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

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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 (FEV$_1$) ($p=0.002$). 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%. In children, the prevalence is even higher, with many countries reporting asthma rates in children over 20%. 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.

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
deaths worldwide each year. Despite a range of drugs for the treatment of asthma, 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. 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.

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 Elixirophyllin 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 bumbuterol 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 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 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. 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). Mean differences and standardized mean differences with 95% confidence intervals (CI) were calculated using an inverse variance model. Odds ratios with 95% CI were calculated using the Mantel–Haenszel statistical method. 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, with children the focus of 17 study arms. One study did not restrict the age of participants, and one study did not report the age of participants. 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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention</th>
<th>Control</th>
<th>Study type</th>
<th>Study length</th>
<th>Population</th>
<th>Age range, years</th>
<th>Average age, years</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Bolus dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anantharaman (1993/1)</td>
<td>27</td>
<td>27</td>
<td>P</td>
<td>30 minutes</td>
<td>Adults</td>
<td>15–40</td>
<td>28</td>
<td>All</td>
<td>A</td>
<td>250 mg</td>
</tr>
<tr>
<td>Anantharaman (1993/2)</td>
<td>27</td>
<td>17</td>
<td>P</td>
<td>30 minutes</td>
<td>Adults</td>
<td>15–40</td>
<td>27</td>
<td>All</td>
<td>A</td>
<td>250 mg</td>
</tr>
<tr>
<td>Appel and Shim (1981)</td>
<td>12</td>
<td>12</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>No data</td>
<td>33</td>
<td>All</td>
<td>A</td>
<td>6 mg/kg</td>
</tr>
<tr>
<td>Coleridge et al (1993/1) (discharged)</td>
<td>16</td>
<td>15</td>
<td>P</td>
<td>50 hours</td>
<td>Adults</td>
<td>No data</td>
<td>34</td>
<td>Not recovered at 30 minutes after salbutamol</td>
<td>A</td>
<td>Not stated</td>
</tr>
<tr>
<td>Coleridge et al (1993/2) (inpatients)</td>
<td>14</td>
<td>14</td>
<td>P</td>
<td>50 hours</td>
<td>Adults</td>
<td>No data</td>
<td>34</td>
<td>Not recovered at 30 minutes after salbutamol</td>
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<td>Not stated</td>
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<tr>
<td>Emerman et al (1986)</td>
<td>20</td>
<td>20</td>
<td>P</td>
<td>90 minutes</td>
<td>Adults</td>
<td>18–45</td>
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<td>All</td>
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<tr>
<td>Evans et al (1980)</td>
<td>6</td>
<td>7</td>
<td>P</td>
<td>24 hours</td>
<td>Adults</td>
<td>No data</td>
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<td>All</td>
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</tr>
<tr>
<td>Fanta et al (1986/1)</td>
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<td>38</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>No data</td>
<td>30</td>
<td>All</td>
<td>A</td>
<td>5.6 mg/kg</td>
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<tr>
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<td>41</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>No data</td>
<td>30</td>
<td>All</td>
<td>A</td>
<td>5.6 mg/kg</td>
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<tr>
<td>Femi-Pearse et al (1977/1)</td>
<td>8</td>
<td>10</td>
<td>P</td>
<td>40 minutes</td>
<td>Adults</td>
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<td>No data</td>
<td>Not stated</td>
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<td>250 mg over 15 minutes</td>
</tr>
<tr>
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<td>15</td>
<td>17</td>
<td>P</td>
<td>40 minutes</td>
<td>Adults</td>
<td>No data</td>
<td>No data</td>
<td>Not stated</td>
<td>A</td>
<td>250 mg over 15 minutes</td>
</tr>
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<td>Greif et al (1985)</td>
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<td>11</td>
<td>P</td>
<td>120 minutes</td>
<td>Adults</td>
<td>15–68</td>
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<td>All</td>
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<td>Huang et al (1993)</td>
<td>10</td>
<td>11</td>
<td>P</td>
<td>48 hours</td>
<td>Adults</td>
<td>22–48</td>
<td>33</td>
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<td>A</td>
<td>To achieve 15 µg/mL</td>
</tr>
<tr>
<td>Johnson et al (1978)</td>
<td>19</td>
<td>20</td>
<td>P</td>
<td>36 hours</td>
<td>Adults</td>
<td>16–65</td>
<td>39</td>
<td>Requiring treatment after 5 mg/kg theophylline and nebulized salbutamol</td>
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<td>5 mg/kg</td>
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<tr>
<td>Lindholm and Helander (1966/1)</td>
<td>29</td>
<td>21</td>
<td>P</td>
<td>30 minutes</td>
<td>Adults</td>
<td>22–73</td>
<td>48</td>
<td>Moderate severity</td>
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<tr>
<td>Lindholm and Helander (1966/2)</td>
<td>29</td>
<td>23</td>
<td>P</td>
<td>30 minutes</td>
<td>Adults</td>
<td>15–73</td>
<td>49</td>
<td>Moderate severity</td>
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<td>19</td>
<td>P</td>
<td>30 minutes</td>
<td>Adults</td>
<td>15–73</td>
<td>49</td>
<td>Moderate severity</td>
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</tr>
<tr>
<td>Montserrat et al (1995)</td>
<td>6</td>
<td>6</td>
<td>P</td>
<td>51 hours</td>
<td>Adults</td>
<td>21–62</td>
<td>41</td>
<td>Failed bronchodilator therapy</td>
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<td>6 mg/kg</td>
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<tr>
<td>Murphy et al (1993)</td>
<td>22</td>
<td>22</td>
<td>P</td>
<td>5 hours</td>
<td>Adults</td>
<td>18–45</td>
<td>28</td>
<td>Failed metaproterenol sulfate</td>
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<tr>
<td>Nakano et al (2006)</td>
<td>10</td>
<td>8</td>
<td>P</td>
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<td>Adults</td>
<td>22–70</td>
<td>47</td>
<td>Only mild to moderate asthmatics included</td>
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<td>To achieve 18 µg/mL</td>
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<table>
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<th>Ongoing dose</th>
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<th>Ongoing dose</th>
<th>Background medication</th>
<th>Gender</th>
<th>Country</th>
<th>Blinding</th>
<th>Funding</th>
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<tr>
<td>None</td>
<td>Adrenaline (sc)</td>
<td>1 mg</td>
<td>None</td>
<td>Oxygen</td>
<td>Mixed</td>
<td>Singapore</td>
<td>Unclear</td>
<td>Hospital</td>
</tr>
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<td>None</td>
<td>Salbutamol (nebulized)</td>
<td>10 mg</td>
<td>None</td>
<td>Oxygen</td>
<td>Mixed</td>
<td>Singapore</td>
<td>Unclear</td>
<td>Hospital</td>
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<td>None</td>
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<td>USA</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.5–0.75 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Hydrocortisone (IV), salbutamol (neb), ipratropium bromide (neb)</td>
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<td>Australia</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.5–0.75 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Hydrocortisone (IV), salbutamol (neb), ipratropium bromide (neb)</td>
<td>Mixed</td>
<td>Australia</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>None</td>
<td>Epinephrine (sc)</td>
<td>0.3 mL</td>
<td>None</td>
<td>None</td>
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<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
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<td>0.014 mg/kg/min</td>
<td>Salbutamol IV</td>
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<td>Hydrocortisone (IV), potassium chloride (IV)</td>
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<td>UK</td>
<td>Single blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Epinephrine (sc)</td>
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<td>Supplemental oxygen</td>
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<td>USA</td>
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<td>2.5 mg at 20 min × 3</td>
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<td>Supplemental oxygen</td>
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<td>USA</td>
<td>Unclear</td>
<td>University/ hospital</td>
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<td>200 µg bolus</td>
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<td>Nigeria</td>
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<td>University</td>
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<td>None</td>
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<td>200 µg over 15 minutes</td>
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<td>Not stated</td>
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<td>Double blind</td>
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<td>Salbutamol IV</td>
<td>4 µg/kg</td>
<td>None</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Israel</td>
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<td>0.6 mg/kg/h</td>
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<td>N/A</td>
<td>N/A</td>
<td>Albuterol (neb), methylprednisone (IV)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University</td>
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<td>1 mg/min</td>
<td>Salbutamol IV</td>
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<td>10 µg/min</td>
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<td>UK</td>
<td>Unclear</td>
<td>Hospital</td>
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<td>250 mg</td>
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<td>0.5 mg</td>
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<td>Isoprenaline</td>
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<td>Mixed</td>
<td>Sweden</td>
<td>Double blind</td>
<td>University</td>
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<td>250 mg</td>
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<td>N/A</td>
<td>Not stated</td>
<td>Mixed</td>
<td>Sweden</td>
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<td>University</td>
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<td>N/A</td>
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<td>Spain</td>
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<td>N/A</td>
<td>N/A</td>
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<td>University/ hospital</td>
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(Continued)
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<tr>
<th>Study ID</th>
<th>Intervention Control</th>
<th>Study type</th>
<th>Study length</th>
<th>Population Age range, years</th>
<th>Average age, years</th>
<th>Inclusion (severity)</th>
<th>Intervention</th>
<th>Bolus dose</th>
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<td>NCT00442338 (2007)10</td>
<td>31</td>
<td>30</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>No data</td>
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<tr>
<td>Rodrigo and Rodrigo (1994)11</td>
<td>45</td>
<td>49</td>
<td>P</td>
<td>120 minutes</td>
<td>Adults</td>
<td>No data</td>
<td>A</td>
<td>5.6 mg/kg</td>
</tr>
<tr>
<td>Rossing et al (1980/1)12</td>
<td>17</td>
<td>16</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>18–45</td>
<td>30</td>
<td>A</td>
</tr>
<tr>
<td>Rossing et al (1980/2)13</td>
<td>17</td>
<td>15</td>
<td>P</td>
<td>60 minutes</td>
<td>Adults</td>
<td>18–45</td>
<td>31</td>
<td>A</td>
</tr>
<tr>
<td>Self et al (1990)14</td>
<td>21</td>
<td>18</td>
<td>P</td>
<td>32 hours</td>
<td>Adults</td>
<td>18–49</td>
<td>32</td>
<td>Failed albuterol and corticosteroids</td>
</tr>
<tr>
<td>Sharma et al (1984/1)15</td>
<td>10</td>
<td>10</td>
<td>P</td>
<td>3 hours</td>
<td>Adults</td>
<td>No data</td>
<td>33</td>
<td>No bronchodilators in previous 24 hours</td>
</tr>
<tr>
<td>Sharma et al (1984/2)16</td>
<td>10</td>
<td>10</td>
<td>P</td>
<td>3 hours</td>
<td>Adults</td>
<td>No data</td>
<td>32</td>
<td>No bronchodilators in previous 24 hours</td>
</tr>
<tr>
<td>Siegel et al (1985)17</td>
<td>20</td>
<td>20</td>
<td>P</td>
<td>3 hours</td>
<td>Adults</td>
<td>18–45</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>Tribe et al (1976)18</td>
<td>12</td>
<td>11</td>
<td>P</td>
<td>3 hours</td>
<td>Adults</td>
<td>17–78</td>
<td>44</td>
<td>A</td>
</tr>
<tr>
<td>Wrenn et al (1991)19</td>
<td>32</td>
<td>35</td>
<td>P</td>
<td>120 minutes</td>
<td>Adults</td>
<td>16 or older</td>
<td>34</td>
<td>A</td>
</tr>
<tr>
<td>Zainudin et al (1994)20</td>
<td>11</td>
<td>14</td>
<td>P</td>
<td>48 hours</td>
<td>Adults</td>
<td>18–60</td>
<td>No data</td>
<td>Severe asthma</td>
</tr>
<tr>
<td>Bien et al (1995)21</td>
<td>19</td>
<td>20</td>
<td>P</td>
<td>24 hours</td>
<td>Children</td>
<td>2–10</td>
<td>6</td>
<td>Excluded: ICU admission, use of systemic corticosteroids</td>
</tr>
<tr>
<td>Carter et al (1993)22</td>
<td>12</td>
<td>9</td>
<td>P</td>
<td>36 hours</td>
<td>Children</td>
<td>5–18</td>
<td>12</td>
<td>Failed albuterol</td>
</tr>
<tr>
<td>D’Avila et al (2008)23</td>
<td>30</td>
<td>30</td>
<td>P</td>
<td>60 minutes</td>
<td>Children</td>
<td>2–5</td>
<td>3</td>
<td>Failed albuterol and corticosteroids</td>
</tr>
<tr>
<td>DiGiulio et al (1993/1)24</td>
<td>16</td>
<td>13</td>
<td>P</td>
<td>35 hours</td>
<td>Children</td>
<td>2–16</td>
<td>7</td>
<td>Failed albuterol</td>
</tr>
<tr>
<td>Hambleton and Stone (1979)25</td>
<td>9</td>
<td>9</td>
<td>P</td>
<td>24 hours</td>
<td>Children</td>
<td>1.5–7</td>
<td>No data</td>
<td>Requiring intense hospital treatment</td>
</tr>
<tr>
<td>Ibrahim et al (1993/1)26</td>
<td>40</td>
<td>40</td>
<td>P</td>
<td>120 minutes</td>
<td>Children</td>
<td>No data</td>
<td>10</td>
<td>No bronchodilators in previous 12 hours</td>
</tr>
<tr>
<td>Ibrahim et al (1993/2)27</td>
<td>40</td>
<td>40</td>
<td>P</td>
<td>120 minutes</td>
<td>Children</td>
<td>No data</td>
<td>10</td>
<td>No bronchodilators in previous 12 hours</td>
</tr>
<tr>
<td>Needleman et al (1995)28</td>
<td>25</td>
<td>20</td>
<td>P</td>
<td>120 minutes</td>
<td>Children</td>
<td>2–18</td>
<td>8</td>
<td>Failed albuterol</td>
</tr>
<tr>
<td>Nuhoglu et al (1998)29</td>
<td>17</td>
<td>19</td>
<td>P</td>
<td>24 hours</td>
<td>Children</td>
<td>2–16</td>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>Ongoing dose</td>
<td>Control</td>
<td>Bolus dose</td>
<td>Ongoing dose</td>
<td>Background medication</td>
<td>Gender</td>
<td>Country</td>
<td>Blinding</td>
<td>Funding</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
<td>--------------</td>
<td>-----------------------</td>
<td>--------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>250 mg</td>
<td>Montelukast</td>
<td>None</td>
<td>14 mg</td>
<td>Inhaled beta-agonist or oxygen</td>
<td>Mixed</td>
<td>Multicenter</td>
<td>Unclear</td>
<td>Industry</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Salbutamol (neb), hydrocortisone (IV)</td>
<td>Mixed</td>
<td>Uruguay</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Epinephrine (sc)</td>
<td>0.3 mL ×3</td>
<td>None</td>
<td>Oxygen</td>
<td>Mixed</td>
<td>USA</td>
<td>Unclear</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Isoproterenol (neb)</td>
<td>2.5 mg ×3</td>
<td>None</td>
<td>Oxygen</td>
<td>Mixed</td>
<td>USA</td>
<td>Unclear</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>To achieve 10–20 µg/mL</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Prednisone (oral), albuterol (neb), oxygen</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>Industry/ university</td>
</tr>
<tr>
<td>None</td>
<td>Salbutamol</td>
<td>250 µg</td>
<td>None</td>
<td>None</td>
<td>Mixed</td>
<td>India</td>
<td>Unclear</td>
<td>Hospital</td>
</tr>
<tr>
<td>None</td>
<td>Terbutaline</td>
<td>250 µg</td>
<td>None</td>
<td>None</td>
<td>Mixed</td>
<td>India</td>
<td>Unclear</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.7 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Metaproterenol</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>None</td>
<td>Salbutamol IV</td>
<td>100 µg</td>
<td>None</td>
<td>Hydrocortisone (IV)</td>
<td>Mixed</td>
<td>Australia</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Methylprednisolone (IV), metaproterenol (neb)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University</td>
</tr>
<tr>
<td>0.6–0.9 mg/kg/h</td>
<td>No infusion</td>
<td>N/A</td>
<td>N/A</td>
<td>Salbutamol (neb), hydrocortisone (IV), oral prednisolone, oxygen</td>
<td>Mixed</td>
<td>Malaysia</td>
<td>Not blind</td>
<td>University</td>
</tr>
<tr>
<td>To achieve 10–20 µg/mL</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Albuterol (neb), methylprednisolone (IV), oxygen</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>I mg/kg</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Albuterol (neb), methylprednisolone (IV), oxygen</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>None</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Prednisolone or prednisone I mg/kg, albuterol 150 µg/kg</td>
<td>Mixed</td>
<td>Brazil</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>To achieve 12–20 mg/L</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Methylprednisolone (IV), albuterol (neb)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.6 mg/kg/h</td>
<td>Salbutamol IV</td>
<td>4 µg/kg</td>
<td>0.6 µg/kg/h</td>
<td>Hydrocortisone (IV)</td>
<td>Mixed</td>
<td>UK</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>None</td>
<td>Adrenaline</td>
<td>0.01 mg/kg</td>
<td>None</td>
<td>None</td>
<td>Mixed</td>
<td>Sudan</td>
<td>Unclear</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>None</td>
<td>Salbutamol</td>
<td>0.15 mg/kg</td>
<td>None</td>
<td>None</td>
<td>Mixed</td>
<td>Sudan</td>
<td>Unclear</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.8–1.0 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Methylprednisolone (IV), albuterol (neb)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>I mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Methylprednisolone (IV), salbutamol</td>
<td>Mixed</td>
<td>Turkey</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
</tbody>
</table>
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 \((p=0.79)\).
<table>
<thead>
<tr>
<th>Ongoing dose</th>
<th>Control</th>
<th>Bolus dose</th>
<th>Ongoing dose</th>
<th>Background medication</th>
<th>Gender</th>
<th>Country</th>
<th>Blinding</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mg/kg/24 h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Epinephrine, hydrocortisone, oxygen, phenylephrine, isoproterenol, ipratropium</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.5–0.8 mg/kg/h</td>
<td>No infusion</td>
<td>N/A</td>
<td>N/A</td>
<td>Albuterol (neb), methylprednisolone (IV), ipratropium</td>
<td>Mixed</td>
<td>USA</td>
<td>Partly blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Salbutamol IV</td>
<td>15 µg/kg</td>
<td>None</td>
<td>Salbutamol (neb), ipratropium (neb)</td>
<td>Mixed</td>
<td>UK</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Magnesium sulfate</td>
<td>25 mg/kg</td>
<td>None</td>
<td>Salbutamol (neb), ipratropium (neb), budesonide, hydrocortisone</td>
<td>Mixed</td>
<td>India</td>
<td>Partly blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Terbutaline</td>
<td>10 µg/kg</td>
<td>0.1 µg/kg/min</td>
<td>Salbutamol (neb), ipratropium (neb), budesonide, hydrocortisone</td>
<td>Mixed</td>
<td>India</td>
<td>Partly blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>25 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Albuterol (neb), methylprednisolone (IV, oxygen)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.9 mg/kg/h</td>
<td>Ketamine</td>
<td>0.5 mg/kg</td>
<td>0.6 mg/kg/h</td>
<td>Salbutamol (neb), ipratropium (neb), hydrocortisone</td>
<td>Mixed</td>
<td>India</td>
<td>Partly blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>1.2 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Hydrocortisone (IV), fenoterol (neb)</td>
<td>Mixed</td>
<td>Brazil</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.6–1.0 mg/kg/h</td>
<td>Terbutaline</td>
<td>20 µg/kg</td>
<td>0.4 µg/kg/h</td>
<td>Methylprednisolone (IV), albuterol (neb)</td>
<td>Mixed</td>
<td>USA</td>
<td>Double blind</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.7–1.1 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Methylprednisolone (IV), salbutamol (neb), ipratropium bromide (neb)</td>
<td>Mixed</td>
<td>Australia</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
<tr>
<td>0.5 mg/kg/h</td>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>Hydrocortisone (IV), Salbutamol (neb)</td>
<td>Mixed</td>
<td>India</td>
<td>Unclear</td>
<td>University/ hospital</td>
</tr>
<tr>
<td>0.5 g over 1 h</td>
<td>Salbutamol IV</td>
<td>None</td>
<td>500 µg over 1 h</td>
<td>Hydrocortisone (IV), oxygen</td>
<td>Not stated</td>
<td>UK</td>
<td>Double blind</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

**Respiratory rate**

An increased respiratory rate is, like heart rate, a sign of an ongoing asthma exacerbation. 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 ($p=0.08$).
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).
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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appel and Shin (1981)W</td>
<td>0.9 0.45</td>
<td>1.26 0.52</td>
<td>12 23.0</td>
<td>-0.36 (-0.75, 0.03)</td>
</tr>
<tr>
<td>Fanta et al (1980)W</td>
<td>1.32 0.5</td>
<td>1.26 0.52</td>
<td>17 38.8</td>
<td>-0.04 (-0.33, 0.25)</td>
</tr>
<tr>
<td>Lindholm and Helander (1966/1)W</td>
<td>1.76 0.69</td>
<td>1.76 0.77</td>
<td>29 21.7</td>
<td>0.00 (-0.51, 0.41)</td>
</tr>
<tr>
<td>Rosser et al (1980)W</td>
<td>1.53 0.58</td>
<td>1.85 0.8</td>
<td>17 16 15.2</td>
<td>-0.32 (-0.80, 0.16)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>75 87 100</td>
<td>-0.15 (-0.33, 0.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 9.00, df = 3 (p = 0.045); I^2 = 90%

Test for overall effect: Z = 1.55 (p = 0.12)

Beta-2 agonists

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanta et al (1980)W</td>
<td>0.23 0.29</td>
<td>0.72 0.51</td>
<td>17 41</td>
<td>-0.49 (-0.70, -0.28)</td>
</tr>
<tr>
<td>Johnson et al (1979)W</td>
<td>0.93 0.35</td>
<td>0.79 0.27</td>
<td>19 20</td>
<td>0.14 (-0.06, 0.34)</td>
</tr>
<tr>
<td>Lindholm and Helander (1966/1)W</td>
<td>0.25 0.05</td>
<td>0.35 0.08</td>
<td>29 23</td>
<td>-0.10 (-0.14, -0.06)</td>
</tr>
<tr>
<td>Rosser et al (1980)W</td>
<td>1.53 0.58</td>
<td>2.11 0.66</td>
<td>15 19</td>
<td>0.001 (-0.05, 0.00)</td>
</tr>
<tr>
<td>Sharma et al (1984)W</td>
<td>0.17 0.09</td>
<td>0.52 0.24</td>
<td>5 10</td>
<td>0.35 (-0.52, -0.18)</td>
</tr>
<tr>
<td>Tribe et al (1979)W</td>
<td>0.8 0.31</td>
<td>1.04 0.55</td>
<td>3 11</td>
<td>0.00 (-0.61, 0.13)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>310 130 100</td>
<td>-0.20 (-0.34, -0.07)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 31.48, df = 6 (p < 0.0001); I^2 = 81%

Test for overall effect: Z = 3.04 (p = 0.002)

Leukotriene receptor antagonists

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0042338 (2007)W</td>
<td>0.06 0.16</td>
<td>0.05 0.16</td>
<td>31 100</td>
<td>0.01 (-0.07, 0.09)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>31 100</td>
<td>0.01 (-0.07, 0.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.24 (p = 0.81)

Placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindholm and Helander (1966/3)W</td>
<td>0.25 0.05</td>
<td>0.04 0.04</td>
<td>29 19</td>
<td>0.21 (0.18, 0.24)</td>
</tr>
<tr>
<td>Montserrat et al (1995)W</td>
<td>1.43 0.07</td>
<td>1.19 0.28</td>
<td>6 6</td>
<td>0.24 (-0.36, 0.84)</td>
</tr>
<tr>
<td>Siegel et al (1980)</td>
<td>0.28 0.45</td>
<td>0.29 3.58</td>
<td>20 0.8</td>
<td>-0.01 (-1.59, 1.57)</td>
</tr>
<tr>
<td>Wenn et al (1991)W</td>
<td>1.48 0.31</td>
<td>1.43 0.11</td>
<td>35 36</td>
<td>0.05 (-0.00, 0.10)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>87 100</td>
<td>0.14 (-0.01, 0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 30.99, df = 3 (p < 0.0001); I^2 = 90%

Test for overall effect: Z = 1.82 (p = 0.07)

Test for subgroup differences: $\chi^2 = 14.17, df = 3 (p = 0.003); I^2 > 78.8%

B

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appel and Shin (1981)W</td>
<td>0.9 0.45</td>
<td>1.26 0.52</td>
<td>12 4.4</td>
<td>-0.36 (-0.75, 0.03)</td>
</tr>
<tr>
<td>Fanta et al (1980)W</td>
<td>1.22 0.5</td>
<td>1.26 0.52</td>
<td>9 38</td>
<td>-0.04 (-0.41, 0.33)</td>
</tr>
<tr>
<td>Fanta et al (1986)W</td>
<td>0.23 0.29</td>
<td>0.72 0.51</td>
<td>9 41</td>
<td>-0.49 (-0.74, -0.24)</td>
</tr>
<tr>
<td>Johnson et al (1979)W</td>
<td>0.93 0.35</td>
<td>0.79 0.27</td>
<td>19 20</td>
<td>0.14 (-0.06, 0.34)</td>
</tr>
<tr>
<td>Lindholm and Helander (1966/1)W</td>
<td>1.76 0.69</td>
<td>1.76 0.77</td>
<td>15 12</td>
<td>0.00 (-0.56, 0.56)</td>
</tr>
<tr>
<td>Lindholm and Helander (1966/2)W</td>
<td>0.25 0.05</td>
<td>0.35 0.08</td>
<td>15 23</td>
<td>-0.10 (-0.14, -0.06)</td>
</tr>
<tr>
<td>NCT0042338 (2007)W</td>
<td>0.06 0.16</td>
<td>0.05 0.16</td>
<td>31 30</td>
<td>0.01 (-0.07, 0.09)</td>
</tr>
<tr>
<td>Rosser et al (1980)W</td>
<td>1.53 0.58</td>
<td>1.85 0.8</td>
<td>9 38</td>
<td>-0.32 (-0.78, 0.14)</td>
</tr>
<tr>
<td>Rosser et al (1980)W</td>
<td>1.53 0.58</td>
<td>2.11 0.66</td>
<td>9 15</td>
<td>-0.58 (-1.09, -0.07)</td>
</tr>
<tr>
<td>Sharma et al (1984)W</td>
<td>0.17 0.09</td>
<td>0.28 0.11</td>
<td>5 10</td>
<td>-0.11 (-0.21, -0.01)</td>
</tr>
<tr>
<td>Sharma et al (1984)W</td>
<td>0.17 0.09</td>
<td>0.52 0.24</td>
<td>5 10</td>
<td>-0.35 (-0.52, -0.18)</td>
</tr>
<tr>
<td>Tribe et al (1979)W</td>
<td>0.8 0.31</td>
<td>1.04 0.56</td>
<td>3 11</td>
<td>-0.24 (-0.62, 0.14)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>150 260 100</td>
<td>-0.15 (-0.25, -0.06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 37.91, df = 11 (p < 0.0001); I^2 = 87%

Test for overall effect: Z = 2.30 (p = 0.001)

Placebo/or drug

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean SD</th>
<th>Control Mean SD</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindholm and Helander (1966/3)W</td>
<td>0.25 0.05</td>
<td>0.04 0.04</td>
<td>29 19</td>
<td>0.21 (0.18, 0.24)</td>
</tr>
<tr>
<td>Montserrat et al (1995)W</td>
<td>1.43 0.07</td>
<td>1.19 0.28</td>
<td>6 6</td>
<td>0.24 (-0.36, 0.84)</td>
</tr>
<tr>
<td>Siegel et al (1980)</td>
<td>0.28 0.45</td>
<td>0.29 3.58</td>
<td>20 0.8</td>
<td>-0.01 (-1.59, 1.57)</td>
</tr>
<tr>
<td>Wenn et al (1991)W</td>
<td>1.48 0.31</td>
<td>1.43 0.11</td>
<td>35 36</td>
<td>0.05 (-0.00, 0.10)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>87 100</td>
<td>0.14 (-0.01, 0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 30.99, df = 3 (p = 0.0001); I^2 = 90%

Test for overall effect: Z = 1.82 (p = 0.07)

Test for subgroup differences: $\chi^2 = 10.65, df = 1 (p = 0.001); I^2 > 90.6%

Figure 3 (Continued)
**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).

**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.
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).
Data are given as the mean difference (95% CI).

**Figure 6** Meta-analysis of respiratory rate (breaths per minute) following intravenous theophylline infusion.

**Note:** Data are given as the mean difference (95% CI).

**A**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline</th>
<th>Control</th>
<th>Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anantharaman (1993/1)</td>
<td>23.5 ± 5.4</td>
<td>14</td>
<td>22.9 ± 6.6</td>
<td>27</td>
</tr>
<tr>
<td>Anantharaman (1995/2)</td>
<td>23.5 ± 5.4</td>
<td>14</td>
<td>18.5 ± 4.1</td>
<td>17</td>
</tr>
<tr>
<td>D’Avila et al (2008)</td>
<td>43.37 ± 8.33</td>
<td>30</td>
<td>41.03 ± 8.51</td>
<td>30</td>
</tr>
<tr>
<td>Hamblen and Stone (1979)</td>
<td>25.42 ± 8.19</td>
<td>9</td>
<td>47.26 ± 7.54</td>
<td>9</td>
</tr>
<tr>
<td>Ream et al (2001)</td>
<td>34.75 ± 9.5</td>
<td>20</td>
<td>35.09 ± 15.03</td>
<td>21</td>
</tr>
<tr>
<td>Singh et al (2014/1)</td>
<td>−11 ± 10</td>
<td>17</td>
<td>−6 ± 4</td>
<td>34</td>
</tr>
<tr>
<td>Singh et al (2014/2)</td>
<td>−11 ± 10</td>
<td>17</td>
<td>−10 ± 7</td>
<td>33</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>121</td>
<td>171</td>
<td>100</td>
<td>2.15 (−0.26, 4.55)</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight (%)</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anantharaman (1993/1)</td>
<td>12 ± 27</td>
<td>4</td>
<td>27</td>
<td>15.3</td>
</tr>
<tr>
<td>Anantharaman (1995/2)</td>
<td>12 ± 27</td>
<td>6</td>
<td>17</td>
<td>16.0</td>
</tr>
<tr>
<td>D’Avila et al (2008)</td>
<td>5 ± 30</td>
<td>9</td>
<td>30</td>
<td>16.1</td>
</tr>
<tr>
<td>Veira et al (2009)</td>
<td>10 ± 24</td>
<td>12</td>
<td>19</td>
<td>16.1</td>
</tr>
<tr>
<td>Wrenn et al (1991)</td>
<td>2 ± 32</td>
<td>7</td>
<td>35</td>
<td>11.8</td>
</tr>
<tr>
<td>Yang and South (1998)</td>
<td>30 ± 81</td>
<td>41</td>
<td>82</td>
<td>24.6</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>221</td>
<td>210</td>
<td>100</td>
<td>0.77 (0.37, 1.61)</td>
</tr>
</tbody>
</table>

**C**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleridge et al (1993)</td>
<td>4.5 ± 2.19</td>
<td>30</td>
<td>4.5 ± 1.08</td>
<td>29</td>
</tr>
<tr>
<td>D’Avila et al (2008)</td>
<td>1.46 ± 0.37</td>
<td>30</td>
<td>1.68 ± 0.35</td>
<td>30</td>
</tr>
<tr>
<td>Needelman et al (1995)</td>
<td>2.17 ± 1.33</td>
<td>25</td>
<td>2 ± 1.13</td>
<td>20</td>
</tr>
<tr>
<td>Ream et al (2001)</td>
<td>4.7 ± 1.34</td>
<td>20</td>
<td>5.1 ± 1.83</td>
<td>21</td>
</tr>
<tr>
<td>Roberts et al (2003)</td>
<td>2.39 ± 1.81</td>
<td>26</td>
<td>3.56 ± 2.33</td>
<td>18</td>
</tr>
<tr>
<td>Self et al (1990)</td>
<td>1.78 ± 0.73</td>
<td>21</td>
<td>1.95 ± 0.81</td>
<td>18</td>
</tr>
<tr>
<td>Strauss et al (1994)</td>
<td>2.56 ± 1.5</td>
<td>14</td>
<td>2.33 ± 1.3</td>
<td>17</td>
</tr>
<tr>
<td>Taiwai et al (2016)</td>
<td>3.25 ± 1.07</td>
<td>24</td>
<td>3.5 ± 1.28</td>
<td>24</td>
</tr>
<tr>
<td>Wheeler et al (2005)</td>
<td>4.4 ± 8.29</td>
<td>13</td>
<td>4.9 ± 12</td>
<td>16</td>
</tr>
<tr>
<td>Wrenn et al (1991)</td>
<td>8.8 ± 1.38</td>
<td>32</td>
<td>9.69 ± 1.56</td>
<td>35</td>
</tr>
<tr>
<td>Yang and South (1998)</td>
<td>2.69 ± 2</td>
<td>81</td>
<td>2.87 ± 2.37</td>
<td>82</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>316</td>
<td>310</td>
<td>100</td>
<td>−0.23 (−0.37, −0.08)</td>
</tr>
</tbody>
</table>

**Figure 7** (Continued)
or oxygen alone, theophylline was inferior to subcutaneous epinephrine,15,19,30 and nebulized iso-proterenol.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 montelukast28 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...
Intravenous theophylline in acute asthma

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.

### Table 9: Subgroup meta-analysis of symptom scores following intravenous theophylline by age group.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Std mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anantharaman (1993)(^7)</td>
<td>-3.7 (2.6) 14 1.9 1.8 27 6.3</td>
<td>-0.84 (-1.51, -0.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anantharaman (1993)(^7)</td>
<td>-3.7 (2.6) 14 2.2 1.9 17 6.0</td>
<td>-0.65 (-1.38, 0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self et al (1990)(^7)</td>
<td>-4.85 (0.23) 21 -4.63 0.38 18 6.5</td>
<td>-0.70 (-1.35, -0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegel et al (1989)(^7)</td>
<td>1.84 (1.34) 20 0.78 1.11 20 6.8</td>
<td>0.84 (0.19, 1.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>69 82 23.3</td>
<td>-0.33 (-1.13, 0.46)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \(z^2=0.54; \gamma^2=16.73, df=3 (p=0.0008); I^2=82\%

Test for overall effect: \(Z=0.82 (p=0.41)\)

### Table 10: Subgroup meta-analysis of FEV1 following intravenous theophylline by blinding of study participants.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Std mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appel and Shim (1981)(^7)</td>
<td>0.9 (0.45) 12 1.26 0.52 12 4.5</td>
<td>-0.38 (-0.75, 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindholm and Helander (1966)(^7)</td>
<td>0.25 (0.05) 10 0.48 0.08 21 9.0</td>
<td>-0.23 (-0.28, -0.18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindholm and Helander (1966)(^7)</td>
<td>0.25 (0.05) 10 0.35 0.08 23 9.0</td>
<td>-0.10 (-0.15, -0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montesert et al (1999)(^7)</td>
<td>1.43 (0.7) 6 1.19 0.28 6 2.6</td>
<td>0.24 (-0.36, 0.84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegel et al (1985)(^7)</td>
<td>0.28 (0.45) 20 0.29 3.58 20 6.5</td>
<td>-0.01 (-1.59, 1.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tribe et al (1976)(^7)</td>
<td>0.8 (0.31) 12 1.04 0.55 11 4.7</td>
<td>-0.24 (-0.61, 0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wenn et al (1991)(^7)</td>
<td>1.48 (0.1) 32 1.43 0.11 35 8.9</td>
<td>0.05 (-0.00, 0.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>112 147 48.2</td>
<td>-0.06 (-0.23, 0.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \(z^2=0.04; \gamma^2=254.64, df=7 (p=0.00001); I^2=97\%

Test for overall effect: Z=0.66 (p=0.51)

Unblinded/Not clear

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aminophylline Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Std mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femi-Pearse et al (1977)(^7)</td>
<td>0.23 (0.29) 9 0.57 0.49 38 6.5</td>
<td>-0.34 (-0.59, -0.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femi-Pearse et al (1977)(^7)</td>
<td>0.23 (0.29) 9 0.72 0.51 41 6.5</td>
<td>-0.49 (-0.74, -0.24)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Johnson et al (1979)(^7)</td>
<td>0.93 (0.35) 19 0.79 0.27 20 7.2</td>
<td>0.14 (-0.06, 0.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00442338 (2007)(^7)</td>
<td>0.06 (0.16) 31 0.05 0.16 30 8.7</td>
<td>0.01 (-0.07, 0.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossing et al (1980)(^7)</td>
<td>1.53 (0.82) 9 1.85 0.8 16 2.3</td>
<td>-0.32 (-0.98, 0.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossing et al (1980)(^7)</td>
<td>1.53 (0.29) 9 2.11 0.66 15 4.6</td>
<td>-0.58 (-0.96, -0.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma et al (1984)(^7)</td>
<td>0.17 (0.09) 5 0.28 0.11 10 8.5</td>
<td>-0.11 (-0.21, -0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma et al (1984)(^7)</td>
<td>0.17 (0.09) 5 0.52 0.24 10 7.6</td>
<td>-0.35 (-0.52, -0.18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>96 180 51.8</td>
<td>-0.22 (-0.37, -0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \(z^2=0.04; \gamma^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: \(z^2=310.51, df=15 (p=0.00001); I^2=95\%

Test for overall effect: Z=2.36 (p=0.01)

Test for subgroup differences: \(z^2=1.78, df=1 (p=0.18); I^2=43.9\%

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**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).

**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).
Figure I (Continued)
### Data are given as odds ratios (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).
In contrast, a more recent meta-analysis analyzed trials directly comparing IV beta-2 agonists with IV theophylline in the treatment of acute asthma. 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. 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. 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. 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.

**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.
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.

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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.

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