Homoeopathic treatment for chronic cough – a multicentric, prospective, observational cohort study

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ABSTRACT

Introduction: Cough is a major symptom of respiratory and some non-respiratory ailments for which patients usually seek primary medical care. Homoeopathy is frequently used for treatment of chronic cough from Upper airway cough syndrome (UACS), Asthma and related syndromes, or Gastroesophageal reflux disease (GERD). Study Design: A multi-centre, prospective, observational cohort study was designed. Study setting: The study was conducted in the outpatient departments of 10 centres of Central Council for Research in Homoeopathy, India from May 2018 – June 2020. Patients: The study enrolled patients of any gender, between 7-65 years of age, presenting cough lasting >8 weeks. Main Outcome Measure(s): Cough Severity Index (CSI) and EQ-5D-5L scales were used to analyse the outcomes. Results: Out of 2397 patients screened, only 706 cases with minimum four follow ups were studied on modified Intention to Treat (mITT) basis. The outcomes of the study were analysed by CSI and EQ-5D-5L scores. The mean of the CSI score at baseline was 19.09 while it reduced to 3.89 in the eighth follow-up with p value p-value<0.05. Phosphorus, Arsenic album, Pulsatilla, Sulphur, Lycopodium and Silica were found to be the most often prescribed medicines.

Keywords: Cough, Homoeopathy, Upper Airway Cough Syndrome, Asthma, Gastroesophageal Reflux Disease

INTRODUCTION

Cough is an important and common symptom of respiratory and non-respiratory ailments. Cough is reported the most frequent complaints, especially in children, given that more than two third of all children suffer from cough within a period of six months [1]. It causes considerable absence from school and work. In India, chronic respiratory disease was estimated to account for 7 per cent of all deaths and 3 per cent of DALY’S lost [2]. In India, chronic cough is reported
approximately 10-20% of the general population and identified as the sixth common reason for hospital outpatient department visits [3, 4, 5].

A cough is usually classified on time duration as acute (that lasts for <3 weeks), subacute (that lasts between 3 and 8 weeks) and chronic (that lasts for >8 weeks) [6, 7]. With a normal chest radiograph in an healthy adult who does not use an ACE-I (Angiotensin Converting enzyme) or cigarettes, chronic cough is most commonly caused by 3 conditions: 1. Upper airway cough syndrome (UACS), 2. Asthma and related syndromes, or 3. Gastroesophageal reflux disease (GERD) [8, 9]. Cough is one of the most common clinical presentations among children, for which they come to general practitioners or clinicians for the treatment and often referred to paediatricians [10]. Antibiotics are frequently prescribed by the doctors which usually provide little benefit and can cause harm [11].

The Cough Severity Index (CSI) questionnaire is designed to be an aid in the assessment of the severity and impact of cough. This scale was developed and validated to quantify patients’ symptoms associated with upper airway chronic cough [12]. CSI includes a set of 10 questions that encompass statements frequently employed by individuals to depict their cough and its impact on their daily lives. The rating scale is 0-4, a Score of 3 or below is considered normal. If the score is higher than 3, cough may be impacting on the persons quality of life [13].

The 5-level EQ-5D version (EQ-5D-5 L) which also includes a visual analogue score (VAS) for well-being, was introduced by the Euro Qol Group in 2009 to improve the instrument’s sensitivity and to reduce ceiling effects. The descriptive system includes the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems with values between zero and 100 [14].

When managing missing data or deviations from protocol, trial authors face difficulties in assessment and deviate from the intention-to-treat approach. These difficulties can explain the substantial increase in use of modified intention to treat (mITT) approach in the medical literature [15].

Homoeopathy is known to have a significant therapeutic effect in cough and other acute respiratory infections [16, 17, 18, 19]. The study presented here aims at finding the most useful group of homeopathic medicines for chronic cough, finding the most useful indications for that group of medicines, and preparing an algorithm for prescribing in cough cases. Preliminary findings of this study were previously published [13, 20]. In this final analysis of the data, the number of analysed cases has gone up from 104 to 706 and the number of analysed medicines from three to nine. In this paper, we present the outcomes related to demographic data and treatment outcomes. The outcomes regarding to the algorithms based on likelihood ratio and polar/non-polar symptoms require an elaborate discussion and is a part of a larger subject [14]. This will therefore be presented in a separate paper.

**MATERIAL AND METHODS**

**Setting and study design**

A multi-centre, prospective, Observational cohort study was conducted on the patients attending the outpatient departments of ten centres of Central Council for Research in Homoeopathy, India: Dr. D. P. Rastogi Central Research Institute (H) Noida; National Homoeopathy Research Institute in Mental Health, Kottayam; Drug Standardization Unit, Hyderabad; Regional Research Institute for Homoeopathy, Mumbai; Dr. A. C. Regional Research Institute for Homoeopathy, Kolkata; Clinical Research Unit (H), Agartala; Regional Research Institute for Homoeopathy Extn., Puri; Drug Proving Unit, Bhubaneswar; Central Research Institute for Homoeopathy, Jaipur; and Regional Research Institute for Homoeopathy, Gudivada. The Homoeopathic physicians, with postgraduation in Homoeopathy, and 5–10 years
of professional experience, posted as Research Officers in consented research centers, were involved as investigators at each center. All of them were trained in the study protocol, case taking, and questionnaire filling and were oriented as per the expected outcomes before the initiation of the study. This study was followed by a pre-trial study reported earlier [21].

All procedures were following the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2013 [22]. Necessary clearance of the 20th meeting of the Institutional Ethical Committee of Central Council for Research in Homoeopathy, Ref No.1-3/2016.17/CCRHR/Tech./20th EC/3242 Dated: 14.02.2017. The trial was registered with the Clinical Trial Registry of India (CTRI) (CTRI/2018/05/013973) registered on 18 May 2018.

Patients of age between 7 and 65 years of either sex with cough lasting longer than 8 weeks were enrolled in the study. While those on antibiotic treatment within 7 days, presenting with haemoptysis or symptoms conforming to aspiration of a foreign body, or those with uncontrolled hypertension or consuming medicines with cough as adverse effects, such as Angiotensin-converting enzyme (ACE) inhibitors were excluded. However, patients were not recommended to stop any other forms of conventional therapy including that for cough. Patients who smoked, abused stimulants, or had an illness that was likely to interfere during this treatment, as well as pregnant and lactating mothers, were also excluded from the trial.

**Study duration**

The duration of the study was 2 years (May 2018–June 2020), but the period was stretched to December 2020 due to poor patient turnover during the Covid19 pandemic.

**Screening and enrolment procedure**

Initially, all patients were screened for cough, based on the age of the patient and the duration of the cough. After the preliminary screening, the patients were screened for 03 specific inclusion conditions, namely UACS, GERD cough, and Asthma and related syndrome. Before enrolment, written informed consent was taken from the patients, or the guardians of the patients for those aged below 18. In addition, assent was taken for those aged between 7 and 17 years. A detailed case history of each patient was recorded in a pre-designed case-taking proforma, and data were entered in a pre-formatted Excel.
spreadsheet. A flowchart describing the process has been depicted in Figure 1.

**Intervention**

The homoeopathic medicines were obtained from government-authorised Good Manufacturing Practices-compliant firms for each center. The medicines were prescribed mostly from the list of eighty medicines named from the Essential Drugs List booklet based on the totality of presenting complaints and individualizing symptoms, after repertorisation [23]. The selection of medicine was further guided by repertorisation. In this study, 30c, 200c and 1M potencies were used. The potency was selected according to the susceptibility of the patient and followed serially by the next higher potency as per the need of the case. The repetition of potency and doses depended on the intensity of the complaint, it was administered four doses a day for 6c potency, twice or thrice a day for 12c and 30c, once a day for 200c and only weekly for 1M dose. However, since the discretion of potency was left to the prescribers, only potencies 30c and above were used.

**Follow-up**

The patients were followed up every 2 weeks during first 8 weeks, then every 4 weeks or up to 12 months after inclusion. In cases where the patient would stop the control before the 4th follow-up, the last data of the patient was carried forward as per modified Intention to Treat (mITT) method.

**Outcome assessment**

The CSI and EQ-SD-5L questionnaires and doctor's causal assignment were filled in every follow-up i.e., every 2 weeks for the first two months, and then, every fortnight for the remaining four months. mITT was applied to both tools. Further, all the enrolled patients were asked to fill out the specifically designed PFR questionnaires – ‘Cough-Related Homoeopathic Symptoms Questionnaire’ and ‘Questionnaire for General Symptoms’ as mentioned above. These questionnaires were filled at baseline only.

The investigators assigned the effect of the prescribed medicine on clinical judgement using ORIDL as “-1: Deterioration of the patient”, “0: No effect”, “1: Some effects (25% improvement)”, “2: Good effects (50% improvement)”, or “3: Very spectacular changes (cure)”, at each follow-up visit.
Statistical analysis

Data obtained during the study was verified and analysed using the SPSS statistical software, P values < 0.05 was considered for statistical significance. Descriptive statistics was represented as number percentage for categorical while the continuous data was tabulated as Mean ± SD or Median (IQR). Friedmans test was applied to assess the pre and post treatment scores of CSI. The Multivariate test was used to compare the mean at the baseline and follow ups. Repeated Measure ANOVA was applied to compare the mean for different time of follow-ups.

The decrease in the mean CSI score suggests improvement in the cough severity in a patient. For the overall analysed population, the mean of the CSI score at baseline was 19.09, whereas after treatment the means were 11.67, 8.54, 5.85, 4.32, 5.81, 5.01, 5.21, 3.89 thereby showing significant results respectively at first and subsequent follow-ups (till 8th) with p value <0.01 shown in Fig. 5.

RESULTS

Flow of patients

A total of 2397 patients were screened, out of which 857 were enrolled. Applying mITT, the data of 706 patients was analysed, with minimum 04 follow ups. The remaining 1691 had to be excluded according to the exclusion criterion. Data of these 706 patients were analysed. The process of analysis has been represented in Figure 2.

Distribution of data

In the overall population analysed (706) for the study, reference at Table no.1, the sample was distributed almost equally between females and males, the proportion of which was 52.97% and 47.03%, respectively, and the most affected age group was between 26-35 years. Among those analysed, 4.8% patients had gastroesophageal reflux disease (GERD), 51.6% of patients were affected with asthma and associated syndromes, and 43.6% of patients had upper airway cough syndrome (UACS).

Duration of Cough

21% patients had cough for 5-10 years and 18% had cough since 2-5years whereas only 14% patients had cough for 1- 2 years. Figure 3 shows the Percentage of patients with their duration of cough.

CSI Scores

Patients suffering from chronic cough face different situations per day, keeping this into view the 10-point CSI questionnaire was used. During the consultation, patients were questioned of how frequently they encounter the same symptom, based on which they were asked to encircle the response on the 5-point Likert scale ranging from 0-4 (0=never; 1=almost never; 2=sometimes; 3=almost always; 4=always). Figure 4 shows the evaluated score. Twenty five percent of the people had chronic cough for > 10 years.

EQ-5D-5L Scores

To access the quality of life, the EQ-5D-5L Scale was used. The means were compared at the baseline and subsequent follow-ups, the increase in mean reflects improvement. The Repeated measure ANOVA was used for comparison. The mean of the EQ VAS score at baseline was 50.59, at 1st and subsequent follow-ups (8th) was 59.18, 63.87, 67.95, 71.78, 72.79, 73.72, 73.79 and 73.79 which showed significant results with p value <0.05. Fig. 6 shows the increase in VAS score at subsequent follow-ups.

Top 10 remedies that were most frequently indicated and found useful in treating chronic cough patients were: Phosphorus (n=130), Arsenicum Album (n=114), Pulsatilla nigricans (n=85), Sulphur (n=65), Lycopodium (n=31), Silicea and Calc Carb (n=25), Bryonia (n=24), Natrum Mur (n=23) and Nux Vomica (n=22) as represented in Fig 7.

Condition specific analysis

Besides an overall analysis for recovery in chronic cough cases, a condition specific analysis was also conducted for UACS and Asthma and related syndromes to evaluate the role of homoeopathic treatment in these conditions. No statistics could be computed for GERD, since there were not enough cases for processing. UACS.

In this study, the mean CSI score of patients with UACS at baseline was 16.45 with SD ± 9.27 while the mean CSI score and SD recorded at 8th follow-up were 3.64 and ±
7.33 at P value <0.001. The average significant improvement in CSI score recorded over the entire duration of study was 12.81.

The average mean difference for EQ VAS recorded for cases suffering from UACS was 23.45. The mean(±SD) and Median (IQR) comparison for the dimensions of EQ-5D-5L i.e., Mobility, self-care, Usual Activity, Pain & Discomfort and Anxiety and depression at the baseline and subsequent follow-up(s) are shown in Table no. 2.

**Asthma and related syndromes:**

For Asthma and associated syndrome, the mean CSI score at the baseline was 21.33 ± 10.14 whereas the mean(±SD) recorded at the 8th follow-up was 3.75 (±5.23), showing a downward trend towards improvement.

The mean difference for EQ-VAS score from baseline to 8th follow-up was found to be 23.93. The improvement in the dimensions of EQ-5D-5L i.e., mobility, self-care, usual activity etc. has been shown in Table no. 3.

**DISCUSSION**

This study highlights the effective role of homoeopathic medicines in treating chronic cough. A pilot study on this subject is reported elsewhere [24]. The prevalence of chronic cough and chronic phlegm are important indicators of respiratory morbidity and mortality. It is associated with an accelerated decline in lung function, and increased hospitalization and mortality [25]. Cough is a frequent reason for prescribing antibiotics by doctors, but antibiotics provide modest benefit. India counts as a top consumer of antibiotics in the world, evidence suggests that between 2000 and 2015, antibiotic consumption increased from 3.2 to 6.5 billion DDDs (103%) while

<table>
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<th>Variable</th>
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<td><strong>Gender (%)</strong></td>
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<td>Asthma &amp; Related Syndrome</td>
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Table 1: Demographic data with morbidity profile of the patients. CSI and EQ-5D-5L scales were used to analyse the outcomes of the study. The mean of scales was compared at the baseline, and at subsequent follow-ups (till 8th) by using the repeated measures ANOVA.
the antibiotic consumption rate increased from 8.2 to 13.6 DIDs (63%) in India. For all the data available for the pathogens, India reports to have the highest anti-microbial resistance. In year 2019 India reported of having the worst Drug Resistance Index (DRI) [26, 27]. With the emergence of antimicrobial resistance (AMR), respiratory complaints have become more difficult to treat. In addition to antibiotics, antitussive medications are also often used for cough, with Codeine being one of the most popular opioid-derivative antitussives. These antitussive medications suppress the cough instead of treating it [28]. In an expert review conducted by S. Birring et al., the currently available cough medications are seldom without side effects; the inability of antitussive medications that can be tolerated is related directly to adverse effects on the central nervous system. There is an urgent and immediate need for novel medicine since there are so few existing that are both effective and safe [29]. Homoeopathy is one potential, cost-effective and therapeutic solution that can reduce the usage of antibiotics, thus also avoiding related adverse effects. Earlier evidence has supported that homoeopathy is beneficial and can reduce the prescription of antibiotics for URTIs and their sequelae [30, 31, 32, 33]. In this paper, we show results of improvement in cough with homoeopathic treatment, assessed by using standardised scales. The results of this study showed significant weekly improvement in chronic cough cases as assessed through two measuring tools, CSI and EQ-5D-5L.

The mean of CSI improvement in our study in about 6 months was 15.2, which is similar to improvements in other (non-Homoeopathy) studies that have used this scale, although the intervention was not homoeopathic in these studies. The study conducted by Simpson et al. compared the CSI score before and after treatment and found an average significant improvement of 12.20, while Shembel et al. conducted a related study, during the first presentation and the most recent follow-up visit recorded, CSI scores for all patients were obtained. At these two points, the mean CSI improvement reported was 16.30 [34, 35]. Further, the mean score of EQ-5D-5L VAS at the last follow up (within 6 months) showed improved quality of life at 73.93 in our study, whereas it was found to be 76.2, 61.4 and 61.0 in other studies of asthma, Interstitial
lung disease and COPD, respectively [36, 37, 38]. Both scales, thus, showed significant improvement with individualised homoeopathic treatment in chronic cough. According to Alan G. Kaplan, response to cough treatment can be seen in as little as two weeks, and at least a six- to eight-week trial is needed to fully evaluate a response to treatment. Some patients may need as long as six months [39]. However, in this prospective, observational cohort study, improvement began to show in second follow-up and translated into major improvement within the first forty days of the treatment following the second follow-up. Due to sustained improvement, many participants reported discontinuation of the twenty-eight remedies were prescribed in total, but Phosphorous, Pulsatilla, Sulphur, Arsenic album, Lycopodium, Calcarea carb. and Causticum were found to be most effective. Results of this study are in other therapies they were reportedly using for cough in the initial days of the treatment.

In patients with UACS, the mean difference at the baseline CSI score vs CSI score at follow-up 2 with p value<0.001 was 9.28, while the mean difference EQ-VAS at baseline and 2nd follow-up was 13.05. For patients with Asthma and related syndrome, the mean difference observed in CSI score and EQ-VAS recorded at 2nd follow-up were 11.79 and 13.86 respectively at p value<0.001.

![Image of pie chart showing duration of cough]

**Fig.3- Percentage of patients with duration of chronic cough**
Fig. 4. Percentage of the response rate against the CSI scores at Baseline

Fig. 5. Mean of CSI at the baseline and subsequent follow-ups till 8th Follow-up; p<0.01
Twenty-eight remedies were prescribed in total, but Phosphorous, Pulsatilla, Sulphur, Arsenic album, Lycopodium, Calcarea carb. and Causticum were found to be most effective. Results of this study are in concordance with previous studies in this respect. For example, in the prospective observational cohort study conducted by Gupta et al, there were six high scoring trial medicines, namely Arsenic, Pulsatilla, Lycopodium, Phosphorus, Stannum and Calcarea carb., which covered majority (86%) of the prescriptions showing positive results [40]. In another study conducted by Mulla et al, cough and wheezing were the most common symptoms in the study which responded well to medicines like Phosphorus, Pulsatilla, Arsenicum, Calcarea carb, Sepia and Kali carbonicum in centesimal potency as well as in Millesimal potency [41].

This study, thus, hints upon the significant effect of individualized homoeopathic medicines in treatment as well as management of chronic cough. Despite extensive medical efforts, chronic cough persists for years, burdening patients, enduring for decades in many cases [42]. Thus, demanding higher and more vigorous doses of conventional medicine which may lead to complications in the end [43, 44].

Another goal in this trial was to establish a treatment algorithm for chronic cough through Prognostic Factor Research. The data generated from this study in this respect will be pooled in with other similar data to assess the prognostic factors that could lead to such a treatment algorithm, which doesn’t fall within the per-view of this article.

Overall, the results indicate that homoeopathic medicines are effective in management of chronic cough in general and, especially in Upper airway cough syndrome, Asthma and related syndromes, or Gastroesophageal reflux disease.
Limitations

Despite successful results, the non-randomised, and unblinded design is still a limitation of this study, as it might have led to bias, both at the prescriber’s and patient’s ends. Without a control group, we cannot ascertain whether the observed effects are truly due to the homoeopathic interventions or the result of natural progression, placebo effects, or other confounding factors. Thus, double blind, randomised controlled trials are, therefore, strongly suggested to confirm the results.

CONCLUSION

This observational study, conducted to assess the effectiveness of homoeopathy in treating chronic cough, holds significant value as it was conducted over a two-year period and encompassed over 700 patients. However, an observational study is not the most suitable design for evaluating effectiveness of any modality due to inherent limitations in establishing causal relationships or for arriving at far-reaching conclusions. If the results of this study are confirmed in more rigorously designed studies such as randomised control trials, Homoeopathy can be projected as a reliable mode for treatment of chronic cough.
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Conflicts of interest

None declared.

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