

# Clinical efficacy of farcosolvin syrup (ambroxol–theophylline–guaiphenesin mixture) in the treatment of acute exacerbation of chronic bronchitis

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**Background:** Acute exacerbations of chronic bronchitis (AECB) are defined as recurrent attacks of worsening bronchial inflammation that are marked by an increase in the volume of daily sputum produced, a change in color of the expectorated sputum, and worsening dyspnea. Farcosolvin® (Pharco Pharmaceuticals, Alexandria, Egypt) is a mixture of ambroxol (15 mg); theophylline (50 mg); and guaiphenesin (30 mg), per 5 mL syrup.

**Objective:** To test the clinical efficacy of Farcosolvin in the treatment of AECB in a randomized, single-blinded, controlled study design.

**Patients and methods:** One hundred patients with AECB were randomized to either Farcosolvin or guaiphenesin treatment groups, in addition to the standard medical treatment for their cases. Baseline clinical symptomatology of breathlessness, cough, and sputum severity scoring were compared before and after 3 and 7 days of treatment in both groups and the differences compared between groups. Changes in perceived improvement were also compared between groups using the Clinical Global Impression of Improvement or Change Scale (CGIC).

**Results:** There were statistically significant improvements in breathlessness and cough scores in both groups (pretreatment versus posttreatment at day 3 and at day 7;  $P < 0.05$ ). There were highly statistically significant differences between groups in improvement in breathlessness and cough scores, after 3 and 7 days treatment, in favor of the Farcosolvin treatment group ( $P < 0.001$ ). Out of 50 patients, 48 (96%) in the Farcosolvin-treated group rated their improvement on the CGIC scale as “much” and “very much” improved, while only 41 patients (82%) reported such a degree of improvement in the control group. The difference was statistically significant ( $P < 0.05$ ).

**Conclusion:** We concluded from our study that Farcosolvin syrup might be safe and effective in improving symptoms in cases of acute exacerbation of chronic bronchitis.

**Keywords:** acute exacerbation of chronic bronchitis, ambroxol, theophylline

## Introduction

Chronic bronchitis (CB) is a progressive disease characterized by chronic increase in the production of mucous. It is defined as the presence of a chronic cough with sputum production for at least three months, in each of two consecutive years, after other causes of cough, such as tuberculosis and lung cancer, have been eliminated.<sup>1,2</sup>

Acute exacerbations of chronic bronchitis (AECB) are defined as recurrent attacks of worsening bronchial inflammation that occur on average 1.5–3 times a year, and are superimposed on baseline CB.<sup>1</sup> These exacerbations are marked by an increase in the volume of daily sputum produced; a change in color of the expectorated sputum (ie, darker, more yellow, more green); and worsening dyspnea.

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Ambroxol is a metabolite of bromhexine and is widely used as a mucolytic. It also induces the synthesis of surfactant in lung alveolar type II cells. By this mechanism, it decreases the work and effort of breathing and can improve respiratory symptoms. It has also been proved to have antioxidant and anti-inflammatory activities.<sup>3</sup>

It became evident that theophylline can exert anti-inflammatory and immunomodulating actions at lower plasma concentrations than those required for bronchodilation.<sup>4</sup> Theophylline inhibits the production and release of pro-inflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$ . The production of the anti-inflammatory cytokine IL-10 is increased.

The guidelines of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) currently recommend consideration of the addition of an oral or intravenous methylxanthine to aerosolized bronchodilators, for management of severe exacerbations of chronic obstructive pulmonary disease (COPD).<sup>5</sup>

The effect of theophylline and ambroxol, when combined together, has been proved to give more than additive effects in improving the mucociliary clearance and increasing the release of respiratory surfactants.<sup>6,7</sup>

Guaiphenesin is a commonly used 'over-the-counter' drug for productive cough. It is reported to increase the volume and reduce the viscosity of tenacious sputum. An US Food and Drug Administration (FDA) review of preparations available 'over-the-counter' concluded that guaiphenesin was an effective expectorant.<sup>8</sup>

Farcosolvin® (Pharco Pharmaceuticals, Alexandria, Egypt) is a cough mixture of ambroxol (15 mg); theophylline (50 mg); guaiphenesin (30 mg), per 5 mL syrup. The purpose of this study is to test the clinical efficacy of Farcosolvin in the treatment of acute exacerbation of chronic bronchitis.

## Methods

### Study design

A pragmatic, randomized, single-blinded, comparative study, designed to determine the efficacy of Farcosolvin syrup in reducing clinical symptom scores under conditions that reflect the usual medical care for AECB (defined as worsening of the baseline symptoms [cough, sputum, and breathlessness] of CB), was conducted.

### Patients

To detect a difference in the mean severity of cough and expectoration score between the two treatment groups of

4 points with a standard deviation (SD) of 5; a *P* value < 0.05; and an approximate power of 90%, we calculated the minimal needed sample size to be 68 patients. One hundred eligible patients were included in the study analysis according to the following criteria defined below.

### Inclusion criteria

Patients were eligible for inclusion in the study if they were a male or female aged  $\geq 45$  years, with a history of smoking and a physician's diagnosis of AECB. The diagnosis of CB was based on the history of cough and expectoration on most days during a period of at least three consecutive months for two consecutive years.<sup>1</sup> AECB was classified as type I according to Anthonisen et al<sup>9</sup> when it met all three of the following criteria: increases in amount of sputum; purulence of sputum; and increasing dyspnea. AECB was classified as type II if it met two of the above three criteria and type III if it met only one criterion.<sup>9</sup>

### Exclusion criteria

Patients were excluded if they had any of the following conditions: heart failure or multiple organ dysfunctions: bronchiectasis; bronchial carcinoma; interstitial lung disease; pneumonia; inability to comply with the study procedures because of dementia; or if they had any other medical problems that in the opinion of the investigator would interfere with the conduct of study.

### Protocol

The study was conducted at Mabarah Hospital and Green Clinics and was approved by the Ethics Committee and all participants provided written informed consent. All consecutive patients presenting to both centers who met the eligibility criteria between November 2005 and October 2006 were allocated sequential numbers as they entered the study.

Patients were randomized into an experimental group, who were treated with Farcosolvin (5 mL syrup three times daily); and a control group, who were treated with a generic guaiphenesin syrup (100 mg per 5 mL three times daily). A block randomization technique was used to ensure that equal numbers were allocated to each group. Treatment was continued for 7 days or until clinical remission, whichever occurred first. In addition to Farcosolvin or guaiphenesin, all patients received standard treatment for their exacerbation as specified by their condition and the guidelines. This was antibiotic (ciprofloxacin 500 mg, twice daily, for 7 days); inhaled or nebulized bronchodilators in the form of salbutamol

(two inhaler puffs or 5 mg in 2 mL saline nebulized); and/or ipratropium 0.5 mg as needed, or up to four times daily. Mucolytics, theophylline and expectorants were not permitted during the trial, except as in the protocol.

Breathlessness was measured on a 7-point Likert scale (Appendix 1). Severity of cough and sputum clearance was measured using the Modified Questionnaire for Ease of Cough and Sputum Clearance.<sup>10</sup> At the end of one week treatment, all patients were asked to grade their impression of improvement or change in their condition using the Clinical Global Impression of Improvement or Change Scale (CGIC),<sup>11</sup> which is a 7-point rated scale where 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worsened; 6 = much worsened; and 7 = very much worsened. Finally, all subjects were interrogated about any possible adverse effects.

## Statistical analysis

The two treatment groups were compared at baseline and at 3 and 7 days, using tests for nonparametric data (Friedman, Kruskal–Wallis and Fisher's exact tests). All tests were two-tailed and a 5% significance level was maintained throughout these analyses. The analyses were carried out using SPSS software (Version 12; SPSS Inc. Chicago, IL, USA).

## Results

The analysis included 100 patients with AECB grouped into two equal sized groups: an experimental group (50 patients), who were treated with Farcosolvin 5 ml syrup three times daily; and a control group (the remaining 50), who were given guaiphenesin syrup 3 times daily.

The two groups were almost matched at baseline in terms of age, smoking history, lung function, oxygen saturation, severity of cough, and breathlessness (Table 1). Also, there was no significant difference between both groups for the concurrent medications they received during the study. All patients needed to be treated with antibiotic and bronchodilators were given on an as-needed basis, except for four patients in the Farcosolvin group and 6 in the Guaiphenesin control group who required regular inhaler use. One patient needed to be given a budesonide dry powder inhaler at doses of 200 µg twice daily at day 3 due to worsening dyspnea.

The effects of treatment on breathlessness scores and cough scores were analyzed by nonparametric statistical methods as the distribution was found by Kolmogorov Smirnov to be not normal ( $P < 0.001$ ).

There was a statistically significant improvement of breathlessness and cough scoring in both groups when compared before and after treatment at day 3 and at day 7 (Tables 2 and 3), using a nonparametric related samples Friedman test ( $P < 0.05$ ).

There was a highly statistically significant difference in improvement in breathlessness score, as well as cough score, in favor of Farcosolvin treatment when the two groups were compared using an independent samples Kruskal Wallis test (Tables 4 and 5).

Out of 50 patients, 48 (96%) in the Farcosolvin treated group rated their improvement on the CGIC scale as “much” and “very much” improved, while only 41 patients (82%) reported the same degree of improvement in the control group. The difference was statistically significant ( $P < 0.05$ ).

Seven subjects reported adverse events in each group, including nausea and heartburn. Five of the subjects treated with Farcosolvin reported nausea compared with four of the subjects treated with guaiphenesin. There were no serious adverse events.

## Discussion

To our knowledge, this is the first study to address the effects of a mixture of theophylline, ambroxol and guaiphenesin in relation to clinical manifestations and severity of symptoms of AECB.

This study showed significant improvement in breathlessness and severity of cough scores in patients treated with the Farcosolvin mixture than those treated with guaiphenesin alone. Both ambroxol and theophylline have been extensively studied in the treatment of CB. Ambroxol has been tested in many large multicenter, randomized, double blind controlled studies in cases of CB. The results confirm the previously seen improvement in symptomatology and the significant reduction in number and severity of exacerbations in groups

**Table 1** Baseline data for each group

	Farcosolvin	Guaiphenesin
Gender: male/female	33/17	35/15
Age (years $\pm$ SD)	62.4 $\pm$ 6.7	61.7 $\pm$ 7.2
Breathlessness score (mean $\pm$ SD)	4.2 $\pm$ 1.0	4.0 $\pm$ 0.9
Breathlessness score (median)	4	4
Cough score (mean $\pm$ SD)	16.0 $\pm$ 1.8	15.8 $\pm$ 1.7
Cough score (median)	16	16
AECB classification frequency (Type I/II/III)	44/6/0	42/8/0
FEV <sub>1</sub> (% of predicted $\pm$ SD)	66 $\pm$ 11	68 $\pm$ 12
O <sub>2</sub> saturation (mean $\pm$ SD)	90.1 $\pm$ 4.2	90.3 $\pm$ 3.6

**Abbreviations:** AECB, acute exacerbations of chronic bronchitis; FEV<sub>1</sub>, forced expiratory volume in 1 second.

**Table 2** Related samples Friedman test for breathlessness scoring in each group

	Measure	N	Median
Farcosolvin	Pretreatment breathlessness score	50	4
	Breathlessness score at day 3	50	2
	Breathlessness score at day 7	50	1
Guaiphenesin	Pretreatment breathlessness score	50	4
	Breathlessness score at day 3	50	3
	Breathlessness score at day 7	50	2

**Table 3** Related samples Friedman test for cough and sputum scoring in each group

	Measure	N	Median
Farcosolvin	Pretreatment cough score	50	16
	Cough score at day 3	50	10
	Cough score at day 7	50	8
Guaiphenesin	Pretreatment cough score	50	16
	Cough score at day 3	50	13
	Cough score at day 7	50	12

**Table 4** Comparison of the effect of Farcosolvin versus Guaiphenesin (control) on breathlessness scoring by Kruskal–Wallis test

	Group	N	Mean rank	Chi square	P-value
Pretreatment breathlessness score	Farcosolvin	50	53.98	1.6	0.206
	Control	50	47.02		
	Total	100			
Breathlessness score at day 3	Farcosolvin	50	39.33	16.8	<0.001
	Control	50	61.67		
	Total	100			
Breathlessness score at day 7	Farcosolvin	50	38.99	18.6	<0.001
	Control	50	62.01		
	Total	100			

**Table 5** Comparison of the effect of Farcosolvin versus Guaiphenesin (control) on cough scoring by Kruskal–Wallis test

	Group	N	Mean rank	Chi square	P-value
Pretreatment cough and sputum score	Farcosolvin	50	51.91	0.243	0.622
	Control	50	49.09		
	Total	100			
Cough and sputum score at day 3	Farcosolvin	50	32.83	37.724	<0.001
	Control	50	68.17		
	Total	100			
Cough and sputum score at day 7	Farcosolvin	50	29.26	54.252	<0.001
	Control	50	71.74		
	Total	100			

treated with ambroxol versus placebo.<sup>12–14</sup> In an open, long-term multicenter study including 5635 patients, ambroxol was effective and well-tolerated for the prophylaxis of exacerbations of chronic bronchitis.<sup>2</sup>

Positive effects have been seen with the use of ambroxol in patients with early hypersecretory CB, including improvement in coughing; dyspnea; color and consistency of sputum; and ease of expectoration, when compared to a control ( $P < 0.05$ ).<sup>13</sup>

Theophylline has also been proven effective in cases of CB and COPD.<sup>4</sup> The accumulated evidence has led theophylline to be recommended as a treatment in addition to aerosolised bronchodilators for severe exacerbations of COPD, in the GOLD guidelines.<sup>5</sup>

The combination of theophylline plus ambroxol has been proven to give more than additive effects in mucociliary clearance and increasing the release of respiratory surfactants.<sup>6,7</sup> This was the basis of our study for the efficacy of the triple mixture of a theophylline, ambroxol, plus an expectorant, in cases with AECB, when sputum amount, content and viscosity changes added to compromised mucociliary clearance and surfactant release are among the factors leading to worsening of symptoms and general condition of patients. Our results, to some extent, can support our assumption that this mixture can be helpful in such patients through working against these factors.

## Conclusion

We concluded from our study that Farcosolvin syrup might be safe and effective in improving symptoms in cases of AECB.

## Disclosure

The authors report no conflicts of interest in this work.

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## Appendices

### Appendix 1 7-point Likert scale for breathlessness

7	Extremely short of breath
6	Very short of breath
5	Quite a bit short of breath
4	Moderate shortness of breath
3	Some shortness of breath
2	A little shortness of breath
1	Not at all short of breath

### Appendix 2 Modified questionnaire for ease of cough and sputum clearance (25-point scale)

#### Cough episodes: frequency

How frequently are you coughing today?

1. **none:** unaware of coughing
2. **rare:** cough now and then
3. **occasional:** less than hourly
4. **frequent:** one or more times an hour
5. **almost constant:** never free of cough or feeling free of the need to cough

How frequently were you coughing last night?

1. **none:** unaware of coughing
2. **rare:** cough in the morning but I wasn't woken from sleep
3. **occasional:** woke a few times but I fell back asleep right away
4. **frequent:** woken many times through the night with fits of coughing
5. **almost constant:** up all night-long with coughing

#### Cough episodes: severity on arising and throughout the day

How severe were your cough episodes on a typical day during the past week?

1. **none:** unaware of coughing
2. **mild:** didn't interfere with usual morning or daily activity
3. **moderate:** must stop activity during coughing episodes
4. **marked:** must stop activity during – and for a brief period after – coughing episodes
5. **severe:** stops all activity for some time and is exhausting; can be accompanied by dizziness, headache, or pain

#### Ease of bringing up sputum during the day

How easy is it to cough up sputum when you cough today?

1. **none:** unaware of coughing at all
2. **easy:** sputum comes up without difficulty after only one or two coughs
3. **somewhat difficult:** most of the sputum comes up but only after several hard coughs
4. **very difficult:** some sputum comes up after hard coughing but there is the feeling that most is still sticking down there
5. **impossible:** there is sputum down there but no matter how hard the coughing nothing comes up

#### Chest discomfort: tightness and/or congestion on arising and throughout the day

How much chest tightness or discomfort do you have today?

1. **none:** unaware of any discomfort
2. **mild:** noticeable now and then but is not bothersome and passes quickly; doesn't limit activity
3. **moderate:** noticeable during light activity, such as walking one block, or up one flight of stairs
4. **marked:** noticeable while washing or dressing in the morning
5. **severe:** almost constant and limits all activity; present even while resting

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