Oral Purified Bacterial Extracts in Chronic Bronchitis and COPD*
Systematic Review

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Background: Oral lyophilized extracts of bacteria species have been used since the early 1970s to improve symptoms and to prevent exacerbations in COPD patients. The value of these treatments, which are thought to be immunomodulating, is poorly understood. Our aim was to quantify the efficacy of oral bacteria extracts in patients with chronic bronchitis and COPD.

Design: Systematic review of randomized trials.

Data sources: Electronic databases, bibliographies, and contact with authors and manufacturers.

Review methods: Randomized comparisons of oral purified bacterial (active) extracts with placebo or no treatment (control) were selected. Meta-analyses were performed using fixed and random-effects models, and the results were expressed as relative risk (RR), odds ratio (OR), number needed to treat for one to benefit (NNTB), or number needed to treat for one to be harmed (NNTH), with 95% confidence interval (CI).

Results: Thirteen trials (1,971 patients), most of which were of low quality, tested OM-85BV (Broncho-Vaxom; OM Pharma; Geneva, Switzerland), LW-50020 (Luivac; ALTANA Pharma; Bad Homburg, Germany), or SL-04. Two trials (731 patients) had appropriate methodologies and reported on exacerbations. The RR in favor of the oral bacterial extract (active) was 0.83 (95% CI, 0.55 to 1.25), and the NNTH was 15.4 (95% CI, 5.5 to ¥; NNTH, 27.5). Five trials (591 patients) reported on observer-assessed improvement of symptoms RR in favor of active extracts was 0.57 (95% CI, 0.49 to 0.66), and the NNTH was 4 (95% CI, 2.8 to 5.4). Two trials (n = 344), reported on patient-assessed improvement (RR, 0.44; 95% CI, 0.31 to 0.61) [NNTH, 4; 95% CI, 3.0 to 5.9]. In two trials (163 patients), the average duration of an exacerbation was shorter with the active extracts (weighted mean difference, $2.7 days; 95% CI, $3.5 to $1.8). Itching or cutaneous eruptions was reported in 3.3% of patients (four trials; 802 patients) who received active extracts compared with 1.0% of control subjects (OR, 2.94 95% CI, 1.12 to 7.69) [NNTH, 50; 95% CI, 14 to 161]. Urologic problems (two trials; 671 patients) were reported in 8% of patients who received active extracts compared with 3.0% of control subjects (OR, 2.62; 95% CI, 1.35 to 5.11) [NNTH, 22; 95% CI, 10 to 61].

Conclusions: Oral purified bacterial extracts improve symptoms in patients with chronic bronchitis and COPD. There is not enough evidence to suggest that they prevent exacerbations. Cutaneous and urologic adverse effects are common. (CHEST 2004; 126:1645–1655)

Key words: bronchitis; COPD; exacerbation; immunotherapy; LW-50020; meta-analysis; OM-85 BV; SL-04; systematic review

Abbreviations: CI = confidence interval; NNTB = number needed to treat for one to benefit; NNTH = number needed to treat for one to be harmed; OR = odds ratio; RR = relative risk; WMD = weighted mean difference

Acute exacerbation of respiratory symptoms is a common complication in patients with chronic bronchitis and COPD. Exacerbations are associated with significant morbidity, mortality,1–3 and costs. In the United States, the annual direct health-care cost of acute COPD exacerbations has been estimated at $18 billion (US dollars),4 and in an average UK Health Authority with a population of 250,000, there are 200 general physician’s consultations and 680 hospital admissions for acute exacerbations per year.5
Strategies that reduce the frequency of acute exacerbations and their severity have clinical, public health, and economic implications. Smoking cessation, vaccination against influenza and pneumococcal pneumonia, antibiotic therapy, and a short course of systemic corticosteroids are the most important strategies to prevent and control exacerbations. Based on two randomized trials showing a 20% reduction of exacerbations, the Global Initiative for Chronic Obstructive Lung Disease also recommended long-term therapy with inhaled steroids for patients with moderate-to-severe COPD who were experiencing recurring exacerbations.

Potentially interesting alternative strategies for an improved control of symptoms and exacerbations in COPD include the use of mucolytic, antioxidant, and immunomodulator agents. For instance, there is evidence from systematic reviews that mucolytic agents reduce the risk of exacerbations.

Since the early 1970s, oral lyophilized (active) extracts of bacteria species, which are frequently responsible for lower respiratory tract infections in patients with COPD, have been used. These remedies are thought to enhance specific and nonspecific immune responses through humoral and cellular immunomodulating activities. One large randomized placebo-controlled trial performed in 1997, the Prevention of Acute Respiratory Infection by an Immunostimulant study, found that treatment with oral purified bacterial extracts reduced the severity of exacerbations and the rate of hospitalizations in COPD patients. However, the total number of exacerbations was similar in both groups. Based on these findings, we performed a systematic review to learn more about the efficacy and harm of these potentially useful drugs in patients with chronic bronchitis and COPD.

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For editorial comment see page 1406

Materials and Methods

Data Sources

We searched without language restriction in the databases MEDLINE, Embase, Lilacs, Biosis, CINAHL, HealthStar, Inspect, and the Cochrane Controlled Trials Register, using combinations of the terms “OM-85 BV,” “Broncho-Vaxom,” “SL-04,” “LW-50020,” “bacterial AND lysate,” “immunotherapy,” “COPD,” and “bronchitis.” Searches were limited to “controlled clinical trial” and “human.” The last electronic search was made in July 2003. Searches were completed through the screening of bibliographies of included reports and relevant reviews. We also contacted authors of the included reports and two manufacturers of bacterial lysates (OM Pharma; Geneva, Switzerland; and Sankyo Pharma; Faellanden, Switzerland), and asked for information on additional trials including unpublished data.

Study Selection

Reports were considered for review if they described randomized comparisons of an oral bacterial (active) extract with placebo or no treatment (control) in adults with chronic bronchitis and COPD, and if they had reported on efficacy or harm. Studies on the prevention of acute respiratory tract infections in otherwise healthy subjects and on immunologic parameters were not considered. There was an intention to consider data from the abstracts of scientific meetings if the study methods were clearly described and data reporting was adequate.

Validity Assessment and Data Extraction

One author (CS) screened all retrieved reports and selected those that were potentially valid. There was an a priori agreement that reports without randomization would be excluded. All authors independently assessed the selected studies for methodological quality. Information was sought for the following six criteria: adequacy of patient enrollment; sequence generation; concealment of allocation; blinding (of patient, caregiver, outcome assessment, and data-analysis); a statement on how drop-outs were handled; and the use of an intention-to-treat analysis. We arbitrarily assigned 1 point for each fulfilled criterion (maximum, 6 points). A quality score of > 3 was considered to be adequate by us. Authors met to compare assigned scores, and discrepancies were resolved by discussion.

Information about bacterial lysate regimens (ie, drug, dose, route of administration, and duration of treatment), the number of patients enrolled into the study and analyzed, the length of follow-up, sponsorship, and outcome measures were entered in standard collection sheets. This was done by one investigator (CS), and the work was cross-checked by the others. The primary outcome measure was the prevention of exacerbation. Definitions of exacerbation were taken as reported in the original trials. Secondary outcome measures were the duration of the exacerbation, the improvement of symptoms as assessed by observers and patients, the rate of hospitalization due to exacerbation, and adverse effects.

Statistical Analysis

Dichotomous data on efficacy and harm were abstracted into 2 × 2 tables. Heterogeneity was assessed graphically using forest plots, and statistically using the χ² test. We planned to perform meta-analyses in which data from individual studies would be pooled using a fixed-effects model if no statistical heterogeneity (p > 0.05) was detected. We explored the causes of heterogene-
ity by studying the features of populations (ie, inclusion and exclusion criteria), interventions (ie, drug regimens), outcomes (ie, clinical heterogeneity), and study quality (ie, methodological heterogeneity). In case of statistical heterogeneity, we decided to pool data using a random-effects model. Consequently, the pooled results would be interpreted with caution. We also planned to examine the influence of individual studies (for instance, small trials or those with inadequate study quality) on the summary effect estimate. The results were presented as relative risks (RRs) or odds ratios (ORs), the number needed to treat for one to benefit (NNTB) or the number needed to treat for one to be harmed (NNTH), with corresponding 95% confidence intervals (CIs). For continuous data (ie, duration of exacerbation), we calculated the weighted mean differences (WMDs), taking into account study size and SDs as reported in the individual trials. Statistical analyses were carried out using a statistical software package (Stata, version 7.0; Stata Corp; College Station, TX).

RESULTS

We retrieved 71 potentially relevant reports, and 58 were subsequently excluded (Fig 1). Four potentially relevant reports contained data from already published studies, but we only considered the original publications. One trial studied patients with recurrent airway infections. We used data on adverse effects only from this study. Two randomized trials did not provide information on our predefined primary or secondary outcome measures. In one study, the number of patients per group was unknown. The other excluded reports were on children, were performed in other clinical settings, were not on randomized trials, or contained immunology data only.

We analyzed data from 13 randomized placebo-controlled trials from seven countries (Switzerland, three trials; Germany, two trials; Yugoslavia, two trials; France, two trials; Egypt, two trials; Canada, one trial; and Italy, one trial) that had been published from 1981 to 1998 (Table 1). Six trials were published in English, three each in

![Figure 1. Study selection process for the systematic review of oral purified bacterial extracts in chronic bronchitis and COPD patients.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22018/ on 06/26/2017)
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Comparisons</th>
<th>Regimen</th>
<th>Follow-up, mo</th>
<th>Risk factors/Study Populations</th>
<th>Age,† yr mean ± SD</th>
<th>FEV1 at Baseline‡</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahrens72/1983</td>
<td>1. OM-85 BV (119) 2. Placebo (111)</td>
<td>1 cap, 7 mg/d, 10 d/mo for 3 mo</td>
<td>6</td>
<td>COPD &quot;repeated exacerbations&quot;</td>
<td>A: 48 (17–82) C: 51 (14–79)</td>
<td>A: 65.3 ± 7.7 C: 66.9 ± 7.7</td>
<td>1/1 author from ALTANA Pharma</td>
</tr>
<tr>
<td>Collet et al16/1997</td>
<td>1. OM-85 BV (191) 2. Placebo (190)</td>
<td>1 cap, 7 mg/d for 1 mo then for 10 d/mo for 3 mo</td>
<td>6</td>
<td>COPD/smokers A, 41%; C, 31%; past hospitalization: A, 63%; C, 68%</td>
<td>A: 48.1 ± 3.5 C: 48.4 ± 3.1</td>
<td>A: 84 ± 26.8% predicted C: 78.6 ± 25.9% predicted</td>
<td>Funded by Jouveinal Inc (St. Laurent, QC, Canada); the project was designed and carried out in complete independence</td>
</tr>
<tr>
<td>Cvoriscec et al73/1989</td>
<td>1. OM-85 BV (52) 2. Placebo (52)</td>
<td>1 cap, 7 mg/d for 1 mo; 2nd mo, no treatment; 3rd, 4th, and 5th mo, 1 cap; 10 d/mo; 6th mo, no treatment</td>
<td>6</td>
<td>Chronic bronchitis and COPD/4 exacerbations/yr, 29%; smokers, 38%</td>
<td>A: 48.1 ± 3.5 C: 48.4 ± 3.1</td>
<td>A: 84 ± 26.8% predicted C: 78.6 ± 25.9% predicted</td>
<td>1/6 authors from OM Pharma (who also supplied the drug)</td>
</tr>
<tr>
<td>Djuric et al74/1989</td>
<td>1. OM-85 BV (34) 2. Placebo (25)</td>
<td>1 cap, 7 mg/d for 1 mo then for 10 d/mo for 5 mo</td>
<td>6</td>
<td>Chronic bronchitis and COPD</td>
<td>A: 43 ± 7 C: 47 ± 5</td>
<td>A: 79.5 ± 8.2% predicted C: 77.1 ± 9.3% predicted</td>
<td>3/5 authors from Luitpold Pharma (Munich, Germany)</td>
</tr>
<tr>
<td>Fischer et al76/1992</td>
<td>1. LW-50020 (150) 2. Placebo (153)</td>
<td>3 mg/d for 3 × 1 mo</td>
<td>6</td>
<td>Chronic bronchitis/smokers, 25%; &gt; 4 respiratory infections during previous 12 mo</td>
<td>A: 35 ± 10 C: 34 ± 10</td>
<td>A: 79.5 ± 8.2% predicted C: 77.1 ± 9.3% predicted</td>
<td>4/5 authors from Luitpold Pharma (Munich, Germany)</td>
</tr>
<tr>
<td>Germonty75/1986</td>
<td>1. SL-04 (30) 2. Placebo (30)</td>
<td>1 mL/d for 20 d/m for 3 mo</td>
<td>6</td>
<td>Chronic bronchitis, 73%; &gt; 3 exacerbations during previous 12 mo</td>
<td>A: 59.5 ± 8.2 C: 62.1 ± 10.7</td>
<td>A: 59.5 ± 8.2 C: 62.1 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>Keller and Hinz23/1984</td>
<td>1. OM-85 BV (39) 2. Placebo (42)</td>
<td>1 cap, 7 mg/d for 1 mo then 10 d/mo for 3 mo</td>
<td>6</td>
<td>COPD/smokers or ex-smokers, 95%</td>
<td>A: 57.1 ± 13.3 C: 56.8 ± 11.4</td>
<td>A: 1.57 L C: 1.55 L</td>
<td></td>
</tr>
<tr>
<td>Khedr76/1993</td>
<td>1. OM-85 BV (72) 2. Placebo (50)</td>
<td>1 cap, 7 mg/d during 10 d/mo for 3 mo</td>
<td>12</td>
<td>Chronic bronchitis</td>
<td>A: 16–55 C: 16–54</td>
<td>A: 54.6 C: 55.5</td>
<td></td>
</tr>
<tr>
<td>Messerle77/1981</td>
<td>1. OM-85 BV (40) 2. Placebo (32)</td>
<td>1 cap, 7 mg/d for 10 d/mo for 3 mo</td>
<td>3</td>
<td>Chronic bronchitis</td>
<td>A: 57.1 ± 13.3 C: 56.8 ± 11.4</td>
<td>A: 1.57 L C: 1.55 L</td>
<td></td>
</tr>
<tr>
<td>Orel et al78/1993</td>
<td>1. OM-85 BV (147) 2. Placebo (143)</td>
<td>1 cap, 7 mg/d for 10 d/mo for 3 mo</td>
<td>6</td>
<td>Chronic bronchitis and COPD/4 exacerbations during a 6-mo period</td>
<td>A: 54.3 ± 1.4% predicted C: 54.4 ± 1.5% predicted</td>
<td>A: 82 ± 8 C: 82 ± 7</td>
<td>2/8 authors from OM Pharma</td>
</tr>
<tr>
<td>Orlandi et al79/1983</td>
<td>1. OM-85 BV (10) 2. Placebo (9)</td>
<td>1 cap, 7 mg/d for 1 mo then for 10 d/mo for 4 mo</td>
<td>4</td>
<td>Chronic bronchitis</td>
<td>52.8 (24–79)</td>
<td>Drug provided by OM Pharma</td>
<td></td>
</tr>
<tr>
<td>Rutishauser et al80/1998</td>
<td>1. LW-50020 (142) 2. Placebo (90)</td>
<td>3 mg/d for 2 × 1 mo interrupted by 1 mo without treatment</td>
<td>4</td>
<td>Recurrent (&gt; 6) respiratory tract (upper and lower) infections during previous year in 80%; smokers, 23%</td>
<td>A: 40.3 ± 13.4 C: 38.8 ± 12.8</td>
<td>A: 40.3 ± 13.4 C: 38.8 ± 12.8</td>
<td>3/6 authors from Sanlyo Pharma (Munich, Germany)</td>
</tr>
<tr>
<td>Tag El Din et al81/1993</td>
<td>1. OM-85 BV (30) 2. Placebo (20)</td>
<td>1 cap, 7 mg/d for 1 mo; 2nd mo, no treatment; 3rd, 4th, and 5th mo, 1 cap, 10 d/mo; 6th mo, no treatment</td>
<td>6</td>
<td>Chronic bronchitis/smokers, 72%</td>
<td>A: 36.1 ± 3.5 C: 34.4 ± 3.1</td>
<td>FEV1 &quot;normal&quot;</td>
<td></td>
</tr>
</tbody>
</table>

*A = active extract; C = control substance.
†Values given as mean ± SD or median (range).
‡Values given as mean ± SD.

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French and German, and one in Italian. From four trials, only data on adverse drug reactions could be analyzed. One trial studied adults and children, and we extracted the data on adults only. No additional data, published or unpublished, were retrieved through contacts with manufacturers or authors. A total of 2,121 patients were randomized, and the original investigators analyzed 1,971 patients. The median dropout rate was 5% (range, 0 to 22%). The median number of analyzed patients was 104 (range, 19 to 381).

Methodological Quality

All trials were placebo-controlled, and there were no head-to-head comparisons. In general, the methodological quality of the studies was poor (Table 2). The median score was 2, with one trial scoring 6 and two scoring 4 (Table 2). One study only (7.7%) reported on consecutive patient enrollment, and two studies (15.4%) reported on the details of the generation of random sequences and of the concealment of treatment allocation. Four studies (30.8%) included a statement on how they had dealt with dropouts, and five studies (38.5%) used an intention-to-treat analysis. Only two studies, however, did not provide details about the blinding of patients and caregivers. Seven trials (53.8%) acknowledged sponsorship by a manufacturer, and in five (38.5%) one or several authors were the collaborators of a manufacturer.

Regimens

Ten studies tested OM-85BV (Broncho-Vaxom; OM Pharma). The usual regimens were one 7-mg capsule daily for 1 month, followed by one capsule daily for 10 days during the second and third month, or one capsule daily during the first 10 days of each month for 3 months. Two studies tested LW-50020 (Luivac; ALTANA Pharma; Bad Homburg, Germany), 3 mg daily for 2 to 3 months. One trial tested SL-04, 1 mL per day during the first 20 days of each month for 3 months. The observation period was 6 months in nine trials (69%), 3 months in one trial, 4 months in two trials, and 12 months in one trial.

Patients

In trials that reported on demographic data, there were more male patients than female patients (median, 60%; range, 43 to 80%). The inclusion criteria were COPD in 6 trials, chronic bronchitis in 10 trials, and more than three episodes of exacerbation within the previous year in 8 trials. In the seven studies that reported on smoking habits, almost half of the analyzed patients (median, 48%; range, 23 to 93%) were smokers or ex-smokers. Lung function was reported in five trials (mild-to-moderate COPD, four trials; severe COPD, one trial).

Outcome Measures

There was a large variation in the reported end points. No more than five trials reported on the same efficacy end point.

Prevention of Exacerbation

Three trials (731 patients) reported on the prevention of exacerbation with OM-85BV or SL-04, and the observation period was always 6 months.
relationship between study quality and treatment efficacy became apparent (Fig 2). One large trial\textsuperscript{16} with good quality did not show any beneficial effect with the use of active extracts. Another large trial\textsuperscript{78} with lower quality, but still acceptable quality, was significantly in favor of the use of active extracts. The largest treatment effect was with the smallest trial,\textsuperscript{75} which also had the lowest quality score. When all three trials were combined, the data were heterogeneous ($p < 0.001$). Using a random-effects model, the difference between the use of active extracts and placebo was not statistically significant (RR, 0.66; 95% CI, 0.41 to 1.08). After the omission of this trial, the pooled RR was 0.83 (95% CI, 0.55 to 1.25). The resulting NNTB was 15.4, and the 95% CI around the point estimate included infinity (95% CI, 5.5 to $\infty$; [for NNTB: 95% CI, 5.5 to 27.5]).

**Average Duration of Exacerbation**

Three trials (223 patients) reported on the average duration of exacerbation with OM-85 BV\textsuperscript{73,74} and SL-04.\textsuperscript{75} The observation period was always 6 months. In all three trials, the duration of exacerbation was significantly shorter with treatment with active extracts compared with the control substance (WMD, $-3.3$ days [in favor of bacterial extracts]). Again, a small, low-quality trial\textsuperscript{75} showed the largest benefit. When this trial was excluded from the combined analysis, the WMD was $-2.7$ days (95% CI, $-3.5$ to $-1.8$) [Fig 3].

**Improvement Assessed by Observers**

Five trials\textsuperscript{22,72,73,76,77} (591 patients) of relatively poor quality reported on the improvement of symptoms assessed by the observers at the end of the study period. All trials tested OM-85BV, and the study periods were 3 months,\textsuperscript{77} 6 months,\textsuperscript{22,72,73} and 12 months.\textsuperscript{76} The event rate scatter suggested consistent superiority with bacterial extracts, relative homogeneity, and little variability in event rates. When all five trials were combined, the data were homogeneous ($p = 0.6$), and the difference between active extracts and placebo was statistically significant in favor of bacterial extracts (RR, 0.57; 95% CI, 0.49 to 0.66) [NNTB, 4; 95% CI, 2.8 to 5.4] (Fig 4).

**Hospitalization**

Data on hospital admission for respiratory problems came from one trial with an observation period of 6 months.\textsuperscript{16} Hospital admission was reported in 31 of 191 patients (16.2%) receiving OM-85-BV and in 44 of 190 patients (23.2%) receiving placebo (RR, 0.70; 95% CI, 0.46 to 1.06) [NNTB, 14; 95% CI, 8.0 to $\infty$; NNTH, 72].

**Adverse Effects**

Skin itching or cutaneous eruptions were reported in 13 of 399 patients (3.3%) receiving OM-85BV,\textsuperscript{16,79} LW-50020,\textsuperscript{24} or SL-04,\textsuperscript{75} and in 4 of 403 control subjects (1%) [OR, 2.94; 95% CI, 1.12 to 7.69] (NNTH, 44; 95% CI, 14 to 161). Urologic problems,
which in one trial were specified as lower urinary tract infections, were reported in 27 of 338 patients (8%) receiving OM-85BV, and in 10 of 333 control subjects (3%) [OR, 2.62; 95% CI, 1.35 to 5.11] (NNTH, 20; 95% CI, 10 to 61). Abdominal problems (e.g., gastroenteritis, nausea, upper abdominal pain, diarrhea, and gastric upset) were reported in 46 of 801 (5.7%) patients receiving OM-85BV and LW-50020, and in 37 of 735 control subjects (5.0%) [OR, 1.24; 95% CI, 0.78 to 1.95]. Allergic reactions (e.g., asthma and rhinitis) were reported in 4 of 341 patients (1.2%) receiving OM-85BV or LW-50020 and in 1 of 291 control subjects (0.3%) [OR, 2.75; 95% CI, 0.47 to 16.3]. Study withdrawal due to adverse reactions was reported in 3 of 213 patients (1.4%) receiving OM-85BV or LW-50020 and in 2 of 208 control subjects (1.0%) [OR, 1.46; 95% CI, 0.25 to 8.50].

**Discussion**

Our systematic review was unable to provide strong evidence that oral immunostimulation with bacterial extracts prevents exacerbations in patients with COPD and chronic bronchitis. Regarding the secondary end points, however, we found an improvement of symptoms, as rated by both patients

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/22018/)

**Figure 3.** The WMD in the average duration of exacerbations with OM-85 BV over an observation period of 6 months. In the two trials, the duration of an exacerbation was significantly shorter with the use of active extracts compared with control substances (WMD, –2.7 days; 95% CI, –3.5 to –1.8).

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/22018/)

**Figure 4.** Improvement assessed by observers. Five trials (591 patients) reported on the improvement of symptoms assessed by the observers at the end of the study period. All trials tested OM-85.
and observers, and a shortening of the average duration of exacerbations of approximately 3 days when pooling the results of studies with limited methodological quality. Hospitalization due to respiratory problems was reported in one high-quality trial. This was the largest of all trials (381 patients), and it provided some evidence that the risk of hospital admission may be reduced with the use of bacterial extracts. Although our systematic review could not find an effect on the prevention of exacerbations, it has to be considered that both a decrease in severity and a reduction in the duration of exacerbations are relevant in the management of COPD patients. For instance, a decrease in the duration of an exacerbation might have an economic impact. Also, it should be taken into account that this therapy is relatively cheap and can be applied intermittently.

In patients for whom data on lung function were available, the majority had mild-to-moderate COPD. Therefore, we do not know whether bacterial extracts would be effective in reducing exacerbations in patients with severe COPD. Strictly speaking, the results from these analyses apply to patients with mild-to-moderate COPD only.

Regarding safety, we could not identify any difference in adverse GI symptoms and study withdrawals due to drug-related adverse effects compared to placebo. However cutaneous eruptions, itching, and lower urinary tract infections are common. We do not know whether one of those adverse effects was severe enough to stop patients from receiving the treatment. The main problem with the use of bacterial extracts may be the increased risk of lower urinary tract infections.

**Robustness of Results**

Our systematic review has some important limitations, and all are related to the relatively quality and limited validity of the original trials. However, it is important to know about methodological weaknesses in the original trials, since only then can such weaknesses be avoided in future trials.

We made strenuous efforts to minimize the risk of selection bias. Relevant reports were searched systematically and without language restriction. Four duplicate reports were identified and excluded from further analysis. The main risk is that biases in the original trials may lead to an overestimation of treatment effect. Indeed, the overall quality of the trials was poor. The included trials, however, reported on clinically homogenous settings, treatment regimens and periods were standardized (in most trials, the observation periods were 6 months), and information on the underlying risk suggested that study populations were comparable. Also, most trials used adequate methods of blinding, minimizing the risk of observer bias. Nevertheless, important methodological items such as patient enrollment, the generation of random sequences, the concealment of treatment allocation, and details about the statistical analysis were seldom reported. Furthermore, most trials were of limited size. The problem with small trials is that they may generate treatment effects by random chance. One of the smallest trials generated the most beneficial effect in favor of bacterial extract, both for the prevention and duration of exacerbation. Heterogeneity of the results was largely explained by this trial. When in sensitivity analyses that trial was excluded, treatment effects moved toward equality.

Pharmaceutical companies sponsored half of the trials. Often, coauthors were the collaborators of a manufacturer. An association between competing interests and authors’ conclusions has been shown repeatedly. In our meta-analysis, however, authors’ conclusions per se were not considered. We do not know how potential competing interests may influence the way a clinical trial is designed and conducted, and the way the data are analyzed and reported.

The trials reported on a large variety of different end points. It was impossible to combine outcome data from more than five trials. The main end point, prevention of exacerbation, was reported in three trials only, and one of those trials was of limited size and quality. Finally, the data were too sparse to allow for formal sensitivity analyses, addressing, for instance, the relative efficacy of different bacterial extracts or the impact of the duration of treatment.

**Future Research**

A question that should be examined in further trials is whether or not bacterial extracts are more effective in preventing exacerbations of COPD in high-risk patients with severely impaired lung function. Further relevant end points to consider are hospital admission, duration of disease-free intervals, saved days of absence of work, and the need for concomitant medications, especially antibiotics and systemic corticosteroids, as all these factors contribute to cost. It may also be of interest to know whether there was an additive or even synergistic effect when different treatments are given concomitantly in these patients, for instance, bacterial extracts with the use of inhaled steroids or mucolytic agents.

In conclusion, given the high prevalence of COPD, the impact of exacerbations on quality of life, and the costs incurred, effective ways for the pre-
vention of exacerbations, and for reductions in the severity and duration of COPD symptoms are needed. So far, there is no strong evidence that oral bacterial extracts reduce the frequency of exacerbations, however, they seem to have a favorable effect on the severity of symptoms. Consequently, the agenda is one of further research rather than of clinical recommendations.

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