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Impact of a homeopathic medication on upper respiratory tract infections in COPD patients: Results of an observational, prospective study (EPOXILO)

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder in which airflow is obstructed. Viral or bacterial upper respiratory tract infections (URTIs) may lead to exacerbations. Homeopathic medication administration to COPD patients during the influenza-exposure period may help to reduce the frequency of common URTIs.

Methods: This prospective, observational, multicenter study was carried out in Cantabria, Spain. Patients with COPD were divided into two groups: group 1 received conventional treatment + homeopathic medication (diluted and dynamized extract of duck liver and heart; Boiron) (OG); group 2 received conventional treatment only (CG). The primary endpoint was the number of URTIs between the 4–5 months follow up (mean 4.72 ± 0.96) from basal to last visit. Secondary endpoints included the duration of URTIs, number and duration of COPD exacerbations, use of COPD drugs, changes in quality of life (QoL), compliance, and adverse events (AEs).

Results: 219 patients were analyzed (OG = 109, CG = 110). There was a significant reduction in mean number of URTIs during the follow-up period in OG compared to CG (0.514 ± 0.722 vs. 1.037 ± 1.519, respectively; p = 0.014). Logistic regression analysis showed a 3.3-times higher probability of suffering ≥2 URTI episodes in CG (p = 0.003, n = 72). OG patients having ≥1 URTI also had a significant reduction in mean URTI duration per episode (3.57 ± 2.44 days OG vs. 5.22 ± 4.17 days CG; p = 0.012). There was no significant difference in mean number of exacerbations, mean duration of exacerbations, or QoL between OG and CG. There was a greater decrease in proportion of patients using corticosteroids for exacerbations between baseline and visit 2 in OG compared to CG (22.1% vs. 7.5% fewer respectively, p = 0.005). Exacerbator phenotype patients had a significant decrease in number of URTIs (0.54 ± 0.72 vs. 1.31 ± 1.81; p = 0.011), and fewer COPD exacerbations (0.9 ± 1.3 vs. 1.5 ± 1.7; p = 0.037) in OG vs. CG, respectively.

Conclusions: Homeopathic medication use during the influenza-exposure period may have a beneficial impact at reducing URTIs' number and duration in COPD patients and at reducing the number of COPD exacerbations in patients with the exacerbator phenotype. Further studies are needed to confirm the effects observed in this study.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder in which airflow is obstructed making it difficult for patients to breathe. The main respiratory symptoms include shortness of breath, wheezing, elevated sputum production, and cough. The disease is one of the most prevalent human health disorders in the world and has been reported to affect over 300 million people worldwide [1]. A recent systematic analysis of data from 188 countries for the Global Burden of Disease Study reported that 3.2 million people worldwide died from

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Abbreviations

ACINAR	Asociación Cántabra de Investigación en Aparato Respiratorio
AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AR	Adverse Reaction
BODE index	Body-mass index (B), the degree of airflow Obstruction (O) and Dyspnea (D), and Exercise capacity (E)
BODEX	Body-mass index (B), degree of airflow Obstruction (O) and Dyspnea (D), Exacerbation (Ex)
CAT	COPD Assessment Test
CEIC	Comité Ético de Investigación Clínica
CG	Control Group
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
FEV	Forced Expiratory Volume
FEV_1	Forced Expiratory Volume in 1 s
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GesEPOC	Guía Española de la EPOC (COPD Spanish Guideline)
LABD	Long-Acting Bronchodilator
MRC	Medical Research Council (dyspnea Scale)
mMRC	Modified Medical Research Council
NA	Not Available
OG	Oscillococcinum group
Q1	Quartile 1
Q3	Quartile 3
QoL	Quality of Life
SAE	Severe Adverse Event
SD	Standard Deviation
URTI	Upper Respiratory Tract Infection(s)

COPD in 2015, an increase of 11.6% compared with 1990 [2]. It has been projected that by 2020 COPD will be the third leading cause of death worldwide and fifth leading cause of years lost through early death or handicap (disability-adjusted life years) [3]. COPD results in significant costs to the healthcare system [3,4] and, in the USA, COPD has been rated amongst the top five most costly medical conditions in patients aged 65 years and above [5]. The main risk factor for COPD is tobacco smoking [6–8]. A recent publication from the EPI-SCAN study estimates that among 21.4 million Spanish people aged 40–80 years around 2,185,764 currently have COPD (10.2%) [9]. It is estimated that 73% of cases of COPD are undiagnosed, thus it is likely that more than 1,595,000 Spanish people are unaware that they have COPD and do not receive any treatment for it. There is a marked prevalence of underdiagnosis in women [10,11].

COPD exacerbations are defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication" [12], and are a major cause of morbidity and mortality. Exacerbations are less common in early COPD [13] but occur an average of three times a year in patients with moderate to severe COPD [14,15]. Exacerbations can lead to tracheal collapse, accelerated loss of lung function, progression to more advanced pulmonary disease, a deterioration in cardiovascular comorbidities, poor health status, impaired activities of daily living, increased health resource utilization, higher healthcare costs, and an increased risk of death [16–20].

Common viral or bacterial upper respiratory tract infections (URTIs) play a major role in the etiology of exacerbations [21–25], especially when the patient is the frequent exacerbator phenotype [23]. Pappi et al. detected bacteria and/or viruses in 78% of 64 patients with exacerbations requiring hospital admission [24]. The causal role of viruses in exacerbation was demonstrated by Mallia et al. in a model of experimental rhinovirus infection [25]. COPD patients with experimental rhinovirus infection developed more lower respiratory tract symptoms, greater airflow limitation, and more systemic and airway inflammation than a control group of smokers with normal spirometry [25]. The key goal of therapy in COPD is to improve symptoms and to prevent exacerbations [19,20,26].

International guidelines recommended that all patients with COPD are vaccinated against influenza, as this helps to reduce hospital admissions and mortality rates, and that older patients and patients with more severe disease are vaccinated against *Streptococcus pneumoniae* to prevent community-acquired pneumonia [12,26–28]. However, these vaccines only protect against influenza and *Pneumococcus* and not against other URTIs that can cause COPD exacerbations. Furthermore, the uptake of these vaccines in COPD patients is low, ranging from 27.3 to 70% for influenza vaccine [12,28–33] and 14.1–56.3% for pneumococcus vaccine [28,29].

Since URTIs are an important cause of exacerbations and inflammation of the airway, a homeopathic medication may be helpful in COPD patients, particularly those with the exacerbator phenotype. Several studies have reported the positive impact of the homeopathic medication Oscillococcinum ® at treating symptoms from influenza and accelerating the recovery [34–36] and well as reducing the incidence of influenza-like syndromes and URTIs including the common cold [37].

There are currently no data available on the usefulness of this homeopathic medication for the management of URTIs in COPD patients during the influenza-exposure period. We carried out an observational study to determine whether its administration to COPD patients during the influenza-exposure period may help to reduce the frequency of common URTIs that can cause exacerbations.

2. Materials and methods

2.1. Study design

This observational, prospective, comparative, multicenter study was carried out between October 2015 and June 2016 in primary care centers in the Cantabria region of northern Spain. First patient was included on October 21, 2015 and last one on February 15, 2016.82% of the inclusions were achieved between October and December 2015. Most physicians involved in this study were general practitioners from the public health system of Cantabria and had no specific training in homeopathy. Two of the physicians were respiratory disease specialists. The study protocol was designed by the epidemiologist and other members of ACINAR (Asociación Cántabra de Investigación en Aparato Respiratorio).

2.2. Study population

Patients who received conventional treatment for COPD were recruited and divided into two groups: group 1 received homeopathic medication during the influenza-exposure period in addition to conventional treatment (homeopathic medication group; OG); and group 2 received conventional treatment only (control group; CG). In order to be respectful of the real medical practice, the addition of the homeopathic medication to their treatment was not randomized.

Patients were included if they were 50–80 years-old and had a diagnosis of COPD (clinical and forced spirometry with post-bronchodilation $FEV_1/FVC < 0.7$). Patients were excluded if they had a history of tobacco consumption of < 10 packs/year. All subjects gave their informed consent before participating in the study.

Assuming a normal distribution, the minimum sample size was calculated as 99 patients per group (ratio OG/CG 1:1) in order to detect a statistically significant difference using the Student's T-test for two

independent samples, with a power of 80% and alpha = 0.05, assuming a standard deviation (SD) of 2.5 in each group. SD was the expected range of URTI episodes (0–10) divided by 4. It was therefore planned to recruit 220 patients (110 patients in OG and 110 in CG) based on a 10% loss.

2.3. Study treatment

The administration of the homeopathic medication was dissociated from the proposal to participate in the study following the standard for observational studies. The recommended dosage schedule for the homeopathic medication (diluted and dynamized extract of duck liver and heart; Oscillococcinum®, Boiron) is one oral dose every week during the influenza-exposure period (autumn and winter).

All other conventional treatments were administered according to clinical criteria and in line with normal clinical practice for the management of COPD patients [38].

2.4. Data collection

Sociodemographic, anthropometric, and clinical data were collected prospectively from clinical records or during a patient interview at inclusion and at two follow-up visits (normally every 2 months ± 15 days during the autumn and winter seasons). These visits are standard practice in the clinical follow-up of COPD patients. The clinical data recorded included: associated comorbidities, concomitant medication, smoking and drinking habits, date of diagnosis of COPD, spirometry values, and FEV_1. No additional diagnostic or therapeutic interventions were performed in order to respect the observational nature of the study.

The COPD patients were classified into one of four possible phenotypes based on GesEPOC guidelines [39,40] and four possible severity groups based on FEV1 values. Global severity was evaluated using the BODE capacity index (body mass index, airflow obstruction, functional dyspnea, and exercise capacity [41], or BODEx index (BODE with exacerbations instead of exercise) [42], and degree of dyspnea was estimated using the Modified Medical Research Council (mMRC) scale (0–4) [43]. Impact of COPD on quality of life (QoL) was measured using the COPD Assessment Test (CAT) questionnaire [44,45].

The following additional data were also recorded at the inclusion and follow-up visits: conventional pharmacological treatments (for stable COPD and during COPD exacerbations), medicines or products taken for the prevention of URTIs, influenza and pneumococcus vaccination status, COPD exacerbations (number of episodes and mean duration of episodes in the previous 12 months and since the last follow-up visit), number and mean duration of URTIs since the last visit. Compliance with homeopathic medication and adverse events (AEs) were recorded at the two follow-up visits.

2.5. Primary endpoints

The primary endpoint was the number of URTIs during the study follow-up period. URTIs included the following infections: influenza and influenza-like syndrome, rhinosinusitis, otitis, laryngitis, epiglottitis, and pharyngoamygdalitis.

2.6. Secondary endpoints

The secondary endpoints included: duration of URTIs, number and duration of exacerbations, consumption of COPD management drugs, changes in QoL (CAT score), compliance, and AEs.

2.7. Compliance and adverse events

Patients were asked about compliance with homeopathic medication at each visit. Compliance was classified as high if ≥ 90% of doses were taken, medium if 75–89% of doses were taken, and low if < 75% of doses were taken. All AEs occurring in the two treatment groups were recorded and their relationship to the study medication determined.

2.8. Statistical analysis

Quantitative variables are described as means, standard deviation (SD), median, minimum, maximum, Q1, and Q3. Qualitative variables are described as number and percentage. Qualitative variables were compared using the Chi-square or Fisher tests. Mean values were compared using the Student's T-test or Mann-Whitney *U* test. For comparison of more than two means, the ANOVA or Kruskal-Wallis tests were used. All tests were performed bilaterally. A p-value of < 0.05 was considered to indicate statistical significance.

All statistical analyses were carried out using SPSS v22.0.

3. Results

3.1. Study population

Thirty-seven active investigators in 21 primary care centers in the Cantabria region of Spain recruited patients for this study. A total of 235 patients were recruited and 219 (93.2%) were included in the final analysis (109 in OG and 110 in CG). Six patients were considered by the investigators to be “not evaluable”, nine had missing data, and one did not fulfil the inclusion criteria (no history of smoking) (Fig. 1).

The overall demographic and clinical characteristics of the two treatment groups were comparable at inclusion (Table 1). 73.5% of the patients were male, mean age was 67.4 years ± 7.8 and 30.1% of patients were current smokers. There were slight though statistically significant differences at the demographic characteristics regarding drinking habits (p = 0.036). Although the number of both active and dangerous alcohol consumption was similar, there were more ex-drinkers and fewer teetotaler history patients in CG. The majority of patients (89.5%) had comorbidities including diabetes, heart failure, atrial

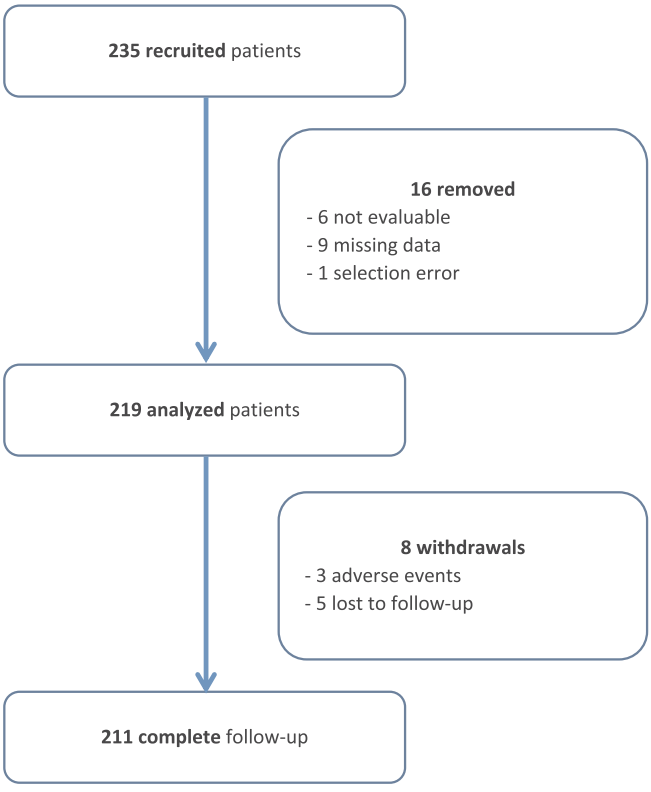

Fig. 1. Flowchart of the patients included and analyzed in the study.

Table 1
Sociodemographic characteristics at inclusion for COPD patients treated with conventional medicines (CG) or with conventional medicines + homeopathic medication (OG).

Characteristic		Homeopathic medicine group (OG)	Control group (CG)	Total	P value
Gender, male (%)		71.6	75.5	73.5	0.514[a]
Age (years)					
Mean (± SD)		66.9 ± 7.9	67.8 ± 7.7	67.4 ± 7.8	0.409 [b]
Median (min-max)		68.2 (50.4–79.6)	69.1 (51.4–80.0)	68.7 (50.4–80.0)	
BMI (kg/m^2)		(*n* = 108)	(*n* = 108)	(*n* = 216)	
Mean (± SD)		28.8 ± 5.5	28.5 ± 5.0	28.7 ± 5.3	0.762[c]
Median (min-max)		28.1 (15.4–45.4)	27.7 (16.8–42.5)	27.9 (15.4–45.4)	
Current smoking, yes (%)		29.4	30.9	30.1	0.802[a]
Mean no. cigarettes/day (± SD)		18.5 ± 8.1	17.1 ± 8.5	17.8 ± 8.3	0.534[b]
Mean no. years smoking (± SD)		37.8 ± 8.7	39.3 ± 9.4	38.6 ± 9.0	0.482[c]
Alcohol consumption, current, yes (%)					
Ex-drinkers		39.4	40.0	39.7	0.036[a]
		7.3	20.0	13.7	
No history of alcohol use		42.2	32.7	37.4	
Comorbidities[d] (%)					
At least one comorbidity		86.2	92.7	89.5	0.117[a]
Diabetes		15.6	30.0	22.8	0.011[a]
Vaccination, yes (%)					
Influenza		67.0	71.8	69.4	0.437[a]
Pneumococcus	23 serotypes	59.6	58.2	58.9	0.827[a]
	13 serotypes	11.9	7.3	9.6	0.242[a]

For all calculations *n* = 109 in OG and *n* = 110 in CG, unless stated otherwise.
[a] Chi-square test.
[b] Mann-Whitney.
[c] T-test.
[d] diabetes, heart failure, atrial fibrillation, arterial hypertension, anxiety/depression, lung cancer, ischemic cardiopathy, and/or osteoporosis.

fibrillation, arterial hypertension, anxiety/depression, lung cancer, ischemic cardiopathy, and/or osteoporosis with no statistical significant difference between the two groups except for diabetes, which was more common in CG (15.6% in OG vs. 30% in CG; p = 0.011). The number of comorbidities per patient did not differ significantly between the two groups (p = 0.072) (data not shown). Vaccination against influenza (69.4%) and pneumococcus 13 serotypes (9.6%) and 23 serotypes (58.9%) was also similar in the two groups (Table 1).

3.2. Baseline COPD data

When the COPD data for the two groups were compared at inclusion (Table 2), only time since COPD diagnosis (9.2 years in OG vs 7.0 years in CG; p = 0.03) was significantly different. There were no significant differences in spirometry values (pre- and post-bronchodilation), FEV_1, COPD severity, BODE index, BODEx index, phenotype distribution, degree of dyspnea, number or duration of exacerbations, or QoL.

The medicines used to treat stable COPD and exacerbations are summarized in Table 2. Oral and parenteral corticosteroids were not used to treat stable COPD. Drug use for stable COPD and exacerbations was similar in the two groups.

In the 12 months prior to inclusion, the mean number of URTIs (declared by the patients) was 0.6 ± 0.9, and the mean number of symptomatic days per URTI was 3.3 ± 5.1. The mean number of COPD exacerbations was 2.1 ± 2.5. The mean number of symptomatic days due to COPD exacerbations was 5.4 ± 4.9 days per exacerbation. None of these values differed significantly between the two groups (Table 2).

3.3. Primary endpoint

There was a significant reduction in mean number of URTIs during the follow-up period in OG compared to CG (0.514 ± 0.722 vs. 1.037 ± 1.519, respectively; p = 0.014) (Fig. 2). The difference between the mean values was −0.52 [95%CI: −0.84; −0.20] (p = 0.001). The follow up mean duration was 4.72 ± 0.96 months (median 4.67, min 0.62, max 6.64) without significant differences between groups (4.78 in OG vs 4.65 in CG, p = 0.178).

Two or more URTI episodes were more frequent in CG than in OG (25.7% vs. 9.5% of patients) (p = 0.029) (Fig. 3). Linear regression analysis showed that there were 40.6% more URTI episodes in CG and logistic regression analysis showed that there was a 3.3-fold greater probability of suffering ≥2 URTI episodes in CG (p = 0.003). This decreased to 2.8 (p = 0.166) when adjusted for possible confusion factors (smoking habit, inhaled corticosteroids, influenza vaccine, age, gender, BODEx index, FEV1, and CAT).

A sub-analysis by clinical phenotype (frequent exacerbator or non-exacerbator) showed a significant difference in mean number of URTIs in the frequent exacerbator subgroup (*n* = 116): in frequent exacerbators the mean number of URTIs was 0.54 ± 0.72 in OG vs. 1.31 ± 1.81 in CG (p = 0.011) (Table 3; Fig. 2). There was no significant difference in mean number of URTIs between non-exacerbators in the two groups (0.51 ± 0.76 in OG vs. 0.77 ± 1.06 in CG; p = 0.370) (Table 3).

3.4. Secondary endpoints

3.4.1. URTIs

In patients having ≥1 URTI (*n* = 98), there was a significant reduction in duration of URTIs per episode in OG compared to CG (3.57 ± 2.44 days in OG patients vs. 5.22 ± 4.17 days in CG; p = 0.012) (Table 4).

3.4.2. COPD exacerbations

There was no significant difference in mean number of COPD exacerbations per patient between the two groups (0.7 ± 1.1 in OG vs. 1.0 ± 1.4 in CG; p = 0.128) (Table 4). Likewise, there was no significant difference in mean duration of exacerbations per episode between OG and CG patients having ≥1 episode (*n* = 91) (6.03 ± 4.23 vs. 6.16 ± 4.52 days, respectively; p = 0.876) (Table 4), or between OG and CG patients overall (*n* = 114) (2.33 ± 3.91 days in OG vs. 3.09 ± 4.51 days in CG; p = 0.140) (Table 4).

In addition to the number of exacerbations, the number of total hospital admissions due to exacerbation was also registered. At visit 1, no difference in mean number of hospitalization due to exacerbation was observed between OG (0.1 ± 0.2) and CG (0.1 ± 0.3)

(p = 0.632). At visit 2, this mean was 0.1 ± 0.3 for both groups (p = 0.777).

When a sub-analysis was performed on patients who were frequent exacerbators, OG patients had significantly fewer exacerbations than CG patients during the follow-up period (0.9 ± 1.3 vs. 1.5 ± 1.7, respectively; p = 0.037) (Table 3).

3.4.3. COPD medications

Consumption of drugs used to treat exacerbations (oral, inhaled, or parenteral corticosteroids, bronchodilators, and antibiotics) did not

Table 2
Clinical data at inclusion for COPD patients treated with conventional medicines (CG) or with conventional medicines + homeopathic medication (OG).

Baseline clinical characteristics	Homeopathic medicine group (OG)	Control group (CG)	Total	P value
Time since COPD diagnosis (years)	(*n* = 106)	(*n* = 107)	(*n* = 213)	0.030[b]
Mean ± SD	9.2 ± 7.6	7.0 ± 5.7	8.1 ± 6.8	
Median (min-max)	8.5 (0–40.1)	6.0 (0–25.0)	7.0 (0–40.1)	
Spirometry	(*n* = 78)	(*n* = 83)	(*n* = 161)	
Pre-bronchodilator				
Mean ± SD	54.4 ± 23.5	55.1 ± 21.1	54.8 ± 22.2	0.835[b]
Median (min-max)	61.0 (0–93.0)	61.1 (0–87.7)	61.0 (0–93.0)	
Post-bronchodilator				
Mean ± SD	50.3 ± 29.7	49.6 ± 28.2	49.9 ± 28.8	0.892[b]
Median (min-max)	61.0 (0–97.0)	59.0 (0–89.0)	61.0 (0–97.0)	
FEV_1	(*n* = 63)	(*n* = 56)	(*n* = 119)	
Mean ± SD	1.9 ± 0.8	1.8 ± 0.7	1.8 ± 0.7	0.863[b]
Median (min-max)	1.7 (0.5–4.0)	1.8 (0.5–4.5)	1.7 (0.5–4.5)	
Severity (%) [d]				
Mild	22.9	25.5	24.2	0.313[c]
Moderate	56.9	51.8	54.3	
Severe	14.7	20.9	17.8	
Very severe	5.5	1.8	3.7	
BODE index	(*n* = 19)	(*n* = 24)	(*n* = 43)	
Mean ± SD	3.9 ± 3.2	3.4 ± 2.9	3.6 ± 3.0	0.595[b]
Median (min-max)	3.0 (1.0–10.0)	3.0 (0–10.0)	3.0 (0–10.0)	
BODEx index	(*n* = 43)	(*n* = 43)	(*n* = 86)	
Mean ± SD	3.2 ± 2.5	2.9 ± 2.3	3.0 ± 2.4	0.650[b]
Median (min-max)	3.0 (0–10.0)	2.0 (0–9.0)	2.5 (0–10.0)	
Phenotype (%)				
Non-exacerbator	28.4	33.6	31.1	0.703[e]
Exacerbator + emphysema	11.9	9.1	10.5	
Mixed COPD + asthma	18.3	12.7	15.5	
Exacerbator + chronic bronchitis	33.9	37.3	35.6	
Not defined	7.3	7.3	7.3	
Degree of dyspnea[a] (%)				
0	6.4	7.3	6.8	0.766[e]
1	30.3	33.6	32.0	
2	38.5	37.3	37.9	
3	15.6	12.7	14.2	
4	4.6	1.8	3.2	
ND	4.6	7.3	5.9	
CAT score (QoL)				
Mean ± SD	11.8 ± 6.5	11.8 ± 6.7	11.8 ± 6.6	0.986[b]
Median (min-max)	11.0 (1.0–34.0)	11.0 (0–31.0)	11.0 (0–34.0)	
Number of exacerbations in previous year				
Mean ± SD	2.2 ± 2.1	2.1 ± 2.9	2.1 ± 2.5	0.346[b]
Median (min-max)	2.0 (0–10.0)	2.0 (0–25.0)	2.0 (0–25.0)	
Duration of exacerbations (days/exacerbation)				
Mean ± SD	5.3 ± 5.2	5.5 ± 4.5	5.4 ± 4.9	0.497[b]
Median (min-max)	4.0 (0–35.0)	4.0 (0–25.0)	4.0 (0–35.0)	
Number of hospital admissions for exacerbations in previous year				
Mean ± SD	0.3 ± 0.7	0.2 ± 0.5	0.2 ± 0.6	0.673[b]
Median (min-max)	0 (0–4.0)	0 (0–2.0)	0 (0–4.0)	
Consumption of drugs for stable COPD (%)				
Oral corticosteroids	NA	NA	NA	
Inhaled corticosteroids	62.4	55.5	58.9	
Parenteral corticosteroids	NA	NA	NA	
Antibiotics	0.9	3.6	2.3	
Short-acting beta 2 agonist bronchodilators	29.4	24.5	26.9	
Long-acting bronchodilators	95.4	97.3	96.3	
Consumption of drugs for exacerbations (%)				
Oral corticosteroids	38.5	30.0	34.2	
Inhaled corticosteroids	25.7	22.7	24.2	
Parenteral corticosteroids	6.4	6.4	6.4	
Antibiotics	70.6	67.3	68.9	
Short-acting beta 2 agonist bronchodilators	55.0	50.9	53.0	
Number of URTIs since the last visit				
Mean ± SD	0.5 ± 0.8	0.6 ± 1.0	0.6 ± 0.9	0.991[b]
Median (min-max)	0 (0–4.0)	0 (0–4.0)	0 (0–4.0)	

(*continued on next page*)

Table 2 (*continued*)

Baseline clinical characteristics	Homeopathic medicine group (OG)	Control group (CG)	Total	P value
Duration of URTI symptoms (days)				
Mean ± SD	3.4 ± 5.6	3.1 ± 4.6	3.3 ± 5.1	0.953[b]
Median (min-max)	0 (0–30.0)	0 (0–21.0)	0 (0–30.0)	

For all calculations $n = 109$ in OG and $n = 110$ in CG, unless stated otherwise.
NA: not applicable.
[a] Modified Medical Research Council (MMRC) scale: 0 = not troubled by breathlessness except on strenuous exercise; 1 = shortness of breath when hurrying on the level or walking up a slight hill; 2 = walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level; 3 = stops for breath after walking about 100 m or after a few minutes on the level; 4 = too breathless to leave the house or breathless when dressing or undressing.
[b] Mann-Whitney.
[c] Fisher.
[d] Severity: mild: $FEV_1 \geq 80\%$; moderate: $50\% \leq FEV_1 < 80\%$; severe: $30\% \leq FEV_1 < 50\%$; very severe: $FEV_1 < 30\%$.
[e] Chi-square test.

differ significantly between the two groups during follow-up. Although there was a large difference in use of inhaled corticosteroids between the two groups (15.6% in OG vs. 24.5% in CG) this was not statistically significant (p = 0.098) (Table 4).

On the other hand, an analysis of changes in corticosteroid administration (oral, inhaled, or parenteral) for exacerbations in patients with data at inclusion and V2 showed that 22.1% less patients in OG used any corticosteroid treatment between inclusion and V2 (change from 54.8% to 32.7%) compared to 7.5% less in CG (change from 41.1% to 33.6%) (p = 0.005). The difference was statistically significant for oral and inhaled corticosteroids (13.5% less patients used oral corticosteroids in OG vs. 2.8% less in CG (p = 0.009) and 14.5% less patients used inhaled corticosteroids in OG vs. 3.8% less in CG (p = 0.014). The difference for parenteral corticosteroids was not statistically significant (5.8% less in OG vs. 2.8% less in CG; p = 0.462).

3.4.4. Pneumococcus and influenza vaccination

There was no significant difference in number of URTIs or exacerbations in OG between patients who had been vaccinated against influenza or pneumococcus and those who had not.

3.4.5. Quality of life

There was no significant difference in QoL (CAT test) between OG and CG patients during the 4–5-month follow-up period (p = 0.846) (Table 4).

3.5. Compliance and AEs

There were six (5.5%) AEs in OG and four (3.6%) in CG (p = 0.538). Three in OG and two in CG were severe AEs. None of these was considered to be related to the study drug.

Three in OG and two in CG were non severe AEs (local intolerance to inhaled bronchodilator, urinary tract infection, respiratory infection, digestive disorder and trembling). Only two AEs were suspected to be related to homeopathic medication: one digestive disorder (mild intensity) and one case of trembling (moderate intensity). For both, imputability study revealed a doubtful relation. Adherence to homeopathic treatment was high in 94.2% of patients at V1 and 92.3% at V2, and medium in 3.9% and 7.7% of patients at V1 and V2, respectively.

4. Discussion

The results of this observational study suggest that administration of a homeopathic medication to COPD patients during the influenza-exposure period may help to reduce the frequency and duration of URTIs that can lead to COPD exacerbations. The incidence of URTIs in patients who took the homeopathic medication (OG) was 50% less than that in the control group (0.51 vs. 1.04, respectively; 0.52 less episodes per patient) (p = 0.001). Furthermore, only 9.5% of patients in OG suffered two or more episodes of URTI during the follow-up period compared to

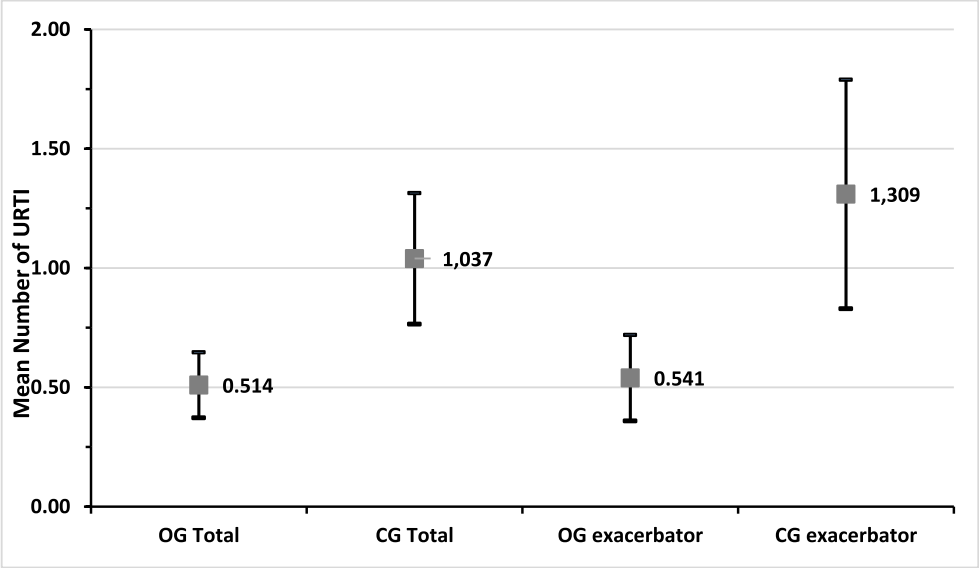

Fig. 2. Mean number of URTIs (± 95%CI) over the study period in the two treatment groups and in patients with the exacerbator phenotype.

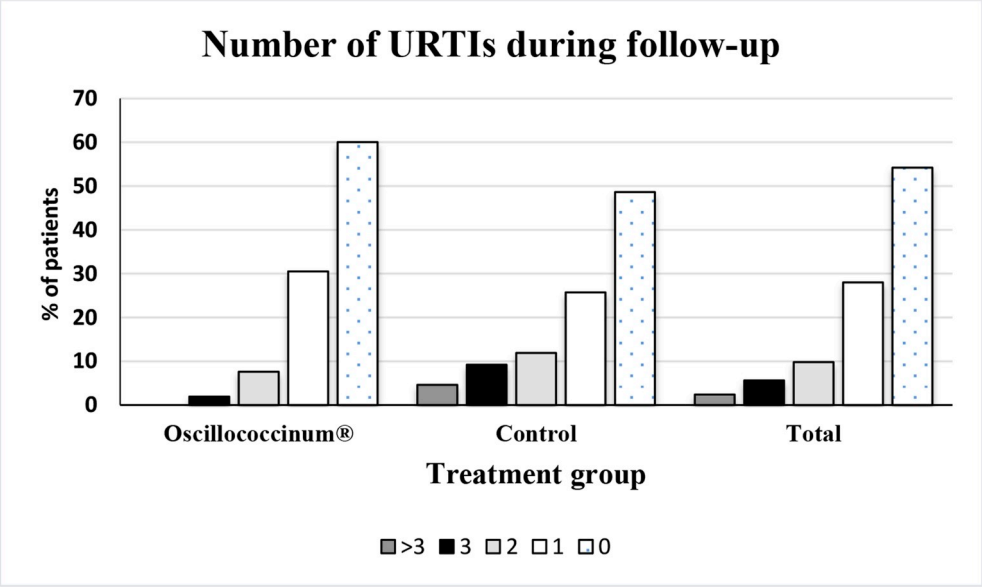

Fig. 3. Comparison of the number of URTIs during follow-up in the two treatment groups (p = 0.029).

25.7% in CG (p = 0.029). These figures were 1.9% vs. 13.8% respectively for patients suffering ≥3 URTIs. The mean duration of symptoms per URTI episode was also significantly less in OG patients (3.57 vs. 5.22 days, respectively; 1.65 days less; p = 0.012). This is a shorter symptom duration than the 0.28 days less [95%CI: 0.50–0.06] reported in a Cochrane review [46]. However, the two studies cannot be compared directly since the Cochrane review described a curative study with a treatment dose of Oscillococcinum® whereas we were interested in COPD patients given a weekly dose during the influenza-exposure period. In addition, the former study was limited to influenza and influenza-like illness whereas we investigated a broader spectrum of URTIs including the common cold. Our results support those of previous studies which reported the benefits of Oscillococcinum® in influenza-like syndrome and URTIs [34–36].

The risk of COPD exacerbations varies considerably between patients and has been related to a number of risk factors including history of previous exacerbations, age > 65 years, COPD severity, high BODE index, poor health status, and presence of comorbidities (for review see Ref. [18]). In the current study, the mean number of exacerbations in the 12 months prior to the study was 2.1 which is similar to an average of 1.5–2 exacerbations per year reported by Viejo-Bañuelos [47]. The mean number of exacerbations during the follow-up period was 1 in CG and 0.7 in OG patients which is low when it is considered that the patients were selected in the autumn and winter months when exacerbations are more likely to occur. Furthermore, the difference between the two groups was not statistically significant. The major determinant for exacerbations in the ECLIPSE study was a history of previous exacerbations [48]. In the current study, a sub-analysis of patients with the exacerbator phenotype showed that the mean number of exacerbations in the follow-up period was 0.9 in OG vs. 1.5 in CG. There were 40% less exacerbations (or 0.6 less episodes) per patient in absolute numbers (p = 0.037). In the follow-up period, the mean duration of exacerbations per episode in patients having ≥1 exacerbation was 6.03 days in OG vs. 6.16 days in CG. This difference was not statistically significant (p = 0.876). Exacerbations lead to a deterioration of lung function, more hospital admissions, poor QoL, and increased healthcare costs [20,47]. It is therefore important to prevent such events from occurring. Our results suggest that studied homeopathic medication could be of particular interest in patients with the exacerbator phenotype, although our results are preliminary and are based on a small subgroup (n = 116) with low statistical power.

The use of homeopathic medicines to manage URTIs and other respiratory diseases is associated with a lower prescription of antibiotics and conventional drugs related to these health problems [49,50]. A reduction in the incidence, duration, and complications of URTIs in COPD patients may have an impact on the prescription of exacerbation-related drugs. We noticed a decrease in consumption of drugs aimed at treating exacerbations (bronchodilators, antibiotics, and corticosteroids), which was statistically significant for corticosteroid (oral and inhaled) use in OG patients between inclusion and visit 2. For all corticosteroids together, irrespective of the route of administration, 22.1% less patients in OG used corticosteroids at V2 compared to 7.5% less in

Table 3
Sub-analysis of URTIs and COPD exacerbations in the follow-up period in patients with the exacerbator or non-exacerbator phenotype.

	Exacerbators			Non-exacerbators		
	OG (n = 61)	CG (n = 55)	P value	OG (n = 39)	CG (n = 48)	P value
Number of URTIs						
Mean ± SD	0.54 ± 0.72	1.31 ± 1.81	**0.011**[a]	0.51 ± 0.76	0.77 ± 1.06	0.370[a]
Median (min-max)	0 (0–3)	1 (0–9)		0 (0–3)	0 (0–4)	
Number of exacerbations						
Mean ± SD	0.9 ± 1.3	1.5 ± 1.7	**0.037**[a]	0.3 ± 0.6	0.4 ± 0.7	0.554[a]
Median (min-max)	1 (0–7)	1 (0–8)		0 (0–2)	0 (0–2)	

OG: group treated with conventional medicines + homeopathic medication; CG: control group treated with conventional medicines only; URTIs: upper respiratory tract infections; SD: standard deviation.

[a] Mann-Whitney.

Table 4
Secondary outcomes data during the follow-up period for COPD patients treated with conventional medicines (CG) or with conventional medicines + homeopathic medication (OG).

	During the 4-month follow-up			
	OG	CG	Total	P value
Duration of URTI symptoms per episode (all patients) (days)	(*n* = 105)	(*n* = 109)	(*n* = 214)	
Mean ± SD	1.45 ± 2.33	2.68 ± 3.97	2.08 ± 3.32	0.021[b]
Median (min-max)	0 (0–12.5)	1.5 (0–24.5)	0 (0–24.5)	
Duration of URTI symptoms per episode (≥1 episode) (days)	(*n* = 42)	(*n* = 56)	(*n* = 98)	
Mean ± SD	3.57 ± 2.44	5.22 ± 4.17	4.52 ± 3.61	0.012[b]
Median (min-max)	2.5 (1.0–12.5)	4.0 (1.0–24.5)	3.5 (1.0–24.5)	
Number of COPD exacerbations	(*n* = 105)	(*n* = 109)	(*n* = 214)	
Mean ± SD	0.7 ± 1.1	1.0 ± 1.4	0.8 ± 1.3	0.128[b]
Median (min-max)	0 (0–7.0)	0 (0–8.0)	0 (0–8.0)	
Duration of COPD exacerbations per episode (all patients) (days)	(*n* = 105)	(*n* = 109)	(*n* = 214)	
Mean ± SD	2.33 ± 3.91	3.09 ± 4.51	2.71 ± 4.24	0.140[b]
Median (min-max)	0 (0–22.5)	0 (0–24.0)	0 (0–24.0)	
Duration of COPD exacerbations per episode (≥1 episode) (days)	(*n* = 40)	(*n* = 51)	(*n* = 91)	
Mean ± SD	6.03 ± 4.23	6.16 ± 4.52	6.10 ± 4.37	0.876[b]
Median (min-max)	5.0 (1.0–22.5)	5.0 (1.0–24.0)	5.0 (1.0–24.0)	
Consumption of drugs relating to COPD exacerbations (%)	(*n* = 109)	(*n* = 110)	(*n* = 219)	
Oral corticosteroids	31.2	32.7	32.0	0.808[c]
Inhaled corticosteroids	15.6	24.5	20.1	0.098[c]
Parenteral corticosteroids	2.8	4.5	3.7	0.721[d]
Antibiotics	56.9	56.4	56.6	0.938[c]
Short-acting beta 2 agonist bronchodilators	46.8	46.4	46.6	0.950[c]
QoL (CAT)[a]	(*n* = 104)	(*n* = 107)	(*n* = 211)	
Mean ± SD	11.0 ± 6.1	11.3 ± 6.6	11.1 ± 6.4	0.846[b]
Median (min-max)	10.0 (1.0–34.0)	10.0 (1.0–31.0)	10.0 (1.0–34.0)	

[a] At the 4-month visit (end of study; EOS)
[b] Mann-Whitney
[c] Chi-square test
[d] Fisher

CG (p = 0.005). This difference could be related to the reduction in requirements of the patients due to the slightly lower incidence of exacerbations in the OG.

Our results are limited by the observational design of the study and the potential bias inherent in the absence of randomization. In addition, there was no blinding to study medication: both the patients and clinicians knew which treatments had been prescribed. Prescriptions are often influenced by participation in a study. Interestingly, we noted a significant decrease in use of oral and inhaled corticosteroids for exacerbations in all patients in our study although the decrease was statistically greater in OG than in CG patients.

The mean duration of the follow up was 4.72 ± 0.96 months. Forthcoming studies should increase it to a minimum of 6 months, which will improve the detection of exacerbations. Finally, the data obtained for the number and duration of URTIs and exacerbations were declarative by the patients. The study is strengthened by the inclusion of two groups which had similar sociodemographic and clinical characteristics at inclusion and, as it was observational, the study reflected real-life conditions.

QoL can also be used as a measure of therapeutic efficacy and the CAT questionnaire is specially adapted for COPD [44,45]. From a pharmacological point of view, only the use of bronchodilators in combination with inhaled corticosteroids has been shown to ameliorate QoL in COPD patients. Analysis of QoL in our study did not reveal a significant difference between the two groups at any visit although the duration of the follow-up (4–5 months) is probably too short to detect any real differences in QoL.

Comorbidities are frequent in COPD patients and can result in difficulties in diagnosis and treatment. A study performed in Madrid reported that 90% of COPD patients had comorbidities with a mean of four diseases per patient [51]. Our study shows a similar proportion of patients (89.5%) suffering from comorbidities but only 46.1% of patients had three or more other diseases. We did not specifically look for some of the most frequent diseases reported in that study (heart failure, chronic liver disease, generalized artherosclerosis, thyroid disease, obesity, disorders of lipid metabolism). It is possible that some of the treatments for comorbidities could have a beneficial effect on COPD itself.

Despite recommendations for annual influenza vaccination in COPD patients [12,26–28], the rate of vaccination in these patients is suboptimal [12,28–33]. The prevalence of influenza vaccination among our COPD patients (69%) in Cantabria was similar to that reported previously by Garrastazu et al. (62.7%) [32]. This low uptake of influenza vaccination is probably linked to cultural attitudes. The homeopathic medication may be of particular interest in helping to reduce the incidence of URTIs during the influenza-exposure period in both vaccinated and unvaccinated patients.

It was well tolerated in our study patients and the low incidence of AEs was similar to that reported previously [37].

5. Conclusions

The results of this observational study show the potential interest of a homeopathic medication in reducing the number and duration of URTIs in patients with COPD. Furthermore, there was a significant reduction in number of exacerbations in patients with the frequent exacerbator phenotype. This homeopathic medication should be used as a complementary treatment to influenza or pneumococcus vaccination during the influenza-exposure period, specifically in COPD patients to complement vaccination or in patients who do not wish to be vaccinated, despite recommendations. Further studies are needed to confirm the effects observed in this study.

Declarations

Ethical approval and consent to participate

The study was performed in compliance with the ethical principles

laid down in the Declaration of Helsinki, and according to Good Clinical Practice and current Spanish national regulations (Order SAS 3470/2009). The study protocol was registred as BOI-OSC-2015-01 and reviewed by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). It was approved by the Clinical Research Ethics Committee of the Hospital Universitario Marqués de Valdecilla-Cantabria on 25 of July 2015. The study was classified by the AEMPS as a post-authorization, prospective, follow-up study.

Authors's information

JG and FO are respiratory disease specialists. SC, AV, JL and JG are member of ACINAR organization (Asociación Cántabra de Investigación en Respiratorio). GD is a medical specialist in homeopathy.

Conflicts of interest

J.L. Garcia-Rivero has received speaker's fees from Boiron Laboratories. G. Diaz Saez was the Medical Director of Boiron Laboratories when the study was carried out and continued to collaborate in the study after leaving this post. A. Viejo Casas has received speaker's fees from Boiron Laboratories. All authors of this study, except for G. Diaz, received fees for including patients.

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Authors's contributions

All authors were involved in the recruitment of patients, except GD. GD was a major contributor in the design and development of the study. All authors contributed to the writing of the manuscript.

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