchodilators with or without steroids, there was no significant differences between theophylline and control. Removal of the two studies comparing theophylline with placebo did not change the outcome.

Subgroup analysis: age of participants

As mentioned earlier, approximately two-thirds of the studies were conducted in adults, with one-third in children. In order to determine whether children responded differently to theophylline compared with adults, we intended to undertake a subgroup meta-analysis of FEV1 and PEFR by the age of participants. Unfortunately, these outcomes were rarely reported in children, as younger people can have great difficulty performing the necessary tests. Instead, we did a subgroup meta-analysis of symptom scores by age (Figure 9).

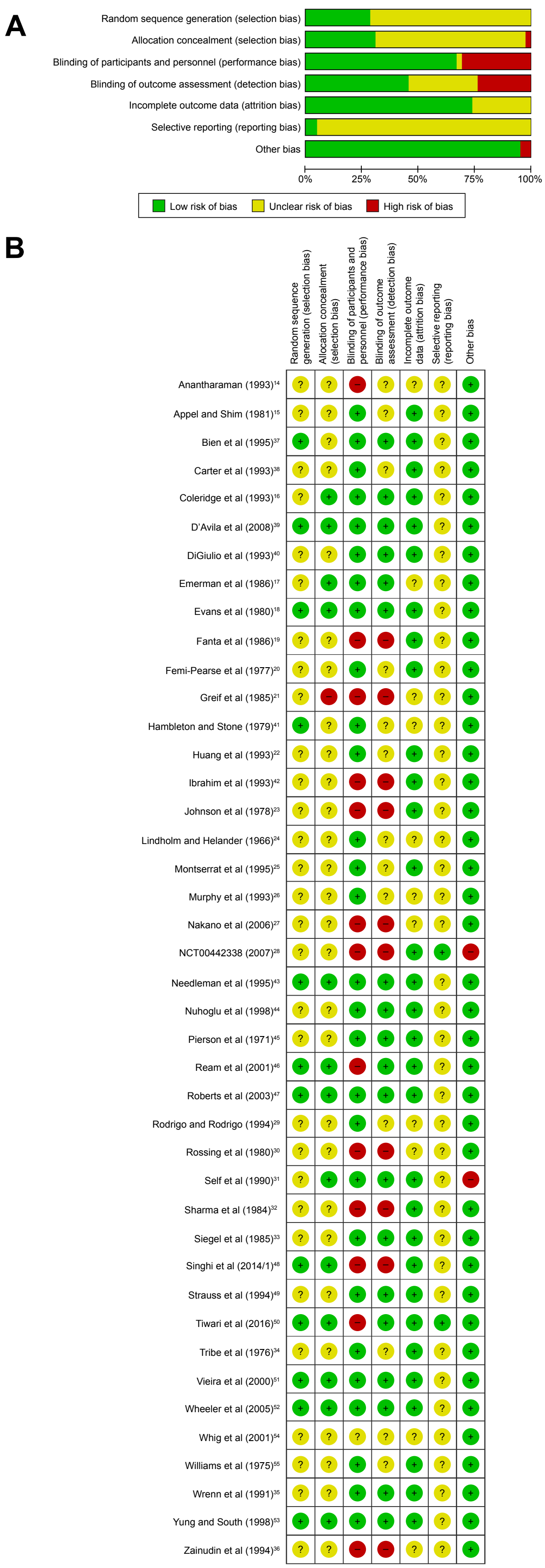


Figure 2 Assessment of study quality.
Notes: (**A**) Risk of bias graph. (**B**) Risk of bias summary. Each included study was assessed for selection bias, performance bias, detection bias, reporting bias, and other bias. Green: low risk of bias; Yellow: unclear risk of bias; Red: high risk of bias.

We found that there was no significant difference between adults and children in terms of symptoms (p=0.38).

Subgroup analysis: blinded vs unblinded studies

In order to determine if blinding had any effect on the primary outcome (FEV1), we conducted a subgroup analysis of blinded vs unblinded studies. Studies that did not mention blinding were regarded as "unblinded". We found a slightly decreased efficacy for theophylline compared with controls in unblinded studies (Figure 10), although the difference between blinded and unblinded studies was not significant (p=0.18). Removal of placebo-controlled trials from the analysis did not change the results (data not shown).

Adverse events

Fortunately, many studies reported on adverse events (Figure 11). Compared with placebo, IV theophylline caused more nausea, vomiting, and cardiovascular adverse events (such as palpitations and arrhythmias) (Figure 11A). There were no differences in abdominal pain, psychological side effects, headaches, seizures, or tremor. Compared with active comparators (Figure 11B), theophylline again caused more nausea and vomiting, but was not different from the active controls in terms of the frequency of psychological side effects, headaches, cardiovascular adverse events, tremor, CPK/CK elevation, or glucosuria/hyperglycemia.

Publication bias

In order to test for publication bias, we created funnel plots (Figure 12). The funnel plot for FEV1 (Figure 12A) did not show significant asymmetry. This was true also for PEFR (Figure 12B), symptom scores (Figure 12C), or heart rate (Figure 12D).

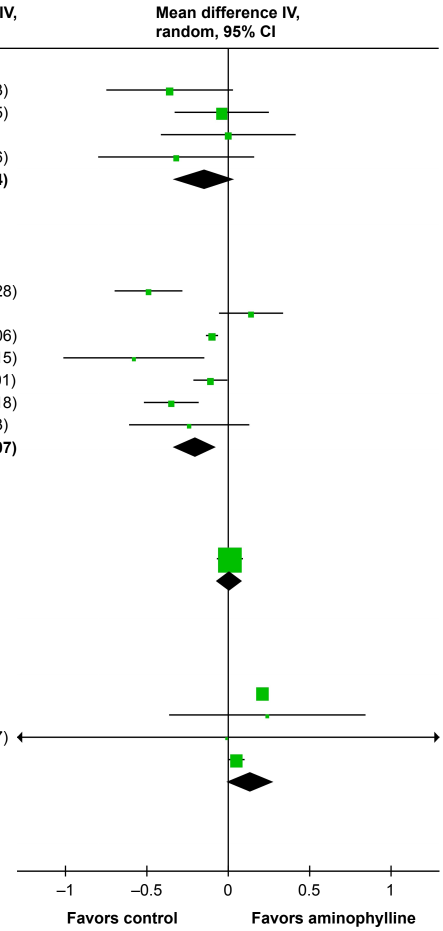
Discussion

Our study has comprehensively reviewed the combined evidence for the efficacy and safety of IV theophylline in acute asthma. We found that theophylline somewhat reduced the heart rate and duration of stay, and was not significantly worse than adrenaline, beta-2 agonists, and leukotriene receptor antagonists. Furthermore, apart from an increase in nausea and vomiting, side effects from theophylline were not significantly different from other treatment regimes. That is, although theophylline was not clinically superior to other treatments, it was not significantly worse either.

However, of great importance was our subgroup analysis of FEV1 by the background medication given to patients (Figure 8). Where the patients were given no medication,

A

Study or subgroup	Aminophylline Mean	Aminophylline SD	Aminophylline Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
Adrenaline								
Appel and Shim (1981)[15]	0.9	0.45	12	1.26	0.52	12	23.0	–0.36 (–0.75, 0.03)
Fanta et al (1986/1)[19]	1.22	0.5	17	1.26	0.52	38	41.5	–0.04 (–0.33, 0.25)
Lindholm and Helander (1966/1)[24]	1.76	0.69	29	1.76	0.77	21	20.3	0.00 (–0.41, 0.41)
Rossing et al (1980/1)[30]	1.53	0.58	17	1.85	0.8	16	15.2	–0.32 (–0.80, 0.16)
Subtotal (95% CI)			**75**			**87**	**100**	**–0.15 (–0.33, 0.04)**
Heterogeneity: τ^2=0.00; χ^2=2.66, *df*=3 (*p*=0.45); I^2=0%								
Test for overall effect: *Z*=1.55 (*p*=0.12)								
Beta-2 agonists								
Fanta et al (1986/2)[19]	0.23	0.29	17	0.72	0.51	41	14.1	–0.49 (–0.70, –0.28)
Johnson et al (1978)[23]	0.93	0.35	19	0.79	0.27	20	14.7	0.14 (–0.06, 0.34)
Lindholm and Helander (1966/2)[24]	0.25	0.05	29	0.35	0.08	23	21.4	–0.10 (–0.14, –0.06)
Rossing et al (1980/2)[30]	1.53	0.58	17	2.11	0.66	15	6.5	–0.58 (–1.01, –0.15)
Sharma et al (1984/1)[32]	0.17	0.09	5	0.28	0.11	10	19.2	–0.11 (–0.21, –0.01)
Sharma et al (1984/2)[32]	0.17	0.09	5	0.52	0.24	10	16.1	–0.35 (–0.52, –0.18)
Tribe et al (1976)[34]	0.8	0.31	12	1.04	0.55	11	8.0	–0.24 (–0.61, 0.13)
Subtotal (95% CI)			**104**			**130**	**100**	**–0.20 (–0.34, –0.07)**
Heterogeneity: τ^2=0.02; χ^2=31.85, *df*=6 (*p*<0.0001); I^2=81%								
Test for overall effect: *Z*=3.04 (*p*=0.002)								
Leukotriene receptor antagonists								
NCT00442338 (2007)[28]	0.06	0.16	31	0.05	0.16	30	100	0.01 (–0.07, 0.09)
Subtotal (95% CI)			**31**			**30**	**100**	**0.01 (–0.07, 0.09)**
Heterogeneity: not applicable								
Test for overall effect: *Z*=0.24 (*p*=0.81)								
Placebo								
Lindholm and Helander (1966/3)[24]	0.25	0.05	29	0.04	0.04	19	47.9	0.21 (0.18, 0.24)
Montserrat et al (1995)[25]	1.43	0.7	6	1.19	0.28	6	5.3	0.24 (–0.36, 0.84)
Siegel et al (1985)[33]	0.28	0.45	20	0.29	3.58	20	0.8	–0.01 (–1.59, 1.57)
Wrenn et al (1991)[35]	1.48	0.1	32	1.43	0.11	35	46.0	0.05 (–0.00, 0.10)
Subtotal (95% CI)			**87**			**80**	**100**	**0.14 (–0.01, 0.28)**
Heterogeneity: τ^2=0.01; χ^2=30.99, *df*=3 (*p*<0.00001); I^2=90%								
Test for overall effect: *Z*=1.82 (*p*=0.07)								
Test for subgroup differences: χ^2=14.17, *df*=3 (*p*=0.003); I^2=78.8%								



B

Study or subgroup	Aminophylline Mean	Aminophylline SD	Aminophylline Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
Active control								
Appel and Shim (1981)[15]	0.9	0.45	12	1.26	0.52	12	4.4	–0.36 (–0.75, 0.03)
Fanta et al (1986/1)[19]	1.22	0.5	9	1.26	0.52	38	4.8	–0.04 (–0.41, 0.33)
Fanta et al (1986/2)[19]	0.23	0.29	9	0.72	0.51	41	8.1	–0.49 (–0.74, –0.24)
Johnson et al (1978)[23]	0.93	0.35	19	0.79	0.27	20	10.1	0.14 (–0.06, 0.34)
Lindholm and Helander (1966/1)[24]	1.76	0.69	15	1.76	0.77	12	2.5	0.00 (–0.56, 0.56)
Lindholm and Helander (1966/2)[24]	0.25	0.05	15	0.35	0.08	23	17.3	–0.10 (–0.14, –0.06)
NCT00442338 (2007)[28]	0.06	0.16	31	0.05	0.16	30	15.8	0.01 (–0.07, 0.09)
Rossing et al (1980/1)[30]	1.53	0.58	9	1.85	0.8	38	3.4	–0.32 (–0.78, 0.14)
Rossing et al (1980/2)[30]	1.53	0.58	9	2.11	0.66	15	2.9	–0.58 (–1.09, –0.07)
Sharma et al (1984/1)[32]	0.17	0.09	5	0.28	0.11	10	14.7	–0.11 (–0.21, –0.01)
Sharma et al (1984/2)[32]	0.17	0.09	5	0.52	0.24	10	11.4	–0.35 (–0.52, –0.18)
Tribe et al (1976)[34]	0.8	0.34	12	1.04	0.56	11	4.5	–0.24 (–0.62, 0.14)
Subtotal (95% CI)			**150**			**260**	**100**	**–0.15 (–0.25, –0.06)**
Heterogeneity: τ^2=0.01; χ^2=37.91, *df*=11 (*p*<0.0001); I^2=71%								
Test for overall effect: *Z*=3.20 (*p*=0.001)								
Placebo/no drug								
Lindholm and Helander (1966/3)[24]	0.25	0.05	29	0.04	0.04	19	47.9	0.21 (0.18, 0.24)
Montserrat et al (1995)[25]	1.43	0.7	6	1.19	0.28	6	5.3	0.24 (–0.36, 0.84)
Siegel et al (1985)[33]	0.28	0.45	20	0.29	3.58	20	0.8	–0.01 (–1.59, 1.57)
Wrenn et al (1991)[35]	1.48	0.1	32	1.43	0.11	35	46.0	0.05 (–0.00, 0.10)
Subtotal (95% CI)			**87**			**80**	**100**	**0.14 (–0.01, 0.28)**
Heterogeneity: τ^2=0.01; χ^2=30.99, *df*=3 (*p*<0.00001); I^2=90%								
Test for overall effect: *Z*=1.82 (*p*=0.07)								
Test for subgroup differences: χ^2=10.65, *df*=1 (*p*=0.001); I^2=90.6%								

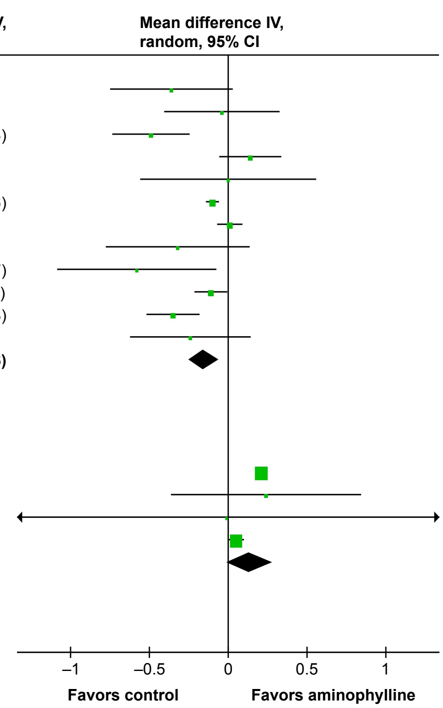


Figure 3 (*Continued*)

C

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
FVC change								
Johnson et al (1978)[23]	1.88	0.61	19	1.85	0.89	20	9.6	0.03 (–0.45, 0.51)
Lindholm and Helander (1966/1)[24]	0.24	0.05	10	0.32	0.02	21	21.9	–0.08 (–0.11, –0.05)
Lindholm and Helander (1966/2)[24]	0.24	0.05	10	0.35	0.08	23	21.7	–0.11 (–0.16, –0.06)
Lindholm and Helander (1966/3)[24]	0.24	0.05	10	–0.1	0.06	19	21.8	0.34 (0.30, 0.38)
Montserrat et al (1995)[25]	2.12	0.95	6	2.32	0.77	6	3.4	–0.20 (–1.18, 0.78)
Wrenn et al (1991)[35]	2.3	0.12	32	2.27	0.12	35	21.6	0.03 (–0.03, 0.09)
Subtotal (95% CI)			**87**			**124**	**100**	**0.04 (–0.16, 0.23)**

Heterogeneity: τ^2=0.05; χ^2=300.86, *df*=5 (*p*<0.00001); I^2=98%
Test for overall effect: *Z*=0.35 (*p*=0.73)
Test for subgroup differences: not applicable

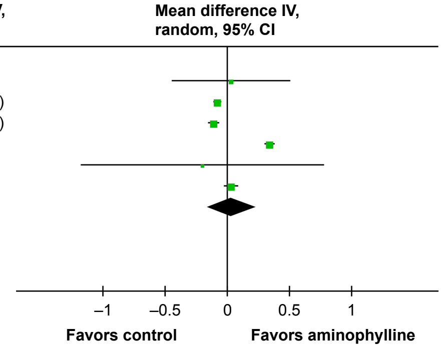


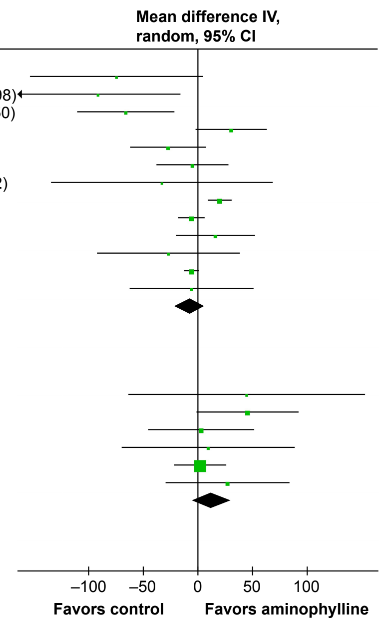
Figure 3 Meta-analysis of FEV1 (**A**, **B**) or FVC (**C**).

Notes: (**A**) Subgroup meta-analysis of FEV1 (in liters [L]) following intravenous theophylline by control type. Controls included adrenaline, beta-2 agonists, leukotriene receptor antagonists, and placebo/no drug. (**B**) Subgroup meta-analysis of FEV1 (L) following intravenous theophylline by control type (pooled active control vs placebo/no drug). (**C**) Meta-analysis of FVC following intravenous theophylline, as measured in L. Data are given as the mean difference (95% CI).

A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Short-term (30 minutes–2 hours)								
Anantharaman (1993/1)[14]	219.2	100.6	14	293.7	156.7	27	2.5	–74.50 (–153.69, 4.69)
Anantharaman (1993/2)[14]	219.2	100.6	14	310.6	113.5	17	2.7	–91.40 (–166.82, –15.98)
Emerman et al (1986)[17]	234	71.9	20	300	71.7	20	6.0	–66.00 (–110.50, –21.50)
Evans et al (1980)[18]	32.76	35.3	6	2.32	22	7	8.6	30.44 (–2.17, 63.05)
Femi-Pearse et al (1977/1)[20]	21.2	20.9	8	48.5	50.9	10	8.0	–27.30 (–62.01, 7.41)
Femi-Pearse et al (1977/2)[20]	29.1	49.6	15	34.1	44.9	17	8.5	–5.00 (–37.95, 27.95)
Greif et al (1985)[21]	257.7	119.1	10	290.7	117.7	11	1.6	–33.00 (–134.42, 68.42)
Ibrahim et al (1993/1)[42]	115	19.1	20	95	22.4	40	15.4	20.00 (9.13, 30.87)
Ibrahim et al (1993/2)[42]	115	19.1	20	121	28.5	40	15.0	–6.00 (–18.17, 6.17)
Johnson et al (1978)[23]	152.75	66.4	19	136.67	46.7	20	7.7	16.08 (–20.12, 52.28)
Williams et al (1975)[55]	134	64	9	161	85	11	3.4	–27.00 (–92.36, 38.36)
Wrenn et al (1991)[35]	193.43	12.8	32	199.18	15.6	35	16.4	–5.75 (–12.56, 1.06)
Zainudin et al (1994)[36]	118.57	71.9	11	124.35	71.7	14	4.3	–5.78 (–62.49, 50.93)
Subtotal (95% CI)			**198**			**269**	**100**	**–7.52 (–21.03, 6.00)**
Heterogeneity: τ^2=278.07; χ^2=41.56, *df*=12 (*p*<0.0001); I^2=71%								
Test for overall effect: *Z*=1.09 (*p*=0.28)								
Long-term (5 hours–24 hours)								
Evans et al (1980)[18]	144.32	133.3	6	99.66	25.2	7	2.7	44.66 (–63.62, 152.94)
Johnson et al (1978)[23]	228.91	66.4	19	183.5	82	20	14.4	45.41 (–1.31, 92.13)
Murphy et al (1993)[26]	358	78	22	355	86	22	13.3	3.00 (–45.52, 51.52)
Nakano et al (2006)[27]	259.4	84.1	10	250	86	8	5.0	9.40 (–69.77, 88.57)
Whig et al (2001)[54]	217.5	46.8	20	215.5	28	20	54.9	2.00 (–21.90, 25.90)
Zainudin et al (1994)[36]	228.62	71.9	11	201.51	71.7	14	9.8	27.11 (–29.60, 83.82)
Subtotal (95% CI)			**88**			**91**	**100**	**12.33 (–5.38, 30.04)**

Heterogeneity: τ^2=0.00; χ^2=3.39, *df*=5 (*p*=0.64); I^2=0%
Test for overall effect: *Z*=1.36 (*p*=0.17)
Test for subgroup difference: χ^2=3.05, *df*=1 (*p*=0.08); I^2=67.2%



B

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Short-term (30 minutes–2 hours)								
Appel and Shim (1981)[15]	42.3	15.6	12	52.3	16.8	12	13.4	–10.00 (–22.97, 2.97)
Coleridge et al (1993)[16]	59.92	23.28	16	57.01	15.41	15	12.8	2.91 (–10.91, 16.73)
Emerman et al (1986)[17]	58	17.99	20	70	18.86	20	14.6	–12.00 (–23.42, –0.58)
Ibrahim et al (1993/1)[42]	61.3	4.4	20	51.7	3.6	40	20.7	9.60 (7.37, 11.83)
Ibrahim et al (1993/2)[42]	61.3	4.4	20	64.8	3.6	40	20.7	–3.50 (–5.73, –1.27)
Rodrigo and Rodrigo (1994)[29]	51.3	16.7	45	56.4	18.6	49	17.9	–5.10 (–12.24, 2.04)
Subtotal (95% CI)			**133**			**176**	**100**	**–2.37 (–10.26, 5.51)**
Heterogeneity: τ^2=77.06; χ^2=80.89, *df*=5 (*p*<0.00001); I^2=94%								
Test for overall effect: *Z*=0.59 (*p*=0.56)								
Long-term (5 hours–48 hours)								
Coleridge et al (1993)[16]	85.67	13.48	16	98.85	37.41	15	12.0	–13.18 (–33.23, 6.87)
Murphy et al (1993)[26]	61	15	22	59	13	22	31.9	2.00 (–6.29, 10.29)
Strauss et al (1994)[49]	80	22	14	79	22	17	17.2	1.00 (–14.56, 16.56)
Yung and South (1998)[53]	22.4	17.99	81	12.2	18.86	82	38.9	10.20 (4.54, 15.86)
Subtotal (95% CI)			**133**			**136**	**100**	**3.19 (–4.84, 11.23)**

Heterogeneity: τ^2=34.84; χ^2=6.92, *df*=3 (*p*=0.07); I^2=57%
Test for overall effect: *Z*=0.78 (*p*=0.44)
Test for subgroup differences: χ^2=0.94, *df*=1 (*p*=0.33); I^2=0%

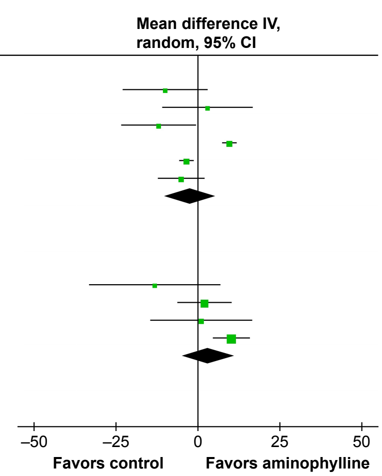


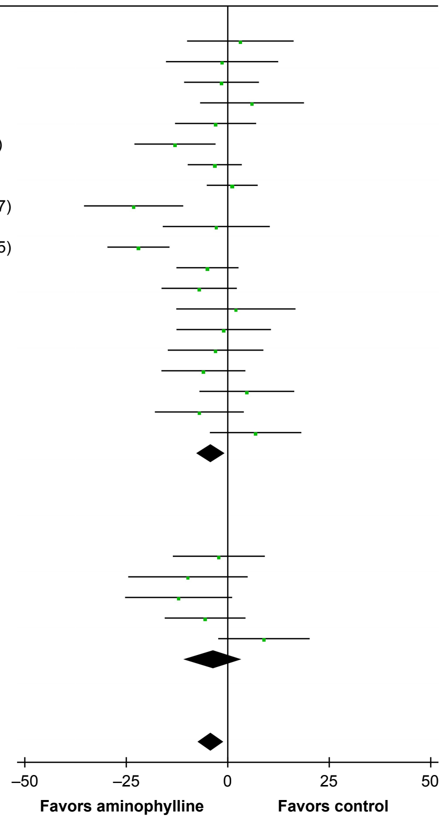
Figure 4 Subgroup meta-analysis of PEFR following intravenous theophylline by time post-infusion, as measured in liters (**A**) or as percent of predicted value (**B**).

Notes: Short-term follow-up was defined as 30 minutes–2 hours post-infusion. Long-term follow-up was defined as 5 hours–36 hours post-infusion. Data are given as the mean difference (95% CI).

Abbreviation: PEFR, peak expiratory flow rate.

A

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Short-term (30 minutes–3 hours)								
Anantharaman (1993/1)[14]	98.4	20.8	14	95.3	19.4	27	3.3	3.10 (–10.02, 16.22)
Anantharaman (1993/2)[14]	98.4	20.8	14	99.8	17.9	17	3.1	–1.40 (–15.22, 12.42)
D'Avila et al (2008)[39]	141.03	17.46	30	142.57	18.95	30	4.6	–1.54 (–10.76, 7.68)
Evans et al (1980)[18]	126.79	12.54	6	120.81	10.72	7	3.4	5.98 (–6.82, 18.78)
Fanta et al (1986/1)[19]	–7	12.37	9	–4	18.49	38	4.3	–3.00 (–12.99, 6.99)
Fanta et al (1986/2)[19]	–7	12.37	9	6	19.21	41	4.3	–13.00 (–22.99, –3.01)
Femi-Pearse et al (1977/1)[20]	–4.2	6.51	8	–1	7.91	10	5.6	–3.20 (–9.86, 3.46)
Femi-Pearse et al (1977/2)[20]	–3.6	9.68	15	–4.7	8.25	17	5.8	1.10 (–5.18, 7.38)
Greif et al (1985)[21]	92.53	14.19	10	115.72	14.36	11	3.5	–23.19 (–35.41, –10.97)
Hambleton and Stone (1979)[41]	135.36	14.19	9	138.19	14.36	9	3.3	–2.83 (–16.02, 10.36)
Ibrahim et al (1993/1)[42]	120	14.19	20	142	14.36	40	5.2	–22.00 (–29.65, –14.35)
Ibrahim et al (1993/2)[42]	120	14.19	20	125	14.36	40	5.2	–5.00 (–12.65, 2.65)
Johnson et al (1978)[23]	107.81	14.21	19	114.85	15.34	20	4.6	–7.04 (–16.31, 2.23)
Montserrat et al (1995)[25]	91	16	6	89	9	6	2.9	2.00 (–12.69, 16.69)
Rossing et al (1980/1)[30]	–7	14.19	9	–6	14.36	16	3.7	–1.00 (–12.64, 10.64)
Rossing et al (1980/2)[30]	–7	14.19	9	–4	14.36	15	3.7	–3.00 (–14.78, 8.78)
Siegel et al (1985)[33]	112	19	20	118	14	20	4.2	–6.00 (–16.34, 4.34)
Tribe et al (1976)[34]	104.9	14.19	12	100.2	14.36	11	3.7	4.70 (–6.98, 16.38)
Williams et al (1975)[55]	119	11	9	126	14	11	3.9	–7.00 (–17.96, 3.96)
Zainudin et al (1994)[36]	105.91	14.19	11	99.05	14.36	14	3.8	6.86 (–4.40, 18.12)
Subtotal (95% CI)			**259**			**400**	**81.9**	**–4.17 (–7.77, –0.56)**
Heterogeneity: τ^2=38.59; χ^2=47.72, *df*=19 (*p*=0.0003); I^2=60%								
Test for overall effect: *Z*=2.27 (*p*=0.02)								
Long-term (24 hours–36 hours)								
DiGiulio et al (1993)[40]	112.6	17.9	16	114.8	13.2	13	3.8	–2.20 (–13.53, 9.13)
Evans et al (1980)[18]	107.15	12.54	6	116.96	14.53	7	2.9	–9.81 (–24.53, 4.91)
Hambleton and Stone (1979)[41]	112.38	14.19	9	124.49	14.36	9	3.3	–12.11 (–25.30, 1.08)
Johnson et al (1978)[23]	106.95	13.47	19	112.53	18.02	20	4.3	–5.58 (–15.53, 4.37)
Zainudin et al (1994)[36]	92.8	14.19	11	83.89	14.36	14	3.8	8.91 (–2.35, 20.17)
Subtotal (95% CI)			**61**			**63**	**18.1**	**–3.59 (–10.75, 3.56)**
Heterogeneity: τ^2=29.48; χ^2=7.22, *df*=4 (*p*=0.12); I^2=45%								
Test for overall effect: *Z*=0.98 (*p*=0.32)								
Total (95% CI)			**320**			**463**	**100**	**–4.08 (–7.26, –0.91)**
Heterogeneity: τ^2=35.11; χ^2=55.12, *df*=24 (*p*=0.0003); I^2=56%								
Test for overall effect: *Z*=2.52 (*p*=0.01)								
Test for subgroup differences: χ^2=0.02, *df*=1 (*p*=0.89); I^2=0%								



B

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Active control								
Anantharaman (1993/1)[14]	98.4	20.8	14	95.3	19.4	27	3.8	3.10 (–10.02, 16.22)
Anantharaman (1993/2)[14]	98.4	20.8	14	99.8	17.9	17	3.6	–1.40 (–15.22, 12.42)
Evans et al (1980)[18]	126.79	12.54	6	120.81	10.72	7	3.9	5.98 (–6.82, 18.78)
Fanta et al (1986/1)[19]	–7	12.37	17	–4	18.49	38	5.6	–3.00 (–11.31, 5.31)
Fanta et al (1986/2)[19]	–7	12.37	17	6	19.21	41	5.6	–13.00 (–21.32, –4.68)
Femi-Pearse et al (1977/1)[20]	–4.2	6.51	8	–1	7.91	10	6.4	–3.20 (–9.86, 3.46)
Femi-Pearse et al (1977/2)[20]	–3.6	9.68	15	–4.7	8.25	17	6.6	1.10 (–5.18, 7.38)
Greif et al (1985)[21]	92.53	14.19	10	115.72	14.36	11	4.1	–23.19 (–35.41, –10.97)
Hambleton and Stone (1979)[41]	135.36	14.19	9	138.19	14.36	9	3.8	–2.83 (–16.02, 10.36)
Ibrahim et al (1993/1)[42]	120	14.19	20	142	14.19	40	6.0	–22.00 (–29.62, –14.38)
Ibrahim et al (1993/2)[42]	120	14.19	20	125	14.19	40	6.0	–5.00 (–12.62, 2.62)
Johnson et al (1978)[23]	107.81	14.21	19	114.85	15.34	20	5.2	–7.04 (–16.31, 2.23)
Rossing et al (1980/1)[30]	–7	14.19	9	–6	14.36	16	4.3	–1.00 (–12.64, 10.64)
Rossing et al (1980/2)[30]	–7	14.19	9	–4	14.36	15	4.2	–3.00 (–14.78, 8.78)
Tribe et al (1976)[34]	104.9	14.19	12	100.2	14.36	11	4.3	4.70 (–6.98, 16.38)
Williams et al (1975)[55]	119	11	9	126	14	11	4.5	–7.00 (–17.96, 3.96)
Subtotal (95% CI)			**208**			**330**	**77.8**	**–5.17 (–9.30, –1.04)**
Heterogeneity: τ^2=43.95; χ^2=43.36, *df*=15 (*p*=0.0001); I^2=65%								
Test for overall effect: *Z*=2.45 (*p*=0.01)								
Placebo/no drug control								
D'Avila et al (2008)[39]	141.03	17.46	30	142.57	18.95	30	5.2	–1.54 (–10.76, 7.68)
DiGiulio et al (1993)[40]	112.6	17.9	16	114.8	13.2	13	4.4	–2.20 (–13.53, 9.13)
Montserrat et al (1995)[25]	91	16	6	89	9	6	3.3	2.00 (–12.69, 16.69)
Siegel et al (1985)[33]	112	19	20	118	14	20	4.8	–6.00 (–16.34, 4.34)
Zainudin et al (1994)[36]	105.91	14.19	11	99.05	14.36	14	4.4	6.86 (–4.40, 18.12)
Subtotal (95% CI)			**83**			**83**	**22.2**	**–0.68 (–5.59, 4.24)**
Heterogeneity: τ^2=0.00; χ^2=2.97, *df*=4 (*p*=0.56); I^2=0%								
Test for overall effect: *Z*=0.27 (*p*=0.79)								
Total (95% CI)			**291**			**413**	**100**	**–4.15 (–7.58, –0.72)**
Heterogeneity: τ^2=36.25; χ^2=49.31, *df*=20 (*p*=0.0003); I^2=59%								
Test for overall effect: *Z*=2.37 (*p*=0.02)								
Test for subgroup differences: χ^2=1.88, *df*=1 (*p*=0.17); I^2=46.9%								

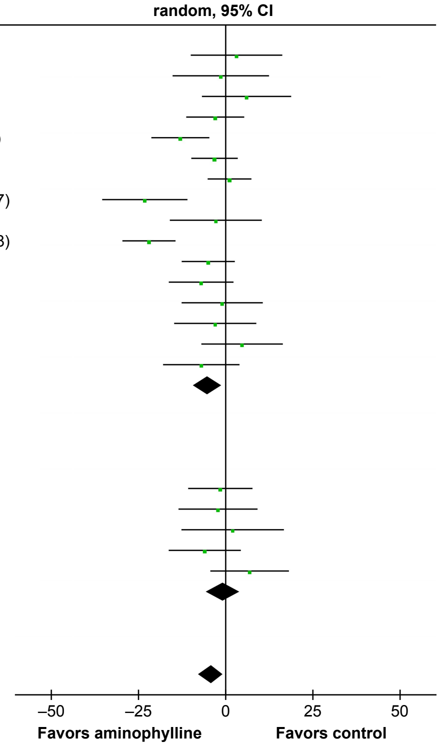


Figure 5 Subgroup meta-analysis of heart rate (beats per minute) following intravenous theophylline by time after infusion (**A**) and by type of control (**B**).

Notes: (**A**) Short-term follow-up was defined as 30 minutes 3 hours post-infusion. Long-term follow-up was defined as 24–36 hours post-infusion. (**B**) Active control was defined as administration of any drug with the aim of reducing the asthma exacerbation. Placebo was defined as a substance given that contains no active ingredient and is designed to maintain blinding of a clinical trial. Data are given as the mean difference (95% CI).

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Anantharaman (1993/1)[14]	23.5	5.4	14	22.9	6.6	27	19.2	0.60 (–3.17, 4.37)
Anantharaman (1993/2)[14]	23.5	5.4	14	18.5	4.1	17	20.8	5.00 (1.56, 8.44)
D'Avila et al (2008)[39]	43.37	8.83	30	41.03	8.51	30	16.4	2.34 (–2.05, 6.73)
Hambleton and Stone (1979)[41]	52.43	8.19	9	47.26	7.54	9	8.4	5.17 (–2.10, 12.44)
Ream et al (2001)[46]	34.75	9.5	20	40.09	15.03	21	7.8	–5.34 (–13.00, 2.32)
Singhi et al (2014/1)[48]	–11	10	17	–16	4	34	14.3	5.00 (0.06, 9.94)
Singhi et al (2014/2)[48]	–11	10	17	–10	7	33	13.1	–1.00 (–6.32, 4.32)
Total (95% CI)			**121**			**171**	**100**	**2.15 (–0.26, 4.55)**

Heterogeneity: τ^2=4.17; χ^2=10.19, *df*=6 (*p*=0.12); I^2=41%
Test for overall effect: *Z*=1.75 (*p*=0.08)

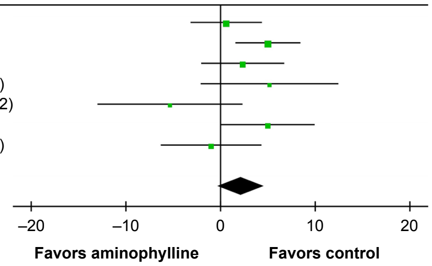
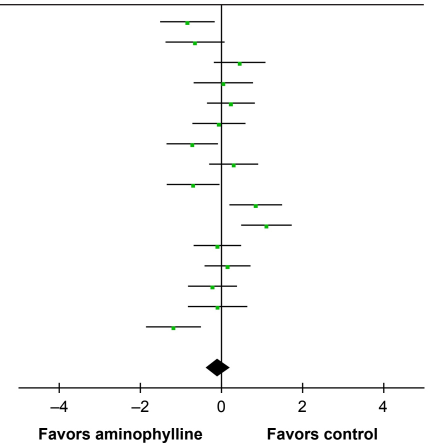


Figure 6 Meta-analysis of respiratory rate (breaths per minutes) following intravenous theophylline infusion.
Note: Data are given as the mean difference (95% CI).

A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Std mean difference IV, random, 95% CI
Anantharaman (1993/1)[14]	–3.7	2.6	14	–1.9	1.8	27	6.1	–0.84 (–1.15, –0.17)
Anantharaman (1993/2)[14]	–3.7	2.6	14	–2.2	1.9	17	5.8	–0.65 (–1.38, 0.08)
Bien et al (1995)[37]	–2.04	1.45	19	–2.59	0.91	20	6.3	0.45 (–0.19, 1.08)
DiGiulio et al (1993)[40]	–3.6	1.9	16	–3.7	2.4	13	5.8	0.05 (–0.69, 0.78)
Needleman et al (1995)[43]	3.05	3.25	25	2.38	2.19	20	6.6	0.23 (–0.36, 0.82)
Nuhoglu et al (1998)[44]	1.94	1.78	17	2.05	1.62	19	6.2	–0.06 (–0.72, 0.59)
Ream et al (2001)[46]	18.6	12.07	20	31.1	20.62	21	6.3	–0.72 (–1.36, –0.09)
Roberts et al (2003)[47]	6.5	1.68	26	6	1.57	18	6.5	0.30 (–0.30, 0.90)
Self et al (1990)[31]	–4.85	0.23	21	–4.63	0.38	18	6.2	–0.70 (–1.35, –0.05)
Siegel et al (1985)[33]	1.84	1.34	20	0.78	1.11	20	6.2	0.84 (0.19, 1.49)
Singhi et al (2014/1)[48]	5.58	3.34	17	3.15	1.23	34	6.4	1.11 (0.48, 1.73)
Singhi et al (2014/2)[48]	5.58	3.34	17	5.96	3.86	33	6.6	–0.10 (–0.69, 0.48)
Tiwari et al (2016)[50]	7.71	1.68	24	7.46	1.62	24	6.7	0.15 (–0.42, 0.72)
Vieira et al (2000)[51]	3.5	0.74	24	3.67	0.77	19	6.5	–0.22 (–0.83, 0.38)
Wheeler et al (2005)[52]	3.9	3.61	13	4.3	4.4	16	5.8	–0.10 (–0.83, 0.64)
Whig et al (2001)[54]	0.07	0.47	20	0.65	0.49	20	6.1	–1.18 (–1.86, –0.51)
Total (95% CI)			**307**			**339**	**100**	**–0.08 (–0.38, 0.22)**

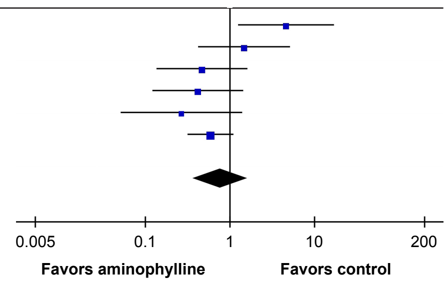
Heterogeneity: τ^2=0.27; χ^2=52.74, *df*=15 (*p*<0.00001); I^2=72%
Test for overall effect: *Z*=0.53 (*p*=0.59)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Anantharaman (1993/1)[14]	12	27	4	27	15.3	4.60 (1.25, 16.97)
Anantharaman (1993/2)[14]	12	27	6	17	16.0	1.47 (0.42, 5.13)
D'Avila et al (2008)[39]	5	30	9	30	16.1	0.47 (0.14, 1.61)
Vieira et al (2000)[51]	10	24	12	19	16.1	0.42 (0.12, 1.43)
Wrenn et al (1991)[35]	2	32	7	35	11.8	0.27 (0.05, 1.39)
Yung and South (1998)[53]	30	81	41	82	24.6	0.59 (0.31, 1.10)
Total (95% CI)		**221**		**210**	**100**	**0.77 (0.37, 1.61)**
Total events	71		79			

Heterogeneity: τ^2=0.46; χ^2=12.02, *df*=5 (*p*=0.03); I^2=58%
Test for overall effect: *Z*=0.69 (*p*=0.49)



C

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Coleridge et al (1993)[16]	4.5	2.19	30	4.5	1.08	29	2.8	0.00 (–0.88, 0.88)
D'Avila et al (2008)[39]	1.46	0.37	30	1.68	0.35	30	64.5	–0.22 (–0.40, –0.04)
Needleman et al (1995)[43]	2.17	1.33	25	2	1.13	20	4.1	0.17 (–0.55, 0.89)
Ream et al (2001)[46]	4.7	1.34	20	5.1	1.83	21	2.2	–0.40 (–1.38, 0.58)
Roberts et al (2003)[47]	2.39	1.81	26	3.56	2.33	18	1.3	–1.17 (–2.45, 0.11)
Self et al (1990)[31]	1.78	0.73	21	1.95	0.81	18	9.0	–0.17 (–0.66, 0.32)
Strauss et al (1994)[49]	2.58	1.5	14	2.33	1.3	17	2.1	0.25 (–0.75, 1.25)
Tiwari et al (2016)[50]	3.25	1.07	24	3.5	1.28	24	4.8	–0.25 (–0.92, 0.42)
Wheeler et al (2005)[52]	4.4	8.29	13	4.9	12	16	0.0	–0.50 (–7.91, 6.91)
Wrenn et al (1991)[35]	8.8	1.38	32	9.69	1.56	35	4.3	–0.89 (–1.59, –0.19)
Yung and South (1998)[53]	2.69	2	81	2.87	2.37	82	4.7	–0.18 (–0.85, 0.49)
Total (95% CI)			**316**			**310**	**100**	**–0.23 (–0.37, –0.08)**

Heterogeneity: τ^2=0.00; χ^2=8.00, *df*=10 (*p*=0.63); I^2=0%
Test for overall effect: *Z*=3.06 (*p*=0.002)

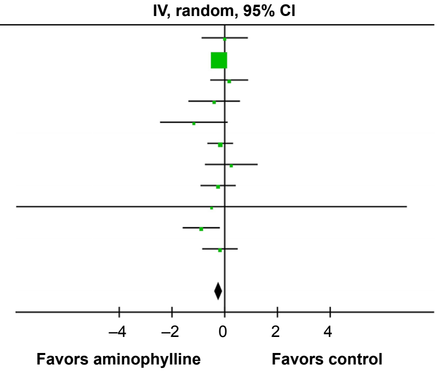
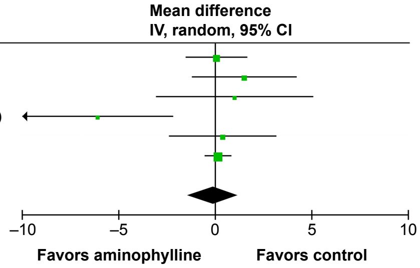


Figure 7 (*Continued*)

D

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Bien et al (1995)[37]	9.44	2.21	19	9.38	2.86	20	23.4	0.06 (–1.54, 1.66)
D'Avila et al (2008)[39]	26	4.92	30	24.5	5.78	30	14.0	1.50 (–1.22, 4.22)
DiGiulio et al (1993)[40]	8.4	6.1	16	7.4	5.1	13	7.9	1.00 (–3.08, 5.08)
Huang et al (1993)[22]	10.3	3.8	10	16.4	5.3	11	8.4	–6.10 (–10.02, –2.18)
Nuhoglu et al (1998)[44]	8.7	4.44	17	8.32	4.04	19	13.5	0.38 (–2.40, 3.16)
Strauss et al (1994)[49]	6.14	1.16	14	6	0.71	17	32.9	0.14 (–0.56, 0.84)
Total (95% CI)			**106**			**110**	**100**	**–0.11 (–1.40, 1.18)**

Heterogeneity: τ^2=1.20; χ^2=10.87, *df*=5 (*p*=0.05); I^2=54%
Test for overall effect: *Z*=0.17 (*p*=0.87)



E

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
D'Avila et al (2008)[39]	95.27	2.32	30	95.47	2.29	30	16.3	–0.20 (–1.37, 0.97)
Nakano et al (2006)[27]	96.6	0.95	10	98.1	0.85	8	18.0	–1.50 (–2.33, –0.67)
Singhi et al (2014/1)[48]	1.5	2.1	17	3.4	1.6	34	16.5	–1.90 (–3.03, –0.77)
Singhi et al (2014/2)[48]	1.5	2.1	17	1.8	1.6	33	16.5	–0.30 (–1.44, 0.84)
Tiwari et al (2016)[50]	4.71	2.35	24	5.42	3.36	24	13.7	–0.71 (–2.35, 0.93)
Yung and South (1998)[53]	94.04	1.96	81	93.01	1.94	82	19.0	1.03 (0.43, 1.63)
Total (95% CI)			**179**			**211**	**100**	**–0.57 (–1.64, 0.51)**

Heterogeneity: τ^2=1.49; χ^2=34.61, *df*=5 (*p*<0.00001); I^2=86%
Test for overall effect: *Z*=1.03 (*p*=0.30)

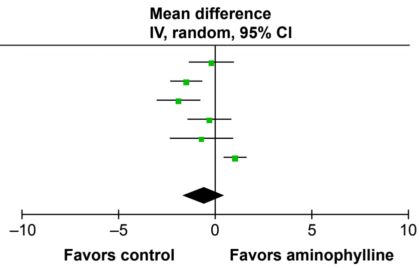


Figure 7 Meta-analysis of symptom scores (**A**), admission rates (**B**), duration of hospital stay (**C**), rescue medication use (**D**), and oxygen saturation (**E**) following intravenous theophylline.
Note: Data are given as standardized mean difference (95% CI) (**A**), odds ratios (95% CI) (**B**), or mean difference (95% CI) (**C**–**E**).

or oxygen alone, theophylline was inferior to subcutaneous epinephrine[15,19,30] and nebulized isoproterenol.[19,30] However, in almost all circumstances, patients admitted to an emergency department for an acute asthma exacerbation are given nebulized beta-2 agonists and IV corticosteroids.[57–59] If these treatments fail, additional treatments are then considered. Our data show that in the context of usual emergency department treatment, IV theophylline is at least as effective as montelukast[28] and IV salbutamol.[23,34]

Existing studies on theophylline point to inconsistencies. For example, Neame et al attempted to determine if salbutamol or theophylline should be used for acute severe

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Bronchodilators only								
NCT00442338 (2007)[28]	0.06	0.16	31	0.05	0.16	30	12.6	0.01 (–0.07, 0.09)
Siegel et al (1985)[33]	0.28	0.45	20	0.29	3.58	20	0.5	–0.01 (–1.59, 1.57)
Subtotal (95% CI)			**51**			**50**	**13.2**	**0.01 (–0.07, 0.09)**
Heterogeneity: τ^2=0.00; χ^2=0.00, *df*=1 (*p*=0.98); I^2=0%								
Test for overall effect: *Z*=0.24 (*p*=0.81)								
Steroids								
Johnson et al (1978)[23]	0.93	0.35	19	0.79	0.27	20	9.8	0.14 (–0.06, 0.34)
Montserrat et al (1995)[25]	1.43	0.7	6	1.19	0.28	6	3.0	0.24 (–0.36, 0.84)
Tribe et al (1976)[34]	0.8	0.31	12	1.04	0.55	11	5.9	–0.24 (–0.61, 0.13)
Wrenn et al (1991)[35]	1.48	0.1	32	1.43	0.11	35	13.1	0.05 (–0.00, 0.10)
Subtotal (95% CI)			**69**			**72**	**31.8**	**0.05 (–0.04, 0.14)**
Heterogeneity: τ^2=0.00; χ^2=3.55, *df*=3 (*p*=0.31); I^2=15%								
Test for overall effect: *Z*=1.17 (*p*=0.24)								
Oxygen only or no additional medication								
Appel and Shim (1981)[15]	0.9	0.45	12	1.26	0.52	12	5.5	–0.36 (–0.75, 0.03)
Fanta et al (1986/1)[19]	0.23	0.2	9	0.57	0.49	38	9.6	–0.34 (–0.54, –0.14)
Fanta et al (1986/2)[19]	0.23	0.2	9	0.72	0.51	41	9.6	–0.49 (–0.69, –0.29)
Rossing et al (1980/1)[30]	1.53	0.58	9	1.85	0.8	16	3.5	–0.32 (–0.87, 0.23)
Rossing et al (1980/2)[30]	1.53	0.58	9	2.11	0.66	15	4.0	–0.58 (–1.09, –0.07)
Sharma et al (1984/1)[32]	0.17	0.09	5	0.28	0.11	10	12.1	–0.11 (–0.21, –0.01)
Sharma et al (1984/2)[32]	0.17	0.09	5	0.52	0.24	10	10.6	–0.35 (–0.52, –0.18)
Subtotal (95% CI)			**58**			**142**	**55.0**	**–0.33 (–0.48, –0.18)**
Heterogeneity: τ^2=0.02; χ^2=16.37, *df*=6 (*p*=0.01); I^2=63%								
Test for overall effect: *Z*=4.44 (*p*<0.00001)								
Total (95% CI)			**178**			**264**	**100**	**–0.17 (–0.29, –0.05)**

Heterogeneity: τ^2=0.03; χ^2=68.63, *df*=12 (*p*<0.00001); I^2=83%
Test for overall effect: *Z*=2.78 (*p*=0.005)
Test for subgroup differences: χ^2=20.51, *df*=2 (*p*<0.0001); I^2=90.2%

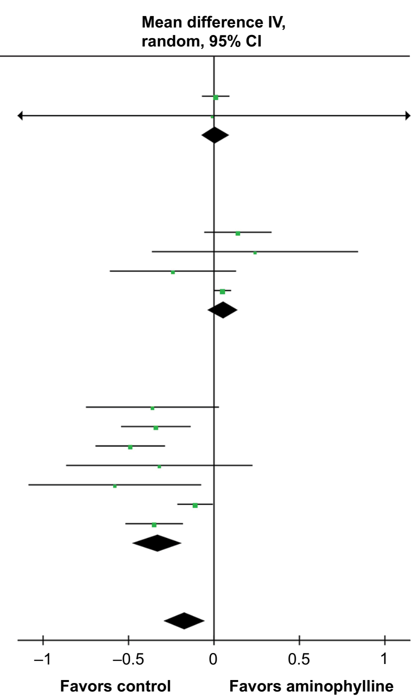


Figure 8 Subgroup meta-analysis of FEV1 following intravenous theophylline by background medication.
Notes: Background medication is defined as the medication given to all participants, in addition to which theophylline or control was added. Subgroups are bronchodilators only, steroids with or without bronchodilators, and oxygen only or no additional medication.

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Std mean difference IV, random, 95% CI
Adults								
Anantharaman (1993/1)[14]	–3.7	2.6	14	–1.9	1.8	27	6.3	–0.84 (–1.51, –0.17)
Anantharaman (1993/2)[14]	–3.7	2.6	14	–2.2	1.9	17	6.0	–0.65 (–1.38, 0.08)
Self et al (1990)[31]	–4.85	0.23	21	–4.63	0.38	18	6.5	–0.70 (–1.35, –0.05)
Siegel et al (1985)[33]	1.84	1.34	20	0.78	1.11	20	6.5	0.84 (0.19, 1.49)
Subtotal (95% CI)			**69**			**82**	**25.3**	**–0.33 (–1.13, 0.46)**
Heterogeneity: τ^2=0.54; χ^2=16.73, *df*=3 (*p*=0.0008); I^2=82%								
Test for overall effect: *Z*=0.82 (*p*=0.41)								
Children								
Bien et al (1995)[37]	–2.04	1.45	19	–2.59	0.91	20	6.6	0.45 (–0.19, 1.08)
DiGiulio et al (1993)[40]	–3.6	1.9	16	–3.7	2.4	13	5.9	0.05 (–0.69, 0.78)
Needleman et al (1995)[43]	3.05	3.25	25	2.38	2.19	20	6.9	0.23 (–0.36, 0.82)
Nuhoglu et al (1998)[44]	1.94	1.78	17	2.05	1.62	19	6.5	–0.06 (–0.72, 0.59)
Ream et al (2001)[46]	18.6	12.07	20	31.1	20.62	21	6.6	–0.72 (–1.36, –0.09)
Roberts et al (2003)[47]	6.5	1.68	26	6	1.57	18	6.8	0.30 (–0.30, 0.90)
Singhi et al (2014/1)[48]	1.72	1.43	33	0.76	0.85	34	7.6	0.81 (0.31, 1.31)
Singhi et al (2014/2)[48]	1.72	1.43	33	2.52	2.7	33	7.7	–0.37 (–0.85, 0.12)
Tiwari et al (2016)[50]	0.27	0.55	24	0.25	0.75	24	7.1	0.03 (–0.54, 0.60)
Vieira et al (2000)[51]	3.5	0.74	24	3.67	0.77	19	6.8	–0.22 (–0.83, 0.38)
Wheeler et al (2005)[52]	3.9	3.61	13	4.3	4.4	16	5.9	–0.10 (–0.83, 0.64)
Subtotal (95% CI)			**250**			**237**	**74.7**	**0.05 (–0.22, 0.31)**
Heterogeneity: τ^2=0.10; χ^2=20.94, *df*=10 (*p*=0.02); I^2=52%								
Test for overall effect: *Z*=0.34 (*p*=0.73)								
Total (95% CI)			**319**			**319**	**100**	**–0.05 (–0.33, 0.22)**
Heterogeneity: τ^2=0.19; χ^2=41.22, *df*=14 (*p*=0.0002); I^2=66%								
Test for overall effect: *Z*=0.36 (*p*=0.72)								
Test for subgroup differences: χ^2=0.78, *df*=1 (*p*=0.38); I^2=0%								

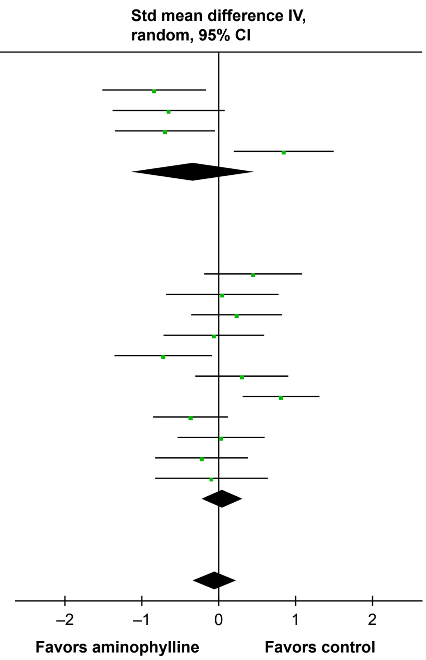


Figure 9 Subgroup meta-analysis of symptom scores following intravenous theophylline by age group.
Notes: Studies were grouped by the age of participants (children or adults). Studies with no stated age group or that did not enrol a particular age group were excluded from this analysis. Data are given as the mean difference (95% CI).

asthma in children.[60] Despite a systematic search for articles, their qualitative analysis failed to draw any conclusions, due to "minimal and inconsistent" evidence.

A retrospective case–control study suggested that administration of theophylline increased hospital stay, compared with inhaled beta-2 agonists and corticosteroids.[61] A meta-analysis by Mitra et al found that, in children, addition of theophylline to nebulized short-acting beta-2 agonists and systemic steroids resulted in better lung function in the first 6 hours of treatment.[62] However, Mitra et al did not investigate the addition of other drugs to the same background therapy.

Study or subgroup	Aminophylline Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Blinded								
Appel and Shim (1981)[15]	0.9	0.45	12	1.26	0.52	12	4.5	–0.36 (–0.75, 0.03)
Lindholm and Helander (1966/1)[24]	0.25	0.05	10	0.48	0.08	21	9.0	–0.23 (–0.28, –0.18)
Lindholm and Helander (1966/2)[24]	0.25	0.05	10	0.35	0.08	23	9.0	–0.10 (–0.15, –0.05)
Lindholm and Helander (1966/3)[24]	0.25	0.05	10	0.04	0.04	19	9.0	0.21 (0.17, 0.25)
Montserrat et al (1995)[25]	1.43	0.7	6	1.19	0.28	6	2.6	0.24 (–0.36, 0.84)
Siegel et al (1985)[33]	0.28	0.45	20	0.29	3.58	20	0.5	–0.01 (–1.59, 1.57)
Tribe et al (1976)[34]	0.8	0.31	12	1.04	0.55	11	4.7	–0.24 (–0.61, 0.13)
Wrenn et al (1991)[35]	1.48	0.1	32	1.43	0.11	35	8.9	0.05 (–0.00, 0.10)
Subtotal (95% CI)			**112**			**147**	**48.2**	**–0.06 (–0.23, 0.11)**
Heterogeneity: τ^2=0.04; χ^2=254.64, *df*=7 (*p*<0.00001); I^2=97%								
Test for overall effect: *Z*=0.66 (*p*=0.51)								
Unblinded/not clear								
Femi-Pearse et al (1977/1)[20]	0.23	0.29	9	0.57	0.49	38	6.5	–0.34 (–0.59, –0.09)
Femi-Pearse et al (1977/2)[20]	0.23	0.29	9	0.72	0.51	41	6.5	–0.49 (–0.74, –0.24)
Johnson et al (1978)[23]	0.93	0.35	19	0.79	0.27	20	7.2	0.14 (–0.06, 0.34)
NCT00442338 (2007)[28]	0.06	0.16	31	0.05	0.16	30	8.7	0.01 (–0.07, 0.09)
Rossing et al (1980/1)[30]	1.53	0.82	9	1.85	0.8	16	2.3	–0.32 (–0.98, 0.34)
Rossing et al (1980/2)[30]	1.53	0.29	9	2.11	0.66	15	4.6	–0.58 (–0.96, –0.20)
Sharma et al (1984/1)[32]	0.17	0.09	5	0.28	0.11	10	8.5	–0.11 (–0.21, –0.01)
Sharma et al (1984/2)[32]	0.17	0.09	5	0.52	0.24	10	7.6	–0.35 (–0.52, –0.18)
Subtotal (95% CI)			**96**			**180**	**51.8**	**–0.22 (–0.37, –0.06)**
Heterogeneity: τ^2=0.04; χ^2=41.21, *df*=7 (*p*<0.00001); I^2=83%								
Test for overall effect: *Z*=2.70 (*p*=0.007)								
Total (95% CI)			**208**			**327**	**100**	**–0.14 (–0.26, –0.02)**
Heterogeneity: τ^2=0.04; χ^2=310.51, *df*=15 (*p*<0.00001); I^2=95%								
Test for overall effect: *Z*=2.36 (*p*=0.02)								
Test for subgroup differences: χ^2=1.78, *df*=1 (*p*=0.18); I^2=43.9%								

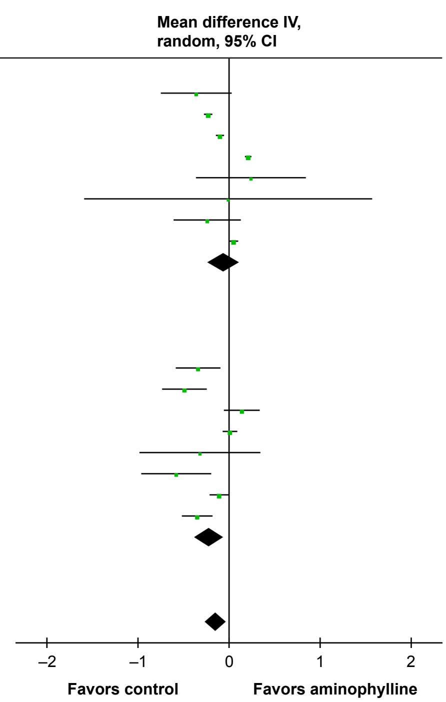


Figure 10 Subgroup meta-analysis of FEV1 following intravenous theophylline by blinding of study participants.
Note: Data are given as the mean difference (95% CI).

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Nausea						
Bien et al (1995)[37]	7	19	0	20	0.9	24.60 (1.29, 469.00)
Huang et al (1993)[22]	3	10	1	11	1.3	4.29 (0.37, 50.20)
Ream et al (2001)[46]	13	20	8	21	2.9	3.02 (0.85, 10.78)
Rodrigo and Rodrigo (1994)[29]	17	45	3	49	2.8	9.31 (2.50, 34.65)
Siegel et al (1985)[33]	2	20	0	20	0.9	5.54 (0.25, 123.08)
Strauss et al (1994)[49]	5	14	0	17	0.9	20.26 (1.01, 407.35)
Whig et al (2001)[54]	8	20	2	20	2.1	6.00 (1.08, 33.27)
Wrenn et al (1991)[35]	3	32	1	35	1.4	3.52 (0.35, 35.67)
Yung and South (1998)[53]	29	81	7	82	3.9	5.98 (2.43, 14.67)
Zainudin et al (1994)[36]	3	11	0	14	0.9	11.94 (0.55, 260.28)
Subtotal (95% CI)		**272**		**289**	**18.0**	**6.05 (3.56, 10.28)**
Total events	90		22			
Heterogeneity: τ^2=0.00; χ^2=3.58, *df*=9 (*p*=0.94); I^2=0%						
Test for overall effect: *Z*=6.66 (*p*<0.00001)						
Vomiting						
Bien et al (1995)[37]	6	19	3	20	2.4	2.62 (0.55, 12.48)
DiGiulio et al (1993)[40]	6	16	2	13	2.0	3.30 (0.54, 20.27)
Murphy et al (1993)[26]	10	22	2	22	2.2	8.33 (1.56, 44.64)
Ream et al (2001)[46]	14	20	7	21	2.8	4.67 (1.25, 17.44)
Siegel et al (1985)[33]	4	20	1	20	1.4	4.75 (0.48, 46.91)
Strauss et al (1994)[49]	2	14	0	17	0.9	7.00 (0.31, 158.83)
Whig et al (2001)[54]	4	20	1	20	1.4	4.75 (0.48, 46.91)
Yung and South (1998)[53]	35	81	8	82	4.0	7.04 (3.00, 16.49)
Subtotal (95% CI)		**212**		**215**	**17.0**	**5.35 (3.14, 9.12)**
Total events	81		24			
Heterogeneity: τ^2=0.00; χ^2=1.84, *df*=7 (*p*=0.97); I^2=0%						
Test for overall effect: *Z*=6.15 (*p*<0.00001)						
Abdominal pain						
Ream et al (2001)[46]	4	20	5	21	2.5	0.80 (0.18, 3.54)
Strauss et al (1994)[49]	2	14	0	17	0.9	7.00 (0.31, 158.83)
Subtotal (95% CI)		**34**		**38**	**3.4**	**1.52 (0.21, 10.79)**
Total events	6		5			
Heterogeneity: τ^2=0.85; χ^2=1.54, *df*=1 (*p*=0.21); I^2=35%						
Test for overall effect: *Z*=0.42 (*p*=0.68)						
Psychological						
Bien et al (1995)[37]	6	19	2	20	2.1	4.15 (0.72, 23.95)
Ream et al (2001)[46]	5	20	6	21	2.7	0.83 (0.21, 3.33)
Rodrigo and Rodrigo (1994)[29]	4	45	5	49	2.7	0.86 (0.22, 3.42)
Siegel et al (1985)[33]	2	20	1	20	1.2	2.11 (0.18, 25.35)
Whig et al (2001)[54]	5	20	1	20	1.4	6.33 (0.67, 60.16)
Yung and South (1998)[53]	3	32	3	35	2.2	1.10 (0.21, 5.90)
Zainudin et al (1994)[36]	23	81	20	82	4.4	1.23 (0.61, 2.47)
Subtotal (95% CI)		**237**		**247**	**16.8**	**1.35 (0.82, 2.20)**
Total events	48		38			
Heterogeneity: τ^2=0.00; χ^2=4.54, *df*=6 (*p*=0.60); I^2=0%						
Test for overall effect: *Z*=1.19 (*p*=0.23)						
Headache						
Murphy et al (1993)[26]	0	22	1	22	0.8	0.32 (0.01, 8.25)
Ream et al (2001)[46]	3	20	3	21	2.1	1.06 (0.19, 5.99)
Rodrigo and Rodrigo (1994)[29]	7	45	3	49	2.6	2.82 (0.68, 11.68)
Strauss et al (1994)[49]	2	14	0	17	0.9	7.00 (0.31, 158.83)
Whig et al (2001)[54]	6	20	1	20	1.5	8.14 (0.88, 75.48)
Yung and South (1998)[53]	15	81	15	82	4.2	1.02 (0.46, 2.24)
Subtotal (95% CI)		**202**		**211**	**12.0**	**1.60 (0.78, 3.30)**
Total events	33		23			
Heterogeneity: τ^2=0.13; χ^2=5.92, *df*=5 (*p*=0.31); I^2=15%						
Test for overall effect: *Z*=1.29 (*p*=0.20)						
Cardiovascular (palpitation, arrhythmia)						
Murphy et al (1993)[26]	9	22	3	22	2.5	4.38 (0.99, 19.36)
Rodrigo and Rodrigo (1994)[29]	11	45	4	49	3.0	3.64 (1.07, 12.43)
Siegel et al (1985)[33]	1	20	1	20	1.0	1.00 (0.06, 17.18)
Whig et al (2001)[54]	1	20	0	20	0.8	3.15 (0.12, 82.16)
Wrenn et al (1991)[35]	2	32	2	35	1.7	1.10 (0.15, 8.30)
Zainudin et al (1994)[36]	7	11	1	14	1.3	22.75 (2.11, 244.87)
Subtotal (95% CI)		**150**		**160**	**10.4**	**3.52 (1.66, 7.49)**
Total events	31		11			
Heterogeneity: τ^2=0.00; χ^2=4.49, *df*=5 (*p*=0.48); I^2=0%						
Test for overall effect: *Z*=3.27 (*p*=0.001)						
Seizure						
Wrenn et al (1991)[35]	0	32	1	35	0.8	0.35 (0.01, 9.00)
Yung and South (1998)[53]	1	81	1	82	1.0	1.01 (0.06, 16.47)
Subtotal (95% CI)		**113**		**117**	**1.8**	**0.65 (0.08, 5.35)**
Total events	1		2			
Heterogeneity: τ^2=0.00; χ^2=0.23, *df*=1 (*p*=0.63); I^2=0%						
Test for overall effect: *Z*=0.40 (*p*=0.69)						
Tremor						
DiGiulio et al (1993)[40]	8	16	5	13	2.5	1.60 (0.36, 7.07)
Murphy et al (1993)[26]	20	22	11	22	2.2	10.00 (1.87, 53.48)
Ream et al (2001)[46]	3	20	11	21	2.5	0.16 (0.04, 0.72)
Rodrigo and Rodrigo (1994)[29]	9	45	15	49	3.7	0.57 (0.22, 1.47)
Siegel et al (1985)[33]	2	20	1	20	1.2	2.11 (0.18, 25.35)
Wrenn et al (1991)[35]	7	32	6	35	3.1	1.35 (0.40, 4.56)
Yung and South (1998)[53]	27	81	20	82	4.5	1.55 (0.78, 3.07)
Zainudin et al (1994)[36]	7	11	0	14	0.9	48.33 (2.28, 1,022.45)
Subtotal (95% CI)		**247**		**256**	**20.6**	**1.50 (0.63, 3.55)**
Total events	83		69			
Heterogeneity: τ^2=0.94; χ^2=22.11, *df*=7 (*p*=0.002); I^2=68%						
Test for overall effect: Z=0.92 (*p*=0.36)						
Total (95% CI)		**1,467**		**1,533**	**100**	**2.57 (1.88, 3.52)**
Total events	373		194			
Heterogeneity: τ^2=0.45; χ^2=84.59, *df*=48 (*p*=0.0009); I^2=43%						
Test for overall effect: *Z*=5.89 (*p*<0.00001)						
Test for subgroup differences: χ^2=29.17, *df*=7 (*p*=0.0001); I^2=76.0%						

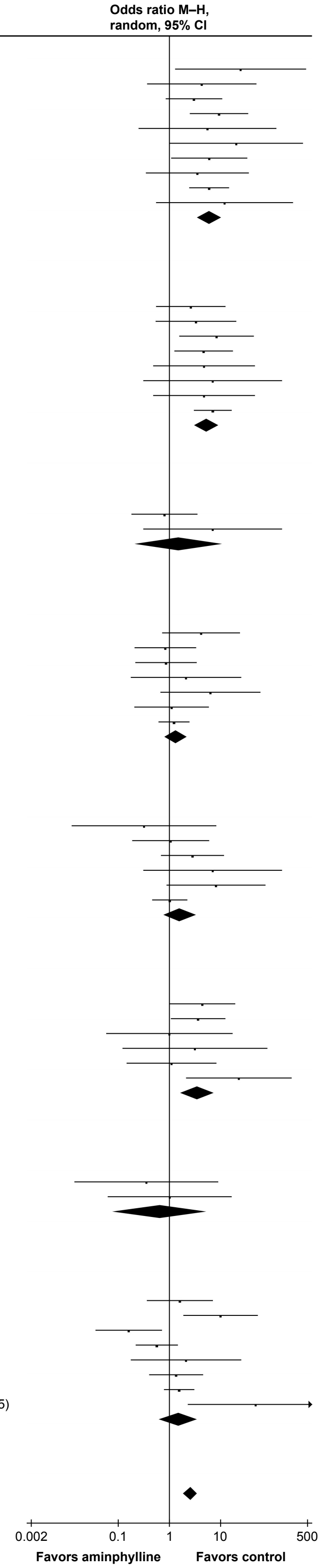


Figure 11 (*Continued*)

B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Nausea						
Appel and Shim (1981)[15]	6	12	0	12	2.2	25.00 (1.21, 516.69)
Sharma et al (1984/1)[32]	1	10	0	10	2.0	3.32 (0.12, 91.60)
Wheeler et al (2005)[52]	9	13	5	16	3.8	4.95 (1.02, 24.10)
Williams et al (1975)[55]	4	9	0	11	2.1	18.82 (0.85, 414.97)
Subtotal (95% CI)		**44**		**49**	**10.1**	**7.37 (2.24, 24.27)**
Total events	20		5			
Heterogeneity: τ^2=0.00; χ^2=1.48, *df*=3 (*p*=0.69); I^2=0%						
Test for overall effect: *Z*=3.28 (*p*=0.001)						
Vomiting						
Appel and Shim (1981)[15]	6	12	0	12	2.2	25.00 (1.21, 516.69)
Singhi et al (2014/1)[48]	9	33	0	34	2.3	26.76 (1.49, 481.69)
Tiwari et al (2016)[50]	0	24	1	24	2.0	0.32 (0.01, 8.25)
Tribe et al (1976)[34]	1	12	0	11	2.0	3.00 (0.11, 81.61)
Wheeler et al (2005)[52]	9	13	7	16	3.9	2.89 (0.62, 13.46)
Williams et al (1975)[55]	1	9	0	11	2.0	4.06 (0.15, 112.39)
Subtotal (95% CI)		**103**		**108**	**14.3**	**4.26 (1.33, 13.59)**
Total events	26		8			
Heterogeneity: τ^2=0.29; χ^2=5.75, *df*=5 (*p*=0.33); I^2=13%						
Test for overall effect: *Z*=2.45 (*p*=0.01)						
Psychological						
Appel and Shim (1981)[15]	3	12	5	12	3.6	0.47 (0.08, 2.66)
Sharma et al (1984/1)[32]	1	10	2	10	2.6	0.44 (0.03, 5.88)
Tribe et al (1976)[34]	0	12	1	11	2.0	0.28 (0.01, 7.62)
Subtotal (95% CI)		**34**		**33**	**8.2**	**0.42 (0.11, 1.59)**
Total events	4		8			
Heterogeneity: τ^2=0.00; χ^2=0.07, *df*=2 (*p*=0.96); I^2=0%						
Test for overall effect: *Z*=1.27 (*p*=0.20)						
Headache						
Greif et al (1985)[21]	0	10	1	11	2.0	0.33 (0.01, 9.16)
Ibrahim et al (1993/2)[42]	4	40	0	40	2.2	9.99 (0.52, 191.90)
Tribe et al (1976)[34]	1	12	2	11	2.6	0.41 (0.03, 5.28)
Wheeler et al (2005)[52]	3	13	3	16	3.5	1.30 (0.21, 7.87)
Williams et al (1975)[55]	2	9	3	11	3.2	0.76 (0.10, 5.96)
Subtotal (95% CI)		**84**		**89**	**13.6**	**1.05 (0.37, 3.00)**
Total events	10		9			
Heterogeneity: τ^2=0.00; χ^2=3.48, *df*=4 (*p*=0.48); I^2=0%						
Test for overall effect: *Z*=0.09 (*p*=0.93)						
Cardiovascular						
Appel and Shim (1981)[15]	8	12	2	12	3.4	10.00 (1.44, 69.26)
Emerman et al (1986)[17]	5	20	4	20	3.9	1.33 (0.30, 5.93)
Greif et al (1985)[21]	0	10	6	11	2.2	0.04 (0.00, 0.86)
Ibrahim et al (1993/1)[42]	0	40	12	40	2.3	0.03 (0.00, 0.49)
Sharma et al (1984/1)[32]	0	10	9	10	2.0	0.01 (0.00, 0.21)
Tiwari et al (2016)[50]	19	24	22	24	3.6	0.35 (0.06, 1.99)
Tribe et al (1976)[34]	0	12	2	11	2.1	0.15 (0.01, 3.55)
Wheeler et al (2005)[52]	0	13	3	16	2.2	0.14 (0.01, 3.04)
Williams et al (1975)[55]	4	9	0	11	2.1	18.82 (0.85, 414.97)
Subtotal (95% CI)		**150**		**155**	**23.7**	**0.35 (0.07, 1.72)**
Total events	36		60			
Heterogeneity: τ^2=4.15; χ^2=30.44, *df*=8 (*p*=0.0002); I^2=74%						
Test for overall effect: *Z*=1.29 (*p*=0.20)						
Tremor						
Appel and Shim (1981)[15]	1	12	0	12	2.0	3.26 (0.12, 88.35)
Greif et al (1985)[21]	0	10	2	11	2.1	0.18 (0.01, 4.27)
Ibrahim et al (1993/2)[42]	0	40	6	40	2.3	0.07 (0.00, 1.21)
Sharma et al (1984/1)[32]	0	10	2	10	2.1	0.16 (0.01, 3.85)
Sharma et al (1984/2)[32]	0	10	5	10	2.1	0.05 (0.00, 1.03)
Tribe et al (1976)[34]	0	12	2	11	2.1	0.15 (0.01, 3.55)
Wheeler et al (2005)[52]	9	13	6	16	3.9	3.75 (0.79, 17.72)
Williams et al (1975)[55]	3	9	2	11	3.2	2.25 (0.29, 17.76)
Subtotal (95% CI)		**116**		**121**	**19.7**	**0.48 (0.12, 1.89)**
Total events	13		25			
Heterogeneity: τ^2=2.00; χ^2=14.94, *df*=7 (*p*=0.04); I^2=53%						
Test for overall effect: *Z*=1.05 (*p*=0.29)						
CPK/CK elevation						
NCT00442338 (2007)[28]	0	31	2	30	2.1	0.18 (0.01, 3.93)
Wheeler et al (2005)[52]	7	13	5	16	3.9	2.57 (0.56, 11.72)
Subtotal (95% CI)		**44**		**46**	**6.1**	**0.96 (0.07, 12.31)**
Total events	7		7			
Heterogeneity: τ^2=2.10; χ^2=2.37, *df*=1 (*p*=0.12); I^2=58%						
Test for overall effect: *Z*=0.03 (*p*=0.97)						
Glucoseurea/hyperglycemia						
NCT00442338 (2007)[28]	1	31	1	30	2.4	0.97 (0.06, 16.19)
Wheeler et al (2005)[52]	12	13	16	16	2.0	0.25 (0.01, 6.74)
Subtotal (95% CI)		**44**		**46**	**4.4**	**0.55 (0.06, 4.64)**
Total events	13		17			
Heterogeneity: τ^2=0.00; χ^2=0.37, *df*=1 (*p*=0.54); I^2=0%						
Test for overall effect: *Z*=0.55 (*p*=0.58)						
Total (95% CI)		**619**		**647**	**100**	**0.98 (0.55, 1.76)**
Total events	129		139			
Heterogeneity: τ^2=1.66; χ^2=79.87, *df*=38 (*p*<0.0001); I^2=52%						
Test for overall effect: *Z*=0.07 (*p*=0.95)						
Test for subgroup differences: χ^2=20.39, *df*=7 (*p*=0.005); I^2=65.7%						

Odds ratio M–H, random, 95% CI

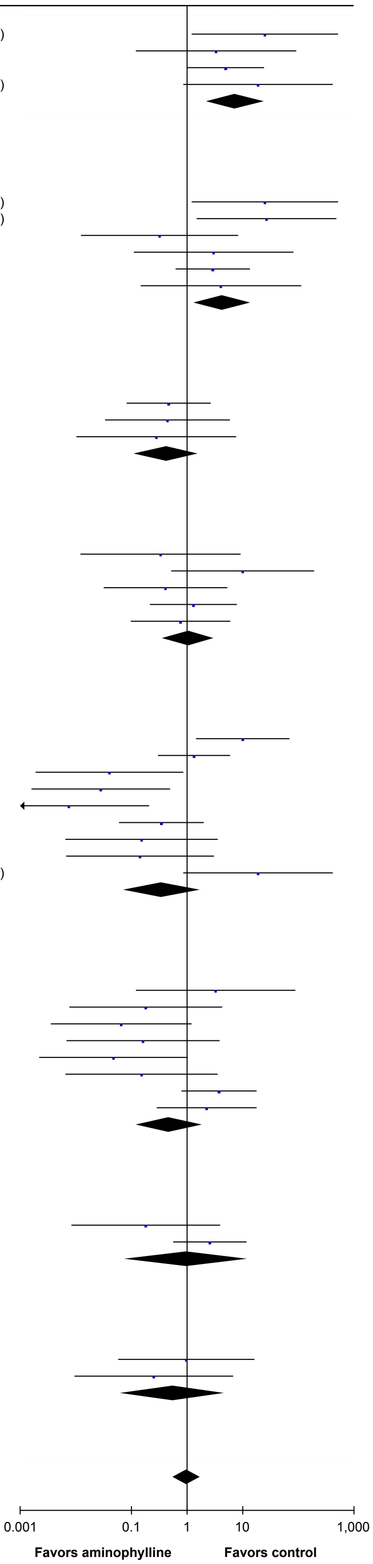


Figure 11 Subgroup meta-analysis of adverse events in placebo-controlled trials (**A**) or active comparator trials (**B**).
Note: Data are given as odds ratios (95% CI).

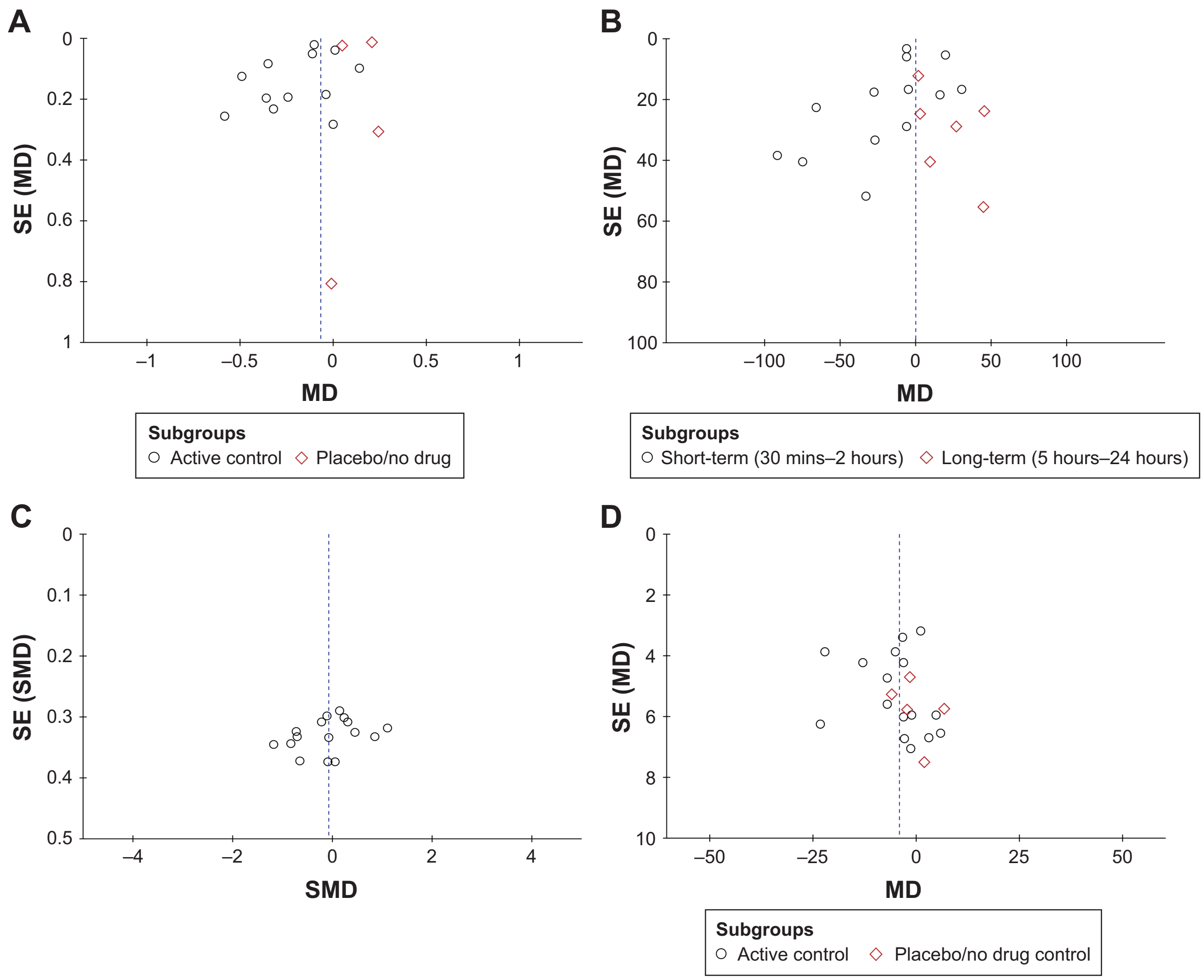


Figure 12 Funnel plot analysis of FEV1 (**A**), PEFR (**B**), symptom score (**C**), and heart rate (**D**).
Abbreviations: SE, standard error; MD, mean difference; PEFR, peak expiratory flow rate; SMD, standardized mean difference.

In contrast, a more recent meta-analysis analyzed trials directly comparing IV beta-2 agonists with IV theophylline in the treatment of acute asthma.[63] In this meta-analysis, Travers et al found no significant differences between IV beta-2 agonists and IV theophylline added to normal treatment in terms of hospital stay, PEFR, FEV1, heart rate, or clinical failure. In addition, Nair et al found that adding IV theophylline to inhaled beta-2 agonists did not provide additional benefit in adults with acute asthma.[64] None of these meta-analyses specifically investigated the role of background medication in the efficacy of theophylline, compared with other additional medications.

Recent data from the UK suggest that, at least in children, theophylline was the third most commonly administered drug in an acute setting, after salbutamol and magnesium sulfate.[65] However, different drugs, especially new, branded formulations of drugs, may differ in cost by a large degree. Indeed, a 2005 study included hospital cost in their analysis.[52] They found that treating their patients with theophylline was as effective as terbutaline, and the total treatment costs were less than a tenth of those with terbutaline.

Limitations of this analysis

We were fortunate to find a significant body of evidence testing the efficacy of theophylline. However, because asthma outcomes can be measured in a large number of different ways, we were limited in the investigations we could carry out. For example, we had planned to do meta-regression, but we felt there were insufficient studies in any one outcome to create a meaningful interpretation of the data.[8]

Conclusion

Our data show that IV theophylline is superior to other treatments with regard to heart rate and duration of hospital stay, and equal to other treatments for almost all our other reported outcomes. Given the very low cost and similar safety profile of theophylline, it must surely be considered a cost-effective treatment for acute asthma exacerbations, especially for developing countries with restricted health budgets.

Acknowledgment

This study was supported by The Xinjiang Uygur Autonomous Region Natural Science Foundation Funded Projects (number: 2017D01C251).

Author contributions

GM developed and designed the concept for the systematic review and meta-analysis; she wrote the initial draft, did interpretation of the analyzed results, and finalized the manuscript. HZ, JL, NT, and LR did literature search, data collection, extraction, and analysis. GM, HZ, JL, NT, and LR wrote different sections of the manuscript. GM did the critical revision of the intellectual content of the article. All authors read and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12:204.
2. Global Asthma Network. The global asthma report 2014. Auckland, New Zealand: Global Asthma Network; 2014.
3. Lundbäck B, Backman H, Lötvall J, Rönmark E. Is asthma prevalence still increasing? *Expert Rev Respir Med*. 2016;10:39–51.
4. WHO. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach [Internet]. WHO [cited May 31, 2017]. Available from: http://www.who.int/gard/publications/GARD_Manual/en/. Accessed May 31, 2017.
5. List of Asthma Medications (62 Compared) [Internet]. Drugs.com [cited May 31, 2017]. Available from: https://www.drugs.com/condition/asthma.html. Accessed May 31, 2017.
6. Theophylline T1633 [Internet]. Sigma-Aldrich [cited May 31, 2017]. Available from: http://www.sigmaaldrich.com/catalog/product/sigma/t1633. Accessed May 31, 2017.
7. Pubchem. aminophylline | C16H24N10O4 – PubChem [Internet] [cited May 31, 2017]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/aminophylline. Accessed May 31, 2017.
8. Higgins JP, Greeen S. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011.
9. Thomas J, Brunton J, Graziosi S. *EPPI-Reviewer 4: Software for Research Synthesis*. EPPI-Centre Software. London: Social Science Research Unit, UCL Institute of Education; 2010.
10. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
11. Rohatgi A. WebPlotDigitizer [Internet]. Austin, Texas, USA; 2017. Available from: http://arohatgi.info/WebPlotDigitizer
12. The Nordic Cochrane Centre. *Review Manager (RevMan)*. The Cochrane Collaboration. Copenhagen; 2014.
13. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.
14. Anantharaman V. Therapeutic regimes for acute bronchial asthma. *Singap Med J*. 1993;34:534–537.
15. Appel D, Shim C. Comparative effect of epinephrine and aminophylline in the treatment of asthma. *Lung*. 1981;159:243–254.
16. Coleridge J, Cameron P, Epstein J, Teichtahl H. Intravenous aminophylline confers no benefit in acute asthma treated with intravenous steroids and inhaled bronchodilators. *Aust N Z J Med*. 1993;23:348–354.
17. Emerman CL, Crafford WA, Vrobel TR. Ventricular arrhythmias during treatment for acute asthma. *Ann Emerg Med*. 1986;15:699–702.
18. Evans WV, Monie RD, Crimmins J, Seaton A. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *Br J Chest*. 1980;74:385–389.
19. Fanta CH, Rossing TH, McFadden ER Jr. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxanthines indicated? *Am J Med*. 1986;80:5–10.
20. Femi-Pearse D, George WO, Ilechukwu ST, Elegbeleye OO, Afonja AO. Comparison of intravenous aminophylline and salbutamol in severe asthma. *Br Med J*. 1977;1:491.
21. Greif J, Markovitz L, Topilsky M. Comparison of intravenous salbutamol (albuterol) and aminophylline in the treatment of acute asthmatic attacks. *Ann Allergy*. 1985;55:504–506.
22. Huang D, O'Brien RG, Harman E, et al. Does aminophylline benefit adults admitted to the hospital for an acute exacerbation of asthma? *Ann Intern Med*. 1993;119:1155–1160.
23. Johnson AJ, Spiro SG, Pidgeon J, Bateman S, Clarke SW. Intravenous infusion of salbutamol in severe acute asthma. *Br Med J*. 1978;1:1013–1015.
24. Lindholm B, Helander E. The effect on the pulmonary ventilation of different theophylline derivatives compared to adrenaline and isoprenaline. *Acta Allergol*. 1966;21:299–306.
25. Montserrat JM, Barbera JA, Viegas C, Roca J, Rodriguez-Roisin R. Gas exchange response to intravenous aminophylline in patients with a severe exacerbation of asthma. *Eur Respir J*. 1995;8:28–33.
26. Murphy DG, McDermott MF, Rydman RJ, Sloan EP, Zalenski RJ. Aminophylline in the treatment of acute asthma when beta 2-adrenergics and steroids are provided. *Arch Intern Med*. 1993;153:1784–1788.
27. Nakano J, Yano T, Yamamura K, et al. Aminophilline suppress the release of chemical mediators in treatment of acute asthma. *Respir Med*. 2006;100:542–550.
28. NCT00442338. Study of MK0476 in Adult Patients With Acute Asthma (0476-334). amp, Dohme Corp, editors. 2007; Available from: http://clinicaltrials.gov/show/NCT00442338. Accessed February 12, 2017.
29. Rodrigo C, Rodrigo G. Treatment of acute asthma. Lack of therapeutic benefit and increase of the toxicity from aminophylline given in addition to high doses of salbutamol delivered by metered-dose inhaler with a spacer. *Chest*. 1994;106:1071–1076.
30. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. *Am Rev Respir Dis*. 1980;122:365–371.
31. Self TH, Abou-Shala N, Burns R, et al. Inhaled albuterol and oral prednisone therapy in hospitalized adult asthmatics. Does aminophylline add any benefit? *Chest*. 1990;98:1317–1321.
32. Sharma TN, Gupta RB, Gupta PR, Purohit SD. Comparison of intravenous aminophylline, salbutamol and terbutaline in acute asthma. *Indian J Chest Dis Allied Sci*. 1984;26:155–158.
33. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. *Am Rev Respir Dis*. 1985;132:283–286.
34. Tribe AE, Wong RM, Robinson JS. A controlled trial of intravenous salbutamol and aminophylline in acute asthma. *Med J Aust*. 1976;2:749–752.
35. Wrenn K, Slovis CM, Murphy F, Greenberg RS. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med*. 1991;115:241–247.

36. Zainudin BM, Ismail O, Yusoff K. Effect of adding aminophylline infusion to nebulised salbutamol in severe acute asthma. *Thorax*. 1994; 49:267–269.
37. Bien JP, Bloom MD, Evans RL, Specker B, O'Brien KP. Intravenous theophylline in pediatric status asthmaticus. A prospective, randomized, double-blind, placebo-controlled trial. *Clin Pediatr Phila*. 1995; 34:475–481.
38. Carter E, Cruz M, Chesrown S, Shieh G, Reilly K, Hendeles L. Efficacy of intravenously administered theophylline in children hospitalized with severe asthma. *J Pediatr*. 1993;122:470–476.
39. D'Avila RS, Piva JP, Marostica PJ, Amantea SL. Early administration of two intravenous bolus of aminophylline added to the standard treatment of children with acute asthma. *Respir Med*. 2008;102:156–161.
40. DiGiulio GA, Kercsmar CM, Krug SE, Alpert SE, Marx CM. Hospital treatment of asthma: lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid. *J Pediatr*. 1993;122:464–469.
41. Hambleton G, Stone MJ. Comparison of IV salbutamol with IV aminophylline in the treatment of severe, acute asthma in childhood. *Arch Child*. 1979;54:391–392.
42. Ibrahim SA, Elgurashi ED, Elkarim OA. Comparative study of intravenous aminophylline subcutaneous adrenaline and nebulised salbutamol in the treatment of acute asthma in children. *Pediatr Rev Commun*. 1993;7:175–182.
43. Needleman JP, Kaifer MC, Nold JT, Shuster PE, Redding MM, Gladstein J. Theophylline does not shorten hospital stay for children admitted for asthma. *Arch Pediatr Adolesc Med*. 1995;149: 206–209.
44. Nuhoglu Y, Dai A, Barlan IB, Basaran MM. Efficacy of aminophylline in the treatment of acute asthma exacerbation in children. *Ann Allergy Asthma Immunol*. 1998;80:395–398.
45. Pierson WE, Bierman CW, Stamm SJ, Van Arsdel PP Jr. Double-blind trial of aminophylline in status asthmaticus. *Pediatrics*. 1971;48: 642–646.
46. Ream RS, Loftis LL, Albers GM, Becker BA, Lynch RE, Mink RB. Efficacy of IV theophylline in children with severe status asthmaticus. *Chest*. 2001;119:1480–1488.
47. Roberts G, Newsom D, Gomez K, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. *Thorax*. 2003;58:306–310.
48. Singhi S, Grover S, Bansal A, Chopra K. Randomised comparison of intravenous magnesium sulphate, terbutaline and aminophylline for children with acute severe asthma. *Acta Paediatr*. 2014;103: 1301–1306.
49. Strauss RE, Wertheim DL, Bonagura VR, Valacer DJ. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. *Pediatrics*. 1994;93:205–210.
50. Tiwari A, Guglani V, Jat KR. Ketamine versus aminophylline for acute asthma in children: a randomized, controlled trial. *Ann Thorac Med*. 2016;11:283–288.
51. Vieira SE, Lotufo JP, Ejzenberg B, Okay Y. Efficacy of IV aminophylline as a supplemental therapy in moderate broncho-obstructive crisis in infants and preschool children. *Pulm Pharmacol Ther*. 2000;13: 189–194.
52. Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. *Pediatr Crit Care Med*. 2005;6:142–147.
53. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Child*. 1998;79:405–410.
54. Whig J, Puri S, Mahajan R, Chopra SC, Mittal N, Malhotra S. Placebo controlled evaluation of intravenous aminophylline in acute asthma. *Lung India*. 2001;19:97–100.
55. Williams SJ, Parrish RW, Seaton A. Comparison of intravenous aminophylline and salbutamol in severe asthma. *Br Med J*. 1975;4:685.
56. Rapid Respiratory Rate – A Sign of Asthma Problems [Internet] [cited May 29, 2017]. Available from: https://www.asthmasymptoms.org/rapid-respiratory-rate.html. Accessed May 29, 2017.
57. Camargo CA, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department. *Proc Am Thorac Soc*. 2009;6: 357–366.
58. Managing acute asthma in clinical settings [Internet]. Australian Asthma Handbook [cited Jun 2, 2017]. Available from: http://www.asthmahandbook.org.au/acute-asthma/clinical. Accessed June 2, 2017.
59. Pollart SM, Compton RM, Elward KS. Management of acute asthma exacerbations. *Am Fam Physician*. 2011;84:40–47.
60. Neame M, Aragon O, Fernandes RM, Sinha I. Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why? *Arch Dis Child Educ Pract*. 2015;100:215–222.
61. Dalabih AR, Bondi SA, Harris ZL, Saville BR, Wang W, Arnold DH. Aminophylline infusion for status asthmaticus in the pediatric critical care unit setting is independently associated with increased length of stay and time for symptom improvement. *Pulm Pharmacol Ther*. 2014;27:57–61.
62. Mitra AA, Bassler D, Watts K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst. Rev. [Internet]. John Wiley & Sons, Ltd; 2005. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001276.pub2/abstract. Accessed June 2, 2017.
63. Travers AH, Jones AP, Camargo CA Jr, Milan SJ, Rowe BH. Intravenous beta2-agonists versus intravenous aminophylline for acute asthma. Cochrane Database Syst. Rev. [Internet]. John Wiley & Sons, Ltd; 2012. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010256/abstract. Accessed June 2, 2017.
64. Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta2-agonists in adults with acute asthma. Cochrane Database Syst. Rev. [Internet]. John Wiley & Sons, Ltd; 2012. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002742.pub2/abstract. Accessed June 2, 2017.
65. Morris I, Lyttle MD, O'Sullivan R, Sargant N, Doull IJM, Powell CVE. Which intravenous bronchodilators are being administered to children presenting with acute severe wheeze in the UK and Ireland? *Thorax*. 2015;70:88–91.