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Original Research Article

Evaluation of the safety and efficacy of codeine phosphate and chlorpheniramine maleate in a fixed dose composition for the management of dry cough in adults: an open label phase IV clinical trial

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ABSTRACT

Background: Dry cough is one of the most common symptoms for which patients seek medical attention. It not only causes discomfort in patients, but also hampers their daily work and routine. Since there is no specific underlying cause for dry cough, a definitive treatment is still not available. Several cough suppressants have been used for the treatment of dry cough including codeine which reduces discomfort. However, some reports suggest that use of codeine at high doses leads to sedation and drowsiness. To evaluate the safety and efficacy of codeine, a clinical trial for fixed dose composition of codeine phosphate and chlorpheniramine maleate was conducted.
Methods: The trial was conducted on 219 adults with prior symptoms of dry cough. Safety was evaluated on the basis of the change in patient's vital parameters, any adverse event or severe adverse event that occurred during the course of study. Efficacy was assessed on the basis of cough severity scores, number of night awakenings due to cough, and overall decline in cough.
Results: According to the investigator's evaluation the product was safe to use as no significant changes in the patient's vital parameters were observed during the course of study. Also, no severe adverse events were reported. Administration of the investigation product significantly decreased cough severity and frequency at the 7th day of the study.
Conclusions: This study suggests, FDC of codeine phosphate 10 mg and chlorpheniramine maleate 4 mg per 5 ml oral syrup is safe and efficacious for the treatment of dry cough.

Keywords: Codeine phosphate, Chlorpheniramine maleate, Dry cough, Fixed-dose composition

INTRODUCTION

Coughing is an act of the respiratory system to expel air from the lungs with an associated perceptible sound. It is one of the first lines of defence to remove noxious substances, foreign bodies, or pathogens present in the respiratory tract.[1] A cough that produces phlegm or mucus is productive while a non-productive dry cough doesn't produce phlegm or mucus. The cause of dry cough can range from allergies to acid reflux, while sometimes there is no specific cause associated with it. An ongoing dry cough can get worse at night impacting the daily routine activities of the patients. Based on the duration of cough, it is typically categorized as acute, which lasts less than 3 weeks; sub-acute, which lasts 3–8 weeks; and chronic, which lasts more than 8 weeks.[2] Among the three categories, acute cough is the most common and has significant implications on public health. People suffering from acute cough not only abstain from work but also incur large expenditures on health care.[3] One of the most common causes of acute cough is viral infections of the upper respiratory tract (URT) collectively referred to as the

common cold.[4,5] It is one of the most ubiquitous infectious diseases striking every adult almost twice a year.[6] These viral infections can lead to mild to severe destruction of the epithelia of upper airway structures resulting in vasodilation and hypersecretion of the upper airway structures. The consequent clinical syndrome includes nasal congestion, nasal discharge, postnasal drip (PND), throat clearing, sneezing, and cough.[6] Of these symptoms, the exact mechanism inducing acute cough is unclear. One of the proposed mechanisms suggests that the production of inflammatory mediators, such as bradykinin, prostaglandins, and tachykinins, causes excessive secretions that result in PND that mechanically stimulates the cough receptors.[7] Another mechanism indicates that viral-induced inflammation of upper airway structures can directly irritate and activate the afferent sensory nerves in the upper airway which causes coughing.[8]

Despite its prevalence, a remedy to acute dry cough has received relatively little attention in the medical literature due to no specific underlying cause. In such a case, non-specific antitussive therapy is used to control the symptoms.[9] Currently, available cough suppressants include centrally acting drugs and peripherally acting antitussives.[10] Centrally acting antitussives inhibit or suppress the cough reflex by depressing the medullary cough center or associated higher centers. This reduces the discharge of nerve impulses to the muscles that produce coughing. Codeine has been used as a standard antitussive for the treatment of cough.[11] Codeine is a methyl ether of morphine that has been in treatment since its isolation in 1832.[11] In a dose-dependent manner of 10, 20, and 50 mg/kg, codeine was found to suppress the cough caused by larynx stimulation.[12] It is widely regarded as the 'gold standard' cough suppressant drug, though some of the side effects such as sedation and drowsiness have been reported to be associated with codeine.[13] However, a study by Dickinson et al indicated that there was no apparent relationship between the degree of cough suppression and drowsiness.[14] Additionally, first-generation antihistamines like chlorpheniramine maleate reduce the frequency of cough and dry up the secretions associated with it. They act by reducing the cholinergic transmission of nerve impulses to the muscles producing cough. The combination of codeine and chlorpheniramine maleate may be useful as an antitussive in the management of nonspecific cough as has been reviewed by Padma.[15] In this study, we examined the safety and efficacy of a fixed-dose combination of codeine phosphate and chlorpheniramine maleate for the management of symptoms of dry cough.

METHODS

Study design

This study is a prospective, single-arm, multi-centric, open-label, prescriber-based, observational, post market surveillance (PMS) study to evaluate the safety and efficacy of a fixed dose combination (FDC) of codeine phosphate 10 mg and chlorpheniramine maleate 4 mg per 5 ml oral syrup in the actual field conditions for the management of symptoms of dry cough. The test product was administered to all the subjects twice daily - morning and evening with or without a meal for 7 days. The dosage as prescribed by the physician was not to exceed 10ml (two teaspoons) at one time. The study treatment period was 7±1 days. The study was initiated with the screening of its first subject on 14 October 2021 which went up to the screening of the last subject on 05 March 2022. The study was completed on its first subject on 20 October 2021 and on the last subject on 11 March 2022. The total duration of the study was 4 months and 27 days.

Study subjects

Adult males and females with ages ranging from 18 to 65 years were enrolled in the study. Individuals having dry cough for less than 7 days with any related symptoms such as throat pain, throat redness, or throat irritation were included in the study. Subjects having fever but not under any antibacterial or antiviral treatment were also recruited. The duration of participation for each subject was planned to be a maximum of 8 days for this study. With an estimated drop-out of approximately 10%, the study proposed to enroll 200 subjects. The subject disposition chart for the study is summarized in Figure 1.

The key exclusion criteria of the subjects were the presence of bronchial mucus or phlegm production in the subjects. Subjects taking medications with known cough-promoting side effects such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were excluded from the study. Subjects with a diagnosis of diseases of pneumonia, asthma, sinusitis, allergic rhinitis, as well as heart disease were not involved in the study. Subjects with known allergy or hypersensitivity to codeine phosphate or chlorpheniramine maleate or any of its components were also not included in the study. During the study, subjects were prohibited from using any medicated confectionery, throat pastille, spray or any product with demulcent properties, any cough medicines or drugs containing antihistamines, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and any other concomitant medication that may interfere with assessment of the study objectives. All the concomitant medications including over-the-counter medications or therapy administered to the subject during the study were recorded.

Study settings

The study was conducted at four centres in India and the complete recruitment was done in the same centres. The four centres were - Santosh Deemed to be University, Ghaziabad, Jaipur Golden Hospital, Delhi, PCMC, Yashwantrao Chavan Memorial Hospital, Pune, and Government Medical College and Government General Hospital, Srikakulam, Andhra Pradesh.

Treatments

The test product was administered twice daily (morning and evening) for 7 days. The dosage was not to exceed 10ml (two teaspoons) each time following the physician's prescription.

Ethics

All the study-related procedures were conducted, evaluated, monitored, and audited for compliance with ICH-GCP guidelines, ethical principles of the declaration of Helsinki, ethical guidelines for biomedical research on human subjects by the Indian Council of Medical Research (ICMR), new drugs and clinical trial rules 2019 and schedule Y (amended version, dated 08/May/2014) and the study protocol. Patients were enrolled in the study following a written approval from the CDSCO registered institutional ethics committees for clinical trials.

Study objectives and endpoints

The primary objective of the current study was to evaluate the safety of FDC of codeine phosphate and chlorpheniramine maleate. Safety was assessed by monitoring the vital signs, adverse events (AEs), serious adverse events (SAEs), unexpected adverse events, and adverse drug reactions and treatment-emergent adverse events (TEAEs).

The secondary objective was to evaluate the efficacy of the FDC of codeine phosphate and chlorpheniramine maleate. Parameters such as change in cough severity, frequency, number of awakenings in the night and total time taken for complete cough relief were assessed. Physical examinations were documented on day 1 (visit 1), day 3±1 (visit 2) and day 7±1 (visit 3) of the study. The change in the efficacy was assessed during the follow-up visit on day 3 and day 7 compared to the baseline (day 1). The flow diagram for the study has been summarized in Figure 2.

Statistical analysis

For this study, 210 patients were enrolled. Statistical analysis was done using statistical package for the social sciences (SPSS) version 26.0. Continuous variables were statistically tested using analysis of variance (ANOVA). Categorical variables were tested using Chi-square test. Primary efficacy analysis was done using ANOVA. Secondary efficacy analysis was done using Wilcoxon signed rank sum test and ANOVA. All safety parameters were analysed using Wilcoxon signed rank sum test and descriptive statistics.

RESULTS

Participant disposition and baseline characteristics

A group of 219 patients were screened in the study out of which 9 subjects failed the screening. 210 subjects were enrolled in the study, of which 10 subjects were lost to follow up (Figure 1). The study on FDC of codeine phosphate and chlorpheniramine maleate was thus completed on a total of 200 subjects. None of the subjects was terminated from the study for any adverse event as per the protocol. Figure 1 shows the summary of the subject disposition in the study. The mean age of patients was 41.23 years and the mean BMI was 24.74 kg/m^2 (Table 1). All the patients were of Indian ethnicity, maximum amongst which were females (52.1%). To monitor the efficacy and safety of the IP, patients were assessed on day 1 (visit 1), day 3 (visit 2), and the final visit on day 7 (visit 3) (Figure 2).

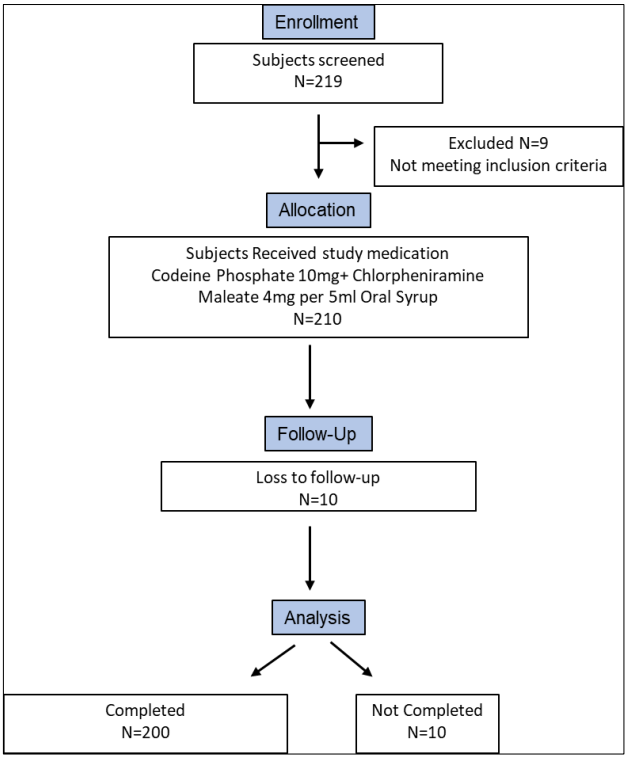

Figure 1: Subject disposition chart.

Table 1: Participant disposition, demographic and baseline characteristics.

Parameter	Mean±SD
Patient	219
Sex M/F n (%)	105/114 (47.9/52.1)
Race ethnicity (%)	Indian (100)
Age (years)	41.23±12.67
Height (in cm)	162.56±8.99
Weight (in kg)	64.82±11.19
BMI (kg/m^2)	24.74±4.45

Safety

The safety profile of investigational product (IP) was found to be favourable in terms of the assessment of vital signs. The IP was well tolerated in respect of adverse events (AEs) reported during the treatment of patients with dry

cough. No deaths or hospitalizations were reported during the study. The vital signs such as blood pressure, pulse rate, respiratory rate, and temperature were assessed at each visit. No significant changes in the vital signs were found during the treatment ($p>0.05$) (Table 2). The only exception was systolic blood pressure where the change was significant. A total of 13 adverse events were reported in 12 patients treated with IP which included headache, sedation, stomach pain, stomach upset, and nausea. All the 13 AEs were mild and none of the adverse events led to a serious adverse event. Of these, 12 AEs were related to the IP and 1 was not related. From the results of this study, it was inferred that FDC of codeine phosphate and chlorpheniramine maleate is safe for the treatment of dry cough.

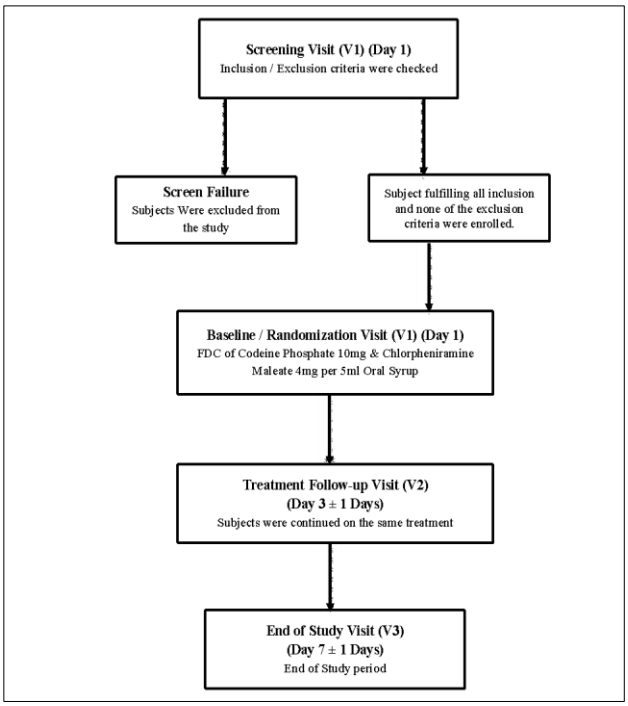

Figure 2: Study activity.

Efficacy

The efficacy of the IP was evaluated on the basis of the mean change in the patient's cough severity and frequency. The scores were assessed during the follow-up visits (visit 2 and visit 3) compared to the baseline (visit 1). Additional parameters such as the mean change in the number of awakenings in the night due to cough, time taken for complete cough relief, and change in score of the throat pain and throat irritation were also monitored.

Cough impact on sleep quality assessment: cough impact on sleep quality (disruption of sleep and frequency of waking up)

Along with a positive impact of IP on cough severity and frequency, an improvement in sleep quality was observed in the subjects. Sleep quality was monitored in terms of disruption of sleep as well as wake-up frequency. Both the parameters were found to be reduced considerably ($p<0.05$) on visit 3 as compared to visit 1 and visit 2 (Figure 4, supplementary Table 2).

Table 2: Vital signs parameters.

Parameters	Mean	N
Pulse rate/min		
Visit 1	89.576±15.101	210
Visit 2	89.118±12.988	203
Visit 3	89.355±12.706	200
Resp. rate/min		
Visit 1	17.84±1.474	210
Visit 2	17.778±1.477	203
Visit 3	17.985±1.595	200
Temperature (F)		
Visit 1	97.759±0.846	210
Visit 2	97.488±0.918	200
Visit 3	97.26±2.391	200
Systolic BP (mmHg)		
Visit 1	128.147±14.978	210
Visit 2	125.133±11.718	203
Visit 3	124.775±10.323	200
Diastolic BP (mmHg)		
Visit 1	80.806±8.183	210
Visit 2	79.852±6.232	203
Visit 3	79.91±5.74	200

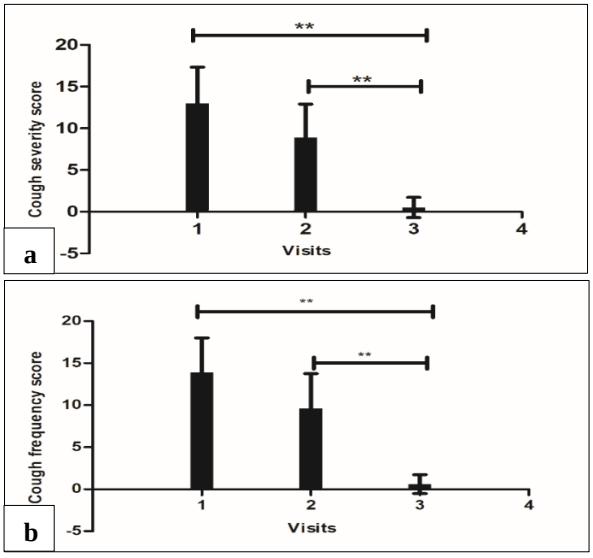

Figure 3: Cough severity and frequency score (a) values represent the mean±SD of the cough severity score, and (b) values represent the mean±SD of cough frequency score.

**Denote significant ($p<0.001$) change between visits

Throat pain and throat irritation score assessment

To investigate the efficacy of the IP in terms of throat improvement, both the throat pain and throat irritation scores were estimated. The scores of both the assessments

almost declined at visit 3 ($p<0.05$) indicating a remarkable improvement in the throat (Figure 5, supplementary Table 3).

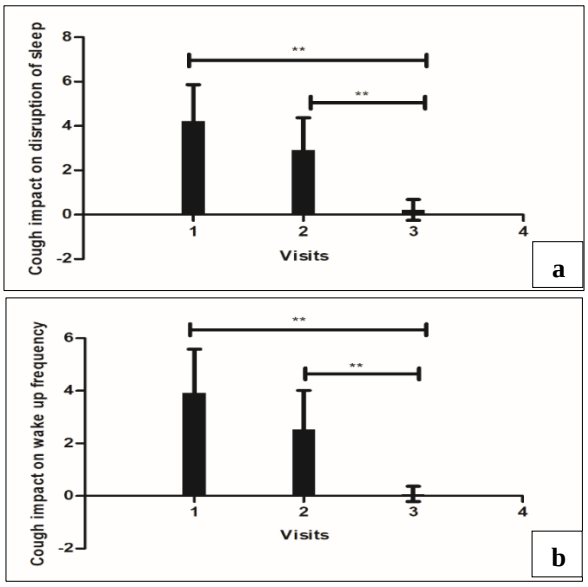

Figure 4: Cough impact on sleep quality (a) values represent the mean±SD of cough impact on disruption of sleep, and (b) values represent the mean±SD of cough impact on wake-up frequency.

**Denote significant ($p<0.001$) change between visits

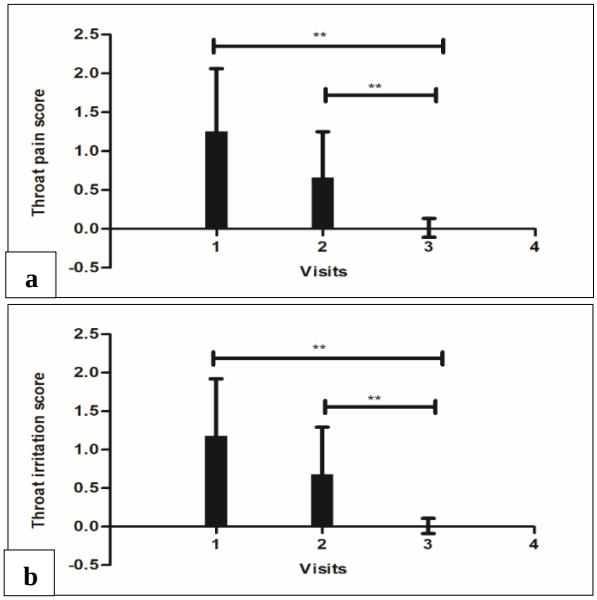

Figure 5: Throat pain and throat irritation score (a) values represent the mean±SD of throat pain score, and (b) values represent the mean±SD of throat irritation score.

**Denote significant ($p<0.001$) change between visits

Cough severity and cough frequency score

Treatment with the IP had a noticeable improvement in the patient's coughing pattern. The cough severity and cough frequency score were reduced significantly ($p<0.05$) over the 7-day treatment period with the IP (supplementary Table 1) (Figure 3). Cough severity score showed a significant decline ($p<0.05$) of 12-fold change observed on visit 3 as compared to visit 1. A 4-times ($p<0.05$) decline in cough frequency score was observed on visit 3 as compared to visit 2 indicating an overall improvement in cough severity and frequency (Figure 3, supplementary Table 1).

Time taken for complete cough relief (days)

To measure the overall efficacy of the IP on cough relief, the score on the visual analog scale (VAS) was monitored. Based on the discomfort, subjects marked on the VAS scale at each visit. The VAS score declined with each visit demonstrating significant improvement in the discomfort due to cough (Figure 6, supplementary table 4). Complete relief from cough was noted by the 3rd visit (day 7) of the study.

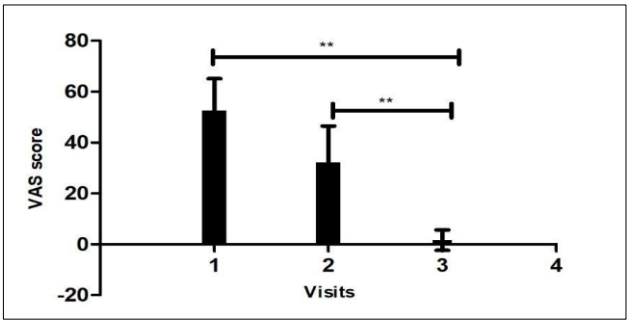

Figure 6: VAS score. Values represent the mean±SD of the VAS score.

**Denote significant ($p<0.001$) change between visits

DISCUSSION

Dry cough has been identified as one of the main reasons for the patients to seek medical care.[16] Coughing is often very troublesome to the patients as it slows down their daily activities. It not only affects their activities during the daytime but also disrupts the night-time sleep influencing the quality of life. Effective management of the dry cough becomes a prerequisite in such a scenario.

One of the most preferred antitussive agents prescribed by the doctors for treating dry cough is codeine. It was first isolated in 1832 and has been used for the treatment of dry cough as early as 1838.[17] It has been found to be efficacious in animal models and has served as a gold standard in the treatment of dry cough.[13] It has been used as a reference for the comparative evaluation of other antitussives. Use of codeine at high doses has been reported to cause sedation and drowsiness.[14] Due to this side effect, it poses an obstacle to be adopted as an antitussive agent by the pharmaceutical industry. However, as the benefits of codeine usage as an antitussive far outweigh its side effects, global regulatory authorities including US FDA have permitted its use for medical

purposes, subject to certain regulations. Internationally, similar drug combinations of codeine and chlorpheniramine are widely available under different brand names in the USA (Pentuss, Codepre, Zodryl AC, and Codar AR) and in other regulated markets as Australia (Codral 4 Flu Tablet, Sandoz), New Zealand (Codral multi action cold and flu tablet), Canada (Robitussin AC) and Japan. In this study, safety and efficacy of codeine phosphate was evaluated in a fixed dose of 10 mg along with chlorpheniramine maleate 4 mg per 5 ml oral syrup for the management of symptoms of dry cough. The study screened 219 subjects having symptoms of dry cough out of which 9 subjects failed during screening and 10 subjects were lost to follow-up. The study was conducted at four centers in India. The treatment started on day 1/visit 1 with follow-up on day 3 (±1)/visit 2 and day 7 (±1)/visit 3/end of study from the start of the treatment.

Data from our study showed that the FDC of codeine phosphate and chlorpheniramine maleate was found to be safe. No significant changes were observed in the patient's vital parameters. A total of 13 AEs were reported in 12 subjects. All the reported AEs were mild in nature and were related to IP. The AEs reported during the study were consistent with the reported side effects of codeine phosphate and chlorpheniramine maleate from previous clinical trials. No SAE was reported during the study. Our study further reveals that the IP was efficacious in the treatment of dry cough. The treatment significantly decreased the cough severity and its frequency on the day 7. Its impact on sleep quality, throat pain and throat irritation were assessed to confirm the efficacy of the investigational product. Based on the VAS score, complete relief from cough was observed on the 7th day. The adverse events associated with drug administration were of mild intensity and without any safety risks to the subjects. Moreover, subjects treated with the IP didn't exhibit any symptoms of addictive behavior or dependence after 7 days of treatment. The safety and efficacy analysis led to the conclusion that FDC of codeine phosphate 10 mg and chlorpheniramine maleate 4 mg per 5 ml oral syrup is safe and efficacious for treatment of dry cough.

The present study had some potential limitations. The small sample size reported in the present study limits the interpretation of the results. Secondly, the study population included patients with dry cough without ascertaining the underlying cause of cough. Further investigation in a larger population with inclusion criteria properly categorizing different causes of dry cough will provide better evidence for the efficacy of the reported combination of codeine phosphate and chlorpheniramine maleate.

CONCLUSION

Codeine presents a safe and cost-effective treatment option for the management of dry cough. It is one of the most widely tested antitussives without any tolerance issues and under prescribed dosage shows consistent efficacy and very mild adverse event profile. From the results of this study, it can be concluded that the FDC of codeine phosphate 10 mg and chlorpheniramine maleate 4 mg per 5 ml oral syrup is a safe and efficacious option for the treatment of dry cough in adults.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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SUPPLEMENTARY DATA

Table 1: Change from baseline in patient's cough severity score in PP population.

	Mean±SD	N	Median	Min, max	CI	P value (paired t-test)
Cough severity						
Visit 1	13.02±4.32	200	12.5	2, 25	(12.42-13.61)	
Visit 2	8.86±4.05	200	8	0, 20	(8.3-9.42)	
Visit 3	0.51±1.2	200	0	0, 10	(0.34-0.68)	
Change between V1 to V2	4.35±2.9	200	4	0, 16	(3.94-4.75)	0.001**
Change between V1 to V3	12.51±4.11	200	12	2, 25	(11.94-13.07)	0.001**
Cough frequency						
Visit 1	13.89±4.13	200	13	3, 28	(13.31-14.46)	
Visit 2	9.61±4.15	200	9	0, 20	(9.03-10.19)	
Visit 3	0.62±1.12	200	0	0, 8	(0.47-0.78)	
Change between V1 to V2	4.52±2.64	200	4	0, 17	(4.15-4.88)	0.001**
Change between V1 to V3	13.27±3.87	200	13	2, 27	(12.73-13.8)	0.001**

Table 2: Change from baseline in cough's impact on sleep quality in PP population.

	Mean (SD)	N	Median	Min, max	CI	P value (paired t-test)
Cough impact on sleep quality (disruption of sleep)						
Visit 1	4.23 ±1.63	200	4	1, 8	(4-4.46)	
Visit 2	2.91±1.464	200	3	0, 6	(2.71-3.11)	
Visit 3	0.22±0.471	200	0	0, 2	(0.16-0.29)	
Change between V1 to V2	1.33±0.944	200	1	0, 6	(1.2-1.46)	0.001**
Change between V1 to V3	4.01±1.53	200	4	1, 8	(3.8-4.22)	0.001**
Cough impact on sleep quality (wake up during last night)						
Visit 1	3.915±1.67	200	4	1, 8	(3.68-4.15)	
Visit 2	2.535±1.479	200	2	0, 6	(2.33-2.74)	
Visit 3	0.08±0.29	199	0	0, 2	(0.04-0.12)	
Change between V1 to V2	1.44±0.993	200	1	0, 6	(1.3-1.58)	0.001**
Change between V1 to V3	3.835±1.642	200	4	0, 8	(3.61-4.06)	0.001**

Table 3: Change from baseline in throat pain and throat irritation score in PP population.

	Mean (SD)	N	Median	Min, max	CI	P value (paired t-test)
Throat pain						
Visit 1	1.26±0.8	200	1	0, 3	(1.15-1.37)	
Visit 2	0.67±0.59	200	1	0, 4	(0.58-0.75)	
Visit 3	0.02±0.12	200	0	0, 1	(0-0.03)	
Change between V1 to V2	0.63±0.6	200	1	0, 2	(0.54-0.71)	0.001**
Change between V1 to V3	1.25±0.78	200	1	0, 3	(1.14-1.35)	0.001**
Throat irritation						
Visit 1	1.18±0.74	200	1	0, 3	(1.08-1.28)	
Visit 2	0.68±0.61	200	1	0, 4	(0.6-0.77)	
Visit 3	0.01±0.1	200	0	0, 1	(0-0.02)	
Change between V1 to V2	0.53±0.62	200	0	0, 3	(0.44-0.62)	0.001**
Change between V1 to V3	1.17±0.73	200	1	0, 3	(1.07-1.27)	0.001**

Table 4: Change from baseline in level of overall discomfort due to cough on VAS scale.

VAS score	Mean (SD)	N	Median	Min, max	CI	P value (paired t-test)
Visit 1	52.61±12.55	200	54	20, 85	(50.87-54.35)	
Visit 2	32.245±14.26	200	30	3, 60	(30.27-34.22)	
Visit 3	1.605±3.98	200	0	0, 28	(1.05-2.16)	
Change between V1 to V2	20.915±9.45	200	20	0, 50	(19.61-22.23)	0.001**
Change between V1 to V3	51.001±12.84	200	51.5	17, 85	(49.23-52.79)	0.001**