Drug Corner

A Prospective, Observational Study to Determine the Demographic Characteristics and Clinical Profile of Indian Patients Presenting with Dry Cough and Effectiveness and Safety of the Fixed-Dose Combination of Codeine Phosphate and Triprolidine Hydrochloride in these Patients

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Objective : Considering the increasing incidence of dry cough in India, this study was intended to evaluate the effectiveness and safety of the fixed-dose combination (FDC) of codeine phosphate and triprolidine hydrochloride.

Methods : Demographics, clinico-etiological profile and quality of life (QoL) of adult patients with dry cough, prescribed with the FDC of codeine phosphate and triprolidine hydrochloridewere determined. Standard tools were used for measuring effectiveness and safety during the study.

Results : Out of 222 (100.0%) patients, mostaged either ≥55 years (31.08%) or 18-35 years (30.18%). Etiology of dry cough presented by more than 20% patients were allergy (43%), environmental factors (25.23%), and respiratory tract infection (23.42%). Significant (p<0.0001) reduction in the mean score of cough frequency, cough severity,and sleep disruption was evident at end of treatment. Approximately 97% patients achieved minimal important differencein a mean (±SD) duration of 5.0 (±0.27) days. Improvement in QoL of patients was also reported withno adverse drug reaction during the study.

Conclusion : In Indian set-up, dry cough was demonstrated equally by both the genders with primary presentation among elderly and young adults. The FDC was found to be effective, and safein the management of *dry cough,* with an overall improvement in QoL.

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Key words **: Dry cough, codeine phosphate, triprolidine hydrochloride, VAS, LCQ score, minimally important difference (MID).**

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree mediated by sensory neurons in the airways. Cough precipitates as a defence mechanism, however in certain situations, it may exacerbate affecting the airway mucosa.[1] Global prevalence of cough is reported to be 9.6%, while 5%-10% prevalence is reported among Indian population.[2] It is one of the most common complaints among Indians at the primary care setting (30%)[3] and outpatient departments (6.5%).[4] Consequently, it is reported as a 'frequent' symptom according to an Indian population-based survey (Age standardized prevalence: 6.5%; rural: 9.4%; urban: 3.7%).[5] Regardless of the etiology, dry cough incidence may adversely affect the quality of life (QoL), sleep, and work productivity,[6] and in chronic cases may lead to urinary incontinence and depression.[7] Multifactorial etiology of dry cough often hinders with the diagnosis and prognosis of this condition.

Though treatment of cough mainly involves treating the underlying cause, yet symptomatic relief remains an important goal to improve the patients' QoL. In this light, antitussives continue to be the mainstay therapy against

Editor's Comment :

- **Dry cough is one of the commonest symptom prevalent equally in both the genders.**
- **Allergy is the most prevalent etiology of dry cough.**
- **Majority of the patients present dry cough with acute severity.**
- **Most Indian physicians prescribe FDC of codeine phosphate and triprolidine hydrochloride due to its effectiveness as a treatment measure.**
- **The FDC is found to be effective, and safe in the management of dry cough, with an overall improvement in QoL.**

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dry cough.[8] A potent antitussive, codeine, is reported as one of the most commonly preferred centrally acting agent, mainly due to its established efficacy through multiple clinical evaluations.[9,10] In addition to the cough suppressant property, codeine also has analgesic and sedative effects, which relieves painful cough experienced during hemoptysis and lung cancer. Number of clinical reports have demonstrated the importance of codeine in the treatment of persistent and painful cough during lung cancer and hemoptysis.[11-13]

The combination of codeine phosphate and triprolidine hydrochloride is commonly used in India. Triprolidine is a first-generation antihistamine that binds to H1 receptor, thereby blocking the actions of endogenous histamines; and hence, used for symptomatic relief of allergy and common cold. Clinical evidences have demonstrated several benefits of codeine in combination with the first-generation antihistamines in relieving cough by virtue of their pharmacodynamic characteristics.[8] Although codeine is proven to be effective in clinical trials, real-world evidence of its utilization in the primary care setting in India is limited. Also, there is paucity of data on the use of codeine and triprolidine combination among patients with dry cough in the Indian setting.

Hence the objective of this prospective, observational study was to explore the clinico-etiological profile and demographic characteristics of adult patients with dry cough recommended with fixed dose combination (FDC) of codeine phosphate and triprolidine hydrochloride as part of routine clinical practice. The effectiveness and safety of this combination was also evaluated in the study patients.

Material and Methods

Study design and patient population :

This prospective, observational, multi-centric study was conducted between October 2018 to March 2019 across 15 centers of India (Nagpur, Indore, Pune [3 sites] and 2 sites each in Chennai, Hyderabad, Nasik, Mumbai and Bhopal). Adult patients with dry cough prescribed with codeine phosphate and triprolidine hydrochloride combination (Phensedyl T; Abbott Healthcare Pvt. Ltd) for symptomatic relief of dry cough (either on the same day of enrolment or a day before) in routine clinical practice were enrolled (dose: 5 ml TID, oral route). Patients with dry cough already on FDC codeine phosphate and triprolidine hydrochloride treatment for ≥2 days, or on treatment with anticholinergics, barbiturates, tricyclic antidepressants or other central nervous system depressants, or with any medical condition deemed unacceptable for inclusion based on the investigator's discretion were excluded from the study. Pregnant and/or lactating women were also not included in the study.

The study involved a baseline visit and a follow-up visit at end of treatment (EOT) on Day 7 (± 1 day).

The study protocol was approved by Conscience independent ethics committeeand conducted in accordance with the principles of Declaration of Helsinki, International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

Study endpoints :

Primary endpoints were demographic characteristics that included age, gender, education, and occupation. Clinico-etiological profile comprised of cough classification, mean cough duration, cough etiologies, cough characteristics (cough severity [100-mm Visual Analog Scale (VAS) score], frequency [7-point Likert scale score], night-time awakenings [10-cm VAS score]), concomitant symptoms, co-morbid illness, and rationale for prescribing the FDC of codeine phosphate and triprolidine hydrochloride.

Secondary endpoints included analyzing effectiveness of the study drug as a measure of mean change in cough frequency score using 7-point Likert scale (0: not at all; 6: constant), mean change in cough severity score using a 100-mm VAS (0: no cough to 100: worst cough ever), proportion of patients with minimal important difference (MID) ie, decrease in VAS severity score by ≥17 mm at Day 5 and/or Day 7, time (in days) for achieving MID, and mean change in sleep disturbance by night-time awakenings score based on a 10-cm VAS (0: best possible sleep to 10: worst possible sleep). All assessments were recorded from baseline to EOT; Day 7 [± 1 day].

The QoL was assessed by mean change in Leicester cough questionnaire (LCQ)-acute score (total and domain scores—physical, psychological, and social).

Safety and tolerability of study drug were also assessed (proportion of patients with adverse drug reactions (ADRs), treatment-emergent adverse events, with serious and fatal ADRs and with ADRs leading to discontinuation of the study drug).

Statistical methods :

No formal sample size calculation was done for this study. Continuous variables were summarized descriptively. Categorical data were summarized as numbers and percentages. Secondary variables were assessed by paired t-test. Statistical tests were performed at 5% level of significance. Statistical analysis was done using Statistical Analysis System® version 9.4 software.

Results

Demographic and clinical characteristics :

Of the 222 (100%) enrolled patients, 113 (50.90%) were

Table 1 — *Summary of Socio Demographics- All Enrolled Analysis Set (N=222)*

Parameter Assessed	Details	n (%)
Gender :		
	Females	113 (50.90%)
	Males	109 (49.10%)
Age :		
	≥55 years	69 (31.08%)
	18-35 years	67 (30.18%)
	36-45 years	55 (24.77%)
	46-54 years	31 (13.96%)
Occupation :		
	Unemployed	118 (53.15%)
	Skilled Worker	72 (32.43%)
	Unskilled Worker	22 (9.91%)
	Semi-Professional	56 (25.22%)
	Professional	28 (12.61%)
	Clerical, shop-owner, farmer	76 (34.23%)
	Semi-Skilled Worker	4 (1.80%)
Education :		
	Graduate or Postgraduate	166 (74.77%)
	Intermediate or Post-High School Diploma	79 (35.59%)
	High School Certificate	59 (26.58%)
	Middle School Certificate	33 (14.87%)
	Primary School Certificate	16 (7.2%)
	Profession or Honors	17 (7.65%)
Socio-economic status :		
	Upper Middle Class	126 (56.76%)
	Lower Middle	50 (22.52%)
	Upper Lower	28 (12.61%)
	Upper Class	17 (7.66%)
	Lower Class	1 (0.45%)

females and 109 (49.10%) were males (Table 1). The mean ±SD age of study population was 45.76 ± 15.47 years. Most enrolled patients aged ≥55 years (69 [31.08%]), followed by 18-35 years (67 [30.18%]), 36-45 years (55 [24.77%]) and least number of patients were in the age group of 46-54 years (31 [13.96%)]. Most study patients were unemployed (118 [53.15%], however ~35% patients were clerks, shop-owner, farmer (n=76) or skilled workers (72 [32.43%]). About 56 patients (25.22%) were semi-professionals, while a small proportion of patients were professionals (28 [12.61%]), unskilled workers (22 [9.90%]) or semi-skilled workers (4[1.80]). Majority of the patients (75%) were graduate or postgraduates (n=166). Based on Kuppuswamy classification, socioeconomic status of most study patients was upper middle class (126 [56.76%]), followed by lower middle (50 [22.52%]), and upper lower class(28 [12.61%]).

Other baseline characteristics :

In this study, the mean ±SDweight and height of overall patients was 63.6±11.31 kg and 1.6±0.09 m respectively, while the mean ± SD waist circumferenceand BMI was 83.0 ± 10.41 cm and 24.6 ± 4.22Kg/m^2 respectively. Of 222 enrolled patients, 33 (14.86%) patients had a history of concomitant symptoms/conditions. Of these 33 (14.86%) patients, most presented with respiratory, thoracic and mediastinal disorders (13 [39.39%]), followed by gastrointestinal (8 [24.24%]), and infections and infestations (7 [21.21%]).

Results of blood parameters, radiological investigations, vital signs and physical examination performed at baseline were comparable with the EOT (Day 7 ± 1) observations.

In view of the study indication, all patients were administered with cough and cold preparations as a concomitant medication. Drugs for obstructive airway diseases (83 [37.4%]) and antihistamines for systemic use (63 [28.4%]) were the commonly used concomitant medications.

Clinico-etiological profile :

Clinical classification of most study patients was acute (199 [89.64%]), followed by sub-acute (12 [5.41%]) and chronic(11 [4.95%]). Approximately 43% patients reported the cough etiology to be allergy (n=95), followed by environmental factors(56 [25.23%]), respiratory tract infection (52 [23.42%]), post infectious cough (25 [11.26%]), and asthma (24 [10.81%]). Less than 10% patients presented gastroesophageal reflux disease (GERD), idiopathic, other risk factor and laryngopharyngeal reflux disease (Fig 1).

Concomitant symptoms are summarized in Fig 2. 'Tiredness' was the most prevalent symptom presentedby 136 (61.26%) patients, followed by sore throat (127 [57.21%]), and nasal discharge/ stuffiness (110 [49.55%]). Concomitant symptoms shown by ≥20% patients included hoarseness of voice (85 [38.29%]), frequent throat clearing (84 [37.84%]), wheezing and shortness of breath (73 [32.88%]), and fever (52 [23.42%]). Co-morbid conditions

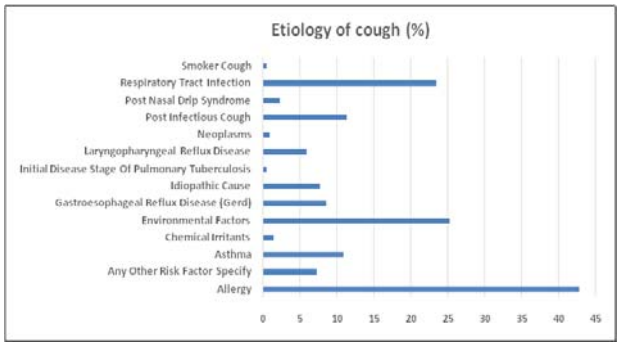

Fig 1 — Etiology of cough

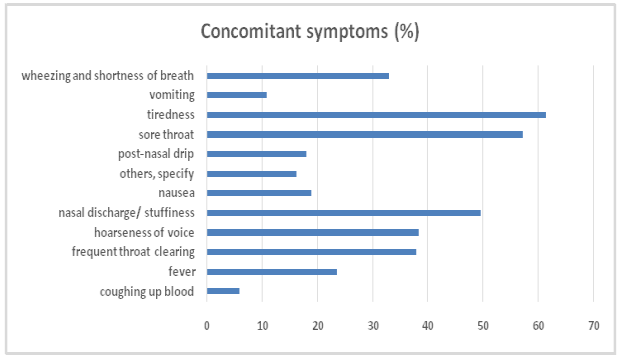

Fig 2 — Concomitant symptoms of cough

presented bye" 10% patients included acidity (32 [14.41%]) and bacterial infection (47 [21.17%]).

This study also recorded the rationale for prescribing the FDC of codeine phosphate and triprolidine hydrochloride. Most patients were recommended the study drug for its effectiveness in dry cough (205 [92.34%]) as a standard of care (80 [36.04%]) and due to its tolerability (73 [32.88%]).

Effectiveness :

The change in mean score of cough based on frequencyfor all enrolled patients at Day 7 compared to baseline are summarized in Fig 3. At Visit 1 (baseline), the mean ±SD score was 4.2±1.13 which significantly ($p<0.0001$) reduced to 0.7± 0.77by EOT (Day 7±1). Similarly, the change in mean score at EOT based on the severity of cough (100 mm VAS scale) indicated a significant ($p<0.0001$) reduction to 10.5 ± 10.68 from 68.0±19.16 (Fig 4). Furthermore, the change in mean score at EOT based on sleep disruption also demonstrated significant ($p<0.0001$) reduction to 0.8 ± 0.89 at EOT (Day 7 ± 1)from baseline score of 5.7 ± 2.41 (Fig 5).

Approximately 97% patients (n=215) achieved MID in a mean (± SD) duration of 5.0±0.27 days.

The mean change in LCQ score from baseline to Day 7 was significant for physical parameter (Mean ± SD: 16.5±7.60; 95% CI for mean: 15.48:17.49; $p<0.0001$), psychological parameter (Mean±SD: 14.7 ± 6.86; 95% CI for mean: 13.80:15.61; $p<0.0001$) and social parameter (Mean±SD: 9.9±4.56; 95% CI for mean: 9.29:10.50; $p<0.0001$), indicating an overall improvement in the QoL of patients with dry cough treated with the FDC of codeine phosphate and triprolidine hydrochloride (Fig 6).

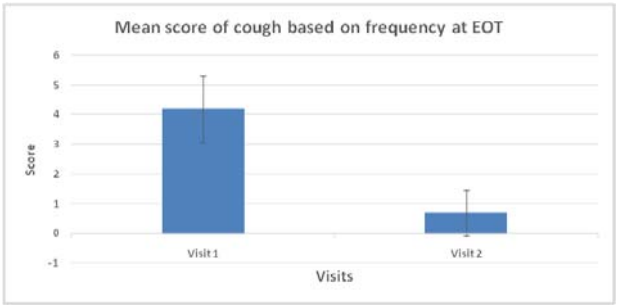

Fig 3 — Summary of Mean Score and Change in Mean Score at EOT from Baseline of Frequency of Cough-All Enrolled Analysis Set (N=222)

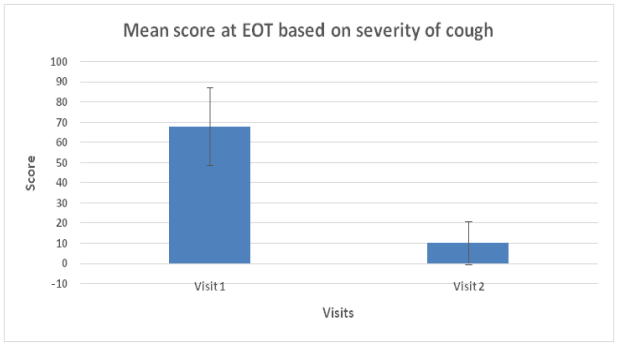

Fig 4 — Summary of Mean Score and Change in Mean Score at EOT from Baseline for Severity of Cough-All Enrolled Analysis Set (N=222)

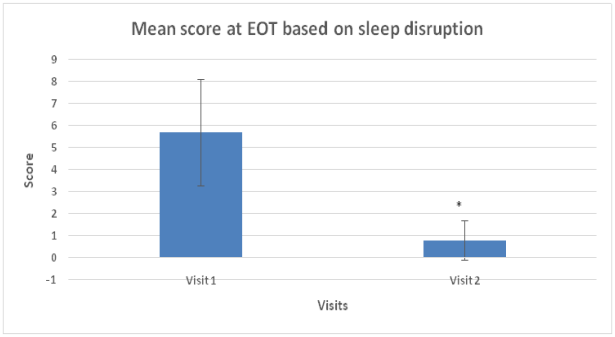

Fig 5 — Summary of Mean Score and Change in Mean Score at EOT from Baseline of Sleep Disruption-All Enrolled Analysis Set (N=222)

Safety :

No serious/non-serious ADRs were reported in the study.

Discussion

Dry cough, which can be acute or chronic, is defined as absence of sputum/phlegm on coughing and is one of the most frequently reported problems among Indian population.[8] Combination therapy may result in greater effectiveness and reduced risk of adverse reactions compared with high-dose monotherapy, at a lower cost, with improved medication concordance.[14] A physician's survey in India found that codeine and/or its combination is preferred as an antitussive in patients with neoplasm postinfectious cough, unexplained cough, and in cough associated with allergy.[15] The codeine-triprolidine combination is available in the Indian market since decades.

In the present study, we assessed the demographic and clinico-etiological profile of patients who have been recommended with codeine phosphate and triprolidine hydrochloride combination for symptomatic cough relief. The effectiveness and safety profile of this combination in the study patients were also assessed.

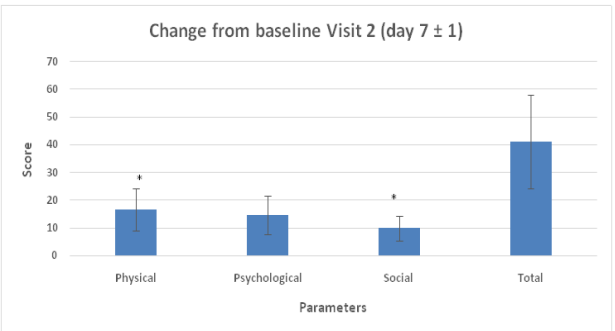

Fig 6 — Summary of Change in Mean Score of LCQ-Score from Baseline to Day 7-All Enrolled Analysis Set (N=222)

This multi-centric, observational study comprised of 222 patients across India who were prescribed with FDC of codeine phosphate and triprolidine hydrochloride for symptomatic relief of dry cough. The proportion of male (49.10%) *versus* female (50.9%) was comparable in this study. Most study patients aged either e"55 years (31.08%) or 18-35 years (30.18%) with a mean ± SD age of 45.76 ± 15.47 years for the study cohort. Occupation of the study cohort was recorded with an aim to establish the etiological association of dry cough among Indian population. More than 50% patients were unemployed which might be attributed to the age being above 55 years or between 18-35 years for most study patients. Occupation of ~35% patients were clerical, shop-owner, farmer or skilled workers which might expose to allergens triggering an incidence of dry cough in susceptible individuals.

Based on Kuppuswamy classification, most patients were classified in upper middle class (56.76%). Clinical classification of dry cough for most study patients was acute (89.64%), followed by sub-acute (5.41%) and chronic (4.95%). This study also recorded the etiology which was 'allergy' for approximately 43% patients, followed by environmental factors (25.23%), and respiratory tract infection (23.42%). Higher prevalence of acute form of cough due to reported etiological factors is in concordance to an Indian questionnaire-based survey conducted among 500 registered physicians.[15]

This study reported the concomitant symptoms of dry cough which was tiredness, sore throat, and nasal discharge/ stuffiness in more than 50% patients. In addition, co-morbid disorders were recorded as bacterial infection (21.17%) or acidity (14.41%).

Amongst the many antitussive agents available for the management of cough, codeine, is one of the most frequently used centrally acting cough suppressant and is considered as the 'gold standard' cough suppressant drug since a long time.[16,17] In this study, most patients were recommended FDC of codeine phosphate and triprolidine hydrochloride for variety reasons that included effectiveness in dry cough (92.34%), as a standard of care (36.04%) and safety profile (well tolerated) (32.88%). This observation is in concordance to an Indian survey that reported codeine as 'ranked 2' recommended antitussive by physicians.[15]

Furthermore, this is the also the first Indian study to evaluate the effectiveness of codeine phosphate and triprolidine hydrochloride combination by means of cough frequency using 7-point Likert scale, cough severity using VAS scale, sleep disruption by 10 cm VAS scale and LCQ score for QoL assessment. These constitute the validated instruments for analyzing the desired parameters. There was a significant reduction in cough frequency, severity, sleep disruption and improvement in QoL score shown by all study patientsat EOT (Day 7 ±1) compared to baseline. These observations corroborate the rationale of 'effectiveness' as reported by most physicians for prescribing the study drug in dry cough management. An Indian study comparing effect of pholcodiene plus promethazine with dextromethorphan plus chlorpheniramine and codeine plus chlorpheniramine also reported reduction in cough frequency and night awakenings after 7 days treatment of each FDC.[18] Moreover, minimally important difference (MID) was exhibited by 95% study patients at Day 5 of treatment as against Day 7 reported by an earlier study on pediatric patients treated with codeine plus chlorpheniramine combination.[18]

No serious/non-serious ADR were reported in this study at the given dose of 5 ml (codeine phosphate 10 mg plus triprolidine 1.25 mg), three times a day, till a maximum of 8 days treatment period. This could be the basis of prescription pattern for dry cough noted among Indian physicians in this study. A previous study reported erythema of the abdomen, epigastric pain and somnolence after 7 days monotherapy with dihydrocodeine but in lung cancer patients.[19]

Limitations

Our study has several strengths. Firstly, this is the first of its kind pan India study which elucidated demographic and clinico-etiological profile of patients with dry cough. Secondly, patients of varying age, socioeconomic status were evaluated. This study has used standard and validated tools to assess effectiveness of study drug. However, as this was a single visit study, with single follow-up, the study could not provide insights on the long-term outcome. Further, being an observational study, no comparator analysis was performed.

Conclusion

Cough is one of the health concerns among Indian population that seeks medical attention due to its manifestation as a secondary clinical condition, in turn impacting the QoL. In Indian set-up, dry cough was demonstrated equally by both the genders with primary presentation among elderly and young adults. Allergy was the most prevalent etiology of dry cough. Majority of the study cohort presented dry cough of acute severity. Most Indian physicians prescribed the study drug due to its effectivenessas a treatment measure. This rationale was supported by the EOTobservations that exhibited reduction in cough frequency, severity, sleep disruption and improved QoL. The FDC of codeine phosphate and triprolidine hydrochloride was found to be safe and well-tolerated by all study patients.

Disclosure

This study was funded by Abbott Healthcare Pvt Ltd. Dr Thomas, Dr Balamurugan and Dr Shah were the

investigators in the study.

Conflict of Interest :

There are no other conflicts of interest to report.

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Lerning Points :

- **Codeine is an important natural opioid found in the poppy resin.**
- **Codeine is a selective cough suppressant at subanalgesic doses, which usually do not cause respiratory depression and constipation, which are common side effects of opioids.**
- **Codeine has good activity by the oral route and is commonly employed for the management of cough, sometimes in combination dose forms with antihistaminics.**
- **Triprolidine is a first generation antihistamine with anticholinergic properties. It is used to combat the symptoms associated with allergies and to provide general relief for cough.**
- **Codeine and tripolidine combination can be used as cough suppression.**
- **Use of combination of codeine and tripolidine should be used cautiously especially in children.**

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