

Long-Lasting Cough (L-LC): Prevalence and Impact in the Pre-COVID Era in Italy. A Multicentric Survey

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Abstract

Introduction: Classification of cough is usually based on its duration even if it is frequently biased by patients' poor accuracy. The comprehensive term of "long-lasting cough" (L-LC) was for the first time introduced in the aim of minimizing the critical role of this bias.

Aim: Aim was to measure the prevalence and the impact of L-LC among Italian adults from the general population, together to their beliefs.

Methods: A self-managed anonymous questionnaire was randomly distributed to a pre-calculated sample from general population. The questionnaire consisted in five blocks of questions on different domains: 1) basic beliefs; 2) general impact; 3) approach to cough; 4) therapeutic expectations and 5) willingness to pay out-of-pocket. Data were reported as frequencies. Statistical comparisons were calculated by means of Chi Square test and $p < 0.05$ was assumed as the minimum level of statistical significance.

Results: Regardless the job, the prevalence of L-LC was 38.9%, and was significantly higher in northern and central regions (both $p < 0.001$). L-LC was generally perceived as a disease *per sé* in 38.2%. L-LC was reported to affect Quality-of-life by 72.2% of respondents, but highly affecting by 27.3% of them. Lung physician was the most preferred (56.2%) first-line specialist to consult in these cases. COPD and lung cancer were slightly, but significantly more feared by active and former smokers of both genders ($p < 0.02$ and $p < 0.01$, respectively). A large proportion of respondents disagree the therapeutic first-line approach with antibiotics (54.8%) and steroids (42.1%) for curing their L-LC, because blindly decided in the majority of cases. Anti-tussive remedies are appreciated by 47.0% of respondents. The willingness to pay even more than 20 € out-of-pocket for receiving any effective reliever against their L-LC was reported by 27.7% of respondents.

Conclusion: The prevalence of L-LC is higher than presumed within the Italian general population. At present, L-LC is largely regarded as "a disease" and no longer as a spy symptom common to different diseases. This belief is curiously in agreement with the most recent scientific evidence on the Cough Hypersensitivity Syndrome. A great proportion of Italians have a proper and restrictive belief versus first-line blind prescriptions for treating L-LC. Anti-tussive agents are highly valued, even if people's willingness to pay out-of-pocket for any reliever remedy is increasingly high. Beliefs on L-LC rapidly changed in the last decade and innovative therapeutic options are anxiously waited in the near future.

Keywords: Long-Lasting Cough; Persistent Cough; Chronic Cough; Cough Impact; General Population

Introduction

Cough is one of the most frequent respiratory symptoms requiring medical consultation, and represents a critical challenge in both clinical and economic terms [1].

Cough is usually classified by its duration: 1) acute cough: the cough lasting for less than three weeks, usually due to common cold or upper respiratory tract infections (URTI), that is self-limiting in the vast majority of cases when occurring in the absence of significant comorbidities; 2) persistent cough: the cough lasting three-to-eight weeks; 3) chronic cough: the cough lasting more than 8 weeks [2-5]. Persistent and chronic cough are not easily discriminated in clinical practice as their duration is mainly calculated only by relying on the patient's memory and accuracy and can then easily overlap. The comprehensive term of "long-lasting cough" (L-LC), born by unifying the persist and the chronic cough duration, was introduced for the first time just in the aim of minimizing the critical role of this bias.

The impact of cough on patient's quality of life ranges from minimal discomfort to disabling symptoms, even if physical impairment, depression, school/work absenteeism or presenteeism are frequent effects of L-LC, together to a substantial economic burden, particularly when of unknown origin [6,7]. While the prevalence of long-lasting cough had been investigated in several studies [8-12], the impact of L-LC was only assessed episodically [6,13,14].

Aim of the Study

Aim of the present study was to measure the prevalence and the impact of L-LC among Italian adults from the general population, together to their beliefs on this particular disorder.

Methods

A self-managed anonymous questionnaire was randomly distributed in paper-form to individuals of general population, and the minimum number for achieving the representativeness was previously calculated ($n=5,056$, by 3% maximum error, and 95% probability). In order to maximise the even national distribution to all Italian regions, the peripheral branches of the study promoters (namely, the peripheral collaborators of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology - CESFAR and of the Italian Cough Association - AIST) were actively involved. They contributed with a pre-defined number of questionnaires that were centralized to the CESFAR Operational Centre. The Italian Centres involved in the survey were 32, and the number of questionnaires to collect in each region was calculated in proportion to their inhabitants. The nine most densely populated regions (namely, Lombardy; Piedmont; Veneto, Emilia Romagna; Tuscany; Lazio; Campania; Puglia, Sicily) had two reference regional centres.

The questionnaire consisted in five blocks of questions pertaining to different domains: 1) basic beliefs; 2) general impact; 3) approach to L-LC; 4) therapeutic expectations, and 5) willingness to pay out-of-pocket (Appendix 1). Respondents were also requested to report their age, gender, smoke habit, job, and region of living. As concerning the economic impact, the willingness to pay out-of-pocket for any effective anti-tussive reliever was also investigated by a pre-defined class of cost (≤ 10 €; 10-20 €; > 20 €) [14].

Data were reported as frequencies. Statistical comparisons were calculated by means of Chi Square test, and $p < 0.05$ was assumed as the minimum level of statistical significance.

The survey was approved by the AIST Ethical Commission in November 2017 and even if anonymous, all subjects were requested of their informed consent before filling the questionnaire.

Results

A total of 8,500 questionnaire were distributed and 5,276 valuable questionnaires were collected: 2,434 (46.1%) from the northern; 729 (13.8%) from the central and 2,111 (40.1%) from the southern regions, respectively. Females were 51.8% by a mean age of 48.7 years, while males were 48.2% by a mean age of 50.3 years. The overall mean age was 49.6 years. The characteristics of the sample are reported in table 1.

Whole sample (n)	5,276
Northern regions	46.1%
Central regions	13.8%
Southern regions	40.1%
Mean age (y)	49.6
Females/males ratio	1.07
Activity	
White collars	37.4%
Workers	21.9%
Retired	16.9%
Housewives	11.6%
Students	6.5%
Unemployed	5.7%
Smoke habit	
Active smokers	20.9%
Former smokers	45.5%
Never smoker	33.6%

Table 1: General characteristics of the sample.

Respondents’ basic beliefs

L-LC cough was generally perceived as a disease *per sé* in 38.2% of respondents, while 17.3% were doubtful (Figure 1). This belief was significantly more pronounced in northern regions and in active smoker males (both $p < 0.001$). On the contrary, cough was mainly regarded as an unspecific spy symptom of different diseases by 44.5% of respondents, being this belief significantly more pronounced in females of southern regions, in retired and in unemployed people ($p < 0.001$; $p < 0.001$; $p < 0.19$, respectively).

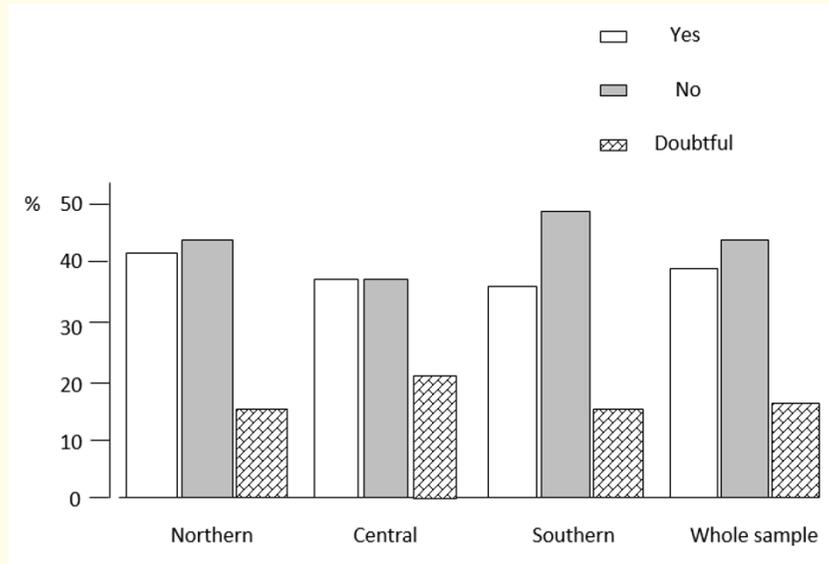


Figure 1: Question: *In your opinion, is cough a disease?* (Response of the whole sample and by regional distribution).

General clinical impact of L-LC

The prevalence of cough lasting at least four weeks was 26.7%, but that of cough lasting more than eight weeks was 12.2% (Figure 2). In other word, the prevalence of L-LC was 38.9%. In particular, the prevalence of L-LC was independent of the job, but significantly higher in northern and central regions (both $p < 0.001$) and in smoker males ($p < 0.005$).

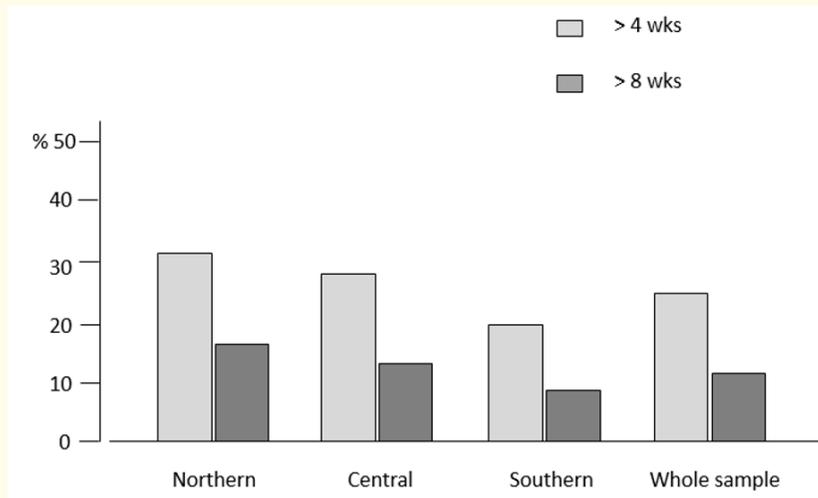


Figure 2: Question: *Duration of your cough over the year* (response of the whole sample and by regional distribution).

L-LC was generally described associated to secretions in 49.2% of the overall sample: in 56.9% and in 53,2% of active smokers and former smokers (both $p < 0.001$), in blue collars (53.1%), in older retired (66.7%) and in unemployed individuals (75.0%), respectively (all $p < 0.001$).

Regardless of the duration of their cough, 13.7% of respondents started worrying seriously about their own condition just after four weeks ($p < 0.001$), without any difference by age, gender and job ($p = ns$).

L-LC was described as affecting daily life and their relationships by 72.2% of respondents, but highly affecting Quality-of-life by 27.3% of respondents, particularly in smokers and in females of southern regions ($p < 0.01$), regardless their job.

Respondents’ approach to L-LC

Lung physician was the most preferred first-line specialist doctor to consult in these cases (56.2%), followed by the otorhinolaryngologists (9.1%) and the allergologist (1.2%). This tendency was equally represented in all the three clusters of Italian regions without any significant difference by age, gender, smoking habit, and job (all $p = ns$). Moreover, after more than four weeks of cough, the occurrence of chronic bronchitis (32.1%); chronic obstructive airway disease – COPD and/or emphysema (15.5.2%); pneumonia (15.0%); lung cancer (8.7%); bronchial asthma and related disorders (8.3%); gastro-oesophageal reflux disease - GORD (1.3%); tuberculosis or psychogenic disorders (both 0.5%) were the most feared causes of L-LC. COPD and lung cancer were slightly, but significantly more feared by active and former smokers of both genders ($p < 0.02$ and $p < 0.01$, respectively), regardless their job and region of living.

Respondents’ therapeutic expectations

Regardless their geographical distribution, age and job, the majority of respondents (54.8%) did not share the conviction that antibiotics can be regarded as the most effective therapeutic option for curing L-LC, even though 21.5% of them were in favour, and 23.7% were doubtful (Figure 3). This belief was significantly more pronounced in females (58.4% vs 50.4% of males, $p < 0.015$), being males significantly more doubtful from this point of view (26.9% vs 21.2%, $p < 0.02$). Also smokers declared the same conviction in 54.8% of cases ($p < 0.001$), such as in 49.4% of active smokers and in 41.4% of former smokers.

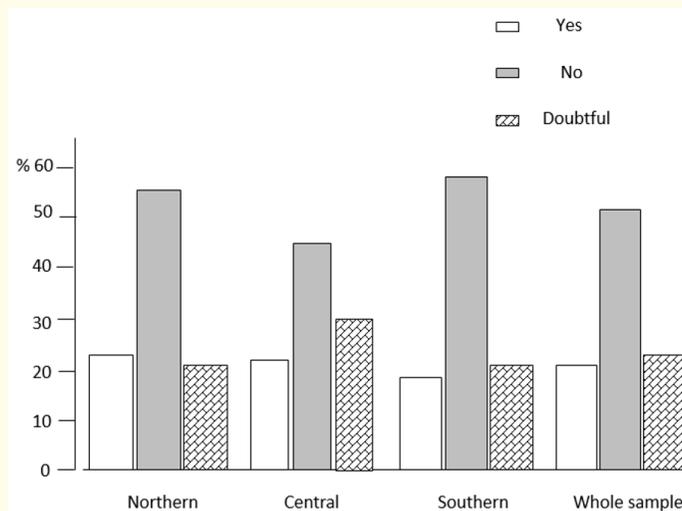


Figure 3: Question: Should long-lasting cough only treated with antibiotics? (Response of the whole sample and by regional distribution).

Systemic steroids were also not perceived as the most appropriate first-line treatment for L-LC in 42.1% of respondents, being doubtful 34.3% of them. This belief was significantly clear in northern regions (44.6%, $p < 0.001$), in older people (42.5%, $p < 0.003$), in females (43.0%, $p < 0.001$), in never smoker (44.6%, $p < 0.001$), and particularly in white collars (range 47.0-55.9%, $p < 0.001$) (Figure 4).

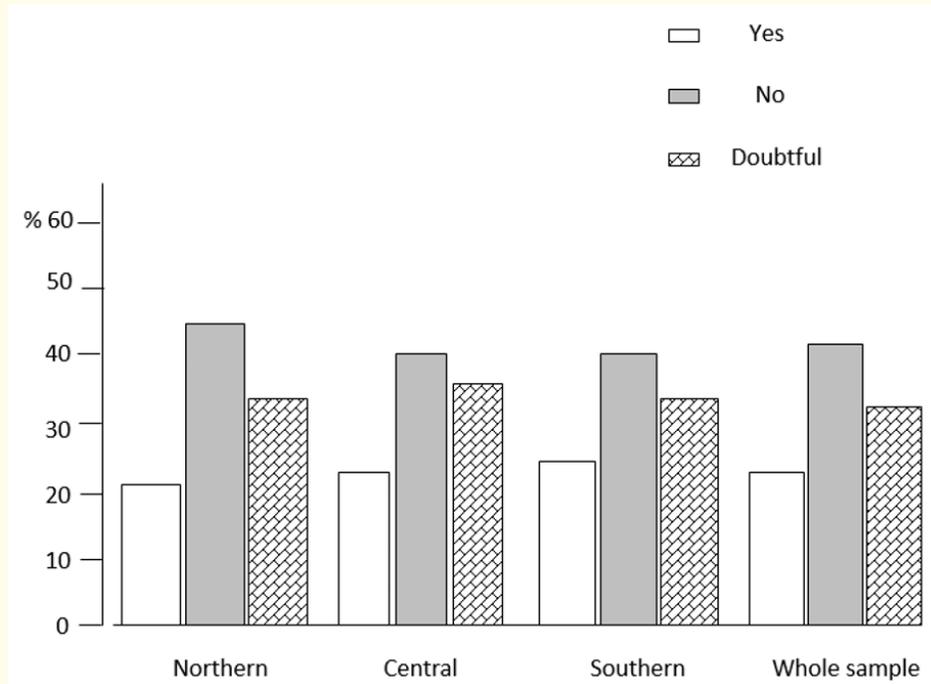


Figure 4: Question: Are systemic steroids always needed in long-lasting cough? (Response of the whole sample and by regional distribution).

Regardless their age, gender, smoking habit and job, anti-tussive drugs were generally perceived as effective by 47.0% of respondents, particularly within northern regions (50.9%) when compared to southern and central ones (44.6% and 40.8%, respectively).

As concerning the way for assuming drugs, the aerosol route of administration was regarded as the one to prefer by 41.2% of respondents, particularly by older smoker males living in northern regions ($p < 0.001$).

Willingness to pay out-of-pocket

The willingness to pay 10-20 € out-of-pocket for receiving any effective reliever against L-LC was affirmed by the majority of respondents, but 27.7% of them claimed their willingness for paying even more that 20 € (Figure 5). This tendency was significant for white collars (32.1%), particularly if smoker males of the Northern regions ($p < 0.001$).

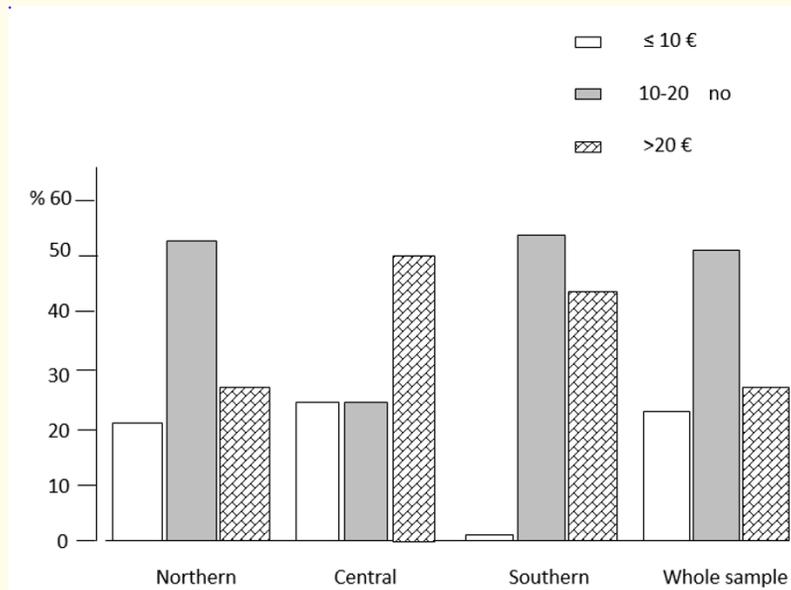


Figure 5: Question: How much are you willing to pay in your pharmacy for receiving an effective anti-tussive drug? (response of the whole sample and by regional distribution).

Discussion

Persistent and chronic cough are frequently reported as distinct entities in respiratory medicine even if they are not easy to discriminate in terms of their true duration in clinical practice. In fact, cough duration can only be clinically calculated on the basis of the patient’s memory and accuracy, and it can then result frequently biased. The comprehensive term “long-lasting cough” (L-LC) was introduced in the present survey just in the aim of minimizing this frequently biased classification. On the other hand, cough duration due to the most frequent causes of cough can partially overlap, depending of their current evolution phase. Actually, bronchial asthma; tobacco smoking; environmental irritants; GORD; post-nasal drip, use of some anti-hypertensive drugs; lung cancer; mediastinal occupation; chronic bronchitis; chronic obstructive pulmonary disease (COPD); bronchiectasis; foreign bodies; cystic fibrosis; lung fibrosis; extra-thoracic causes; OSAS; laryngeal dysfunction; psychological disorders can cause cough of variable duration in different periods of their natural history.

In general, 30 - 40% of subjects with L-LC are not presently receiving a precise diagnosis and care of their cough [5,6] and the etiology of L-LC is not defined in more than 10-20% of cases even after an appropriate diagnostic approach [4]: these are the cases of the “so called” idiopathic cough [15,16]. Recently, the scientific community no longer tends to regards L-LC merely as a spy symptom of different diseases in recent years, but rather as a disease *per sé*, namely the Cough Hypersensitivity Syndrome, due to the enhancement of the intrinsic reactivity of the peripheral neural endings and receptors within the airway structural tissues [16].

In the present study, L-LC showed a substantial overall prevalence (40.9%), being 14.2% the prevalence of the “traditionally defined” chronic cough. These figures contribute to highlight the progressive increase of L-LC within the general population when compared to

corresponding data obtained a few years ago [17]. On the other hand, environmental conditions were progressively impairing in Western countries [18] and also in Italy [19] due to uncontrolled urbanization and exposure to industrial, occupational, and traffic pollutants and irritants. All these factors likely are likely contribute to support and explain the increasing prevalence of L-LC observed in Italy over the last decades. These results are in general concordance with those of other European and extra-European studies on the global epidemiology of chronic cough in adults [1,9,12,13,20].

Stemming from this evidence and considering the historically consolidated conviction that cough only represents a non-specific spy symptom shared by several diseases, it is even more surprising that near 40% of respondents of the present study affirmed that L-LC should be regarded as a “disease *per sé*”. The unexpected high frequency of this belief is particularly challenging as it corresponds to the most recent scientific vision on L-LC, namely the “cough hypersensitivity syndrome”: the particular condition due to the exalted status of peripheral airway sensory nerves within the airway structures occurring independently of the aetiology of cough [15,16]. This evidence appears quite important as it is highly presumable that the vast majority of public opinion was absolutely unaware of this recent scientific position of cough experts.

As L-LC confirms a clear impact on subjects [6,14], the effective approach to L-LC still represents a critical issue that is emphasised in the present study by the analysis of people’s beliefs on the current therapeutic approach. It is well known that the first-line prescription of antibiotics and/or systemic steroids for managing cough is discouraged by national and international evidence and guidelines [3,4,21-23]. However, despite the still large prescription of antibiotics and/or systemic steroids for managing L-LC in our Country, a high proportion of respondents affirmed to disagree with this non-specific first-line approach (independently of their age, gender, and job), because “blindly decided”, such as not supported by any clear and objective diagnostic evidence in the majority of cases. Consequently, this widespread belief recorded in the general population, even if likely unaware of any scientific statement, aligns to and share the cultural position recently assumed by the scientific community.

Nevertheless, it should not be forgotten that a not negligible proportion of respondents (around 40%) still is convinced of the primary role of these drugs in long-lasting cough even if blindly prescribed. Several factors can likely influence this first-line approach in our opinion: the doctors’ uncertainty on the true cause of L-LC, only episodically investigated appropriately in clinical practice; the wrong patients’ expectations [24], particularly in older and low cultured respondents; the widespread attitude to seek for medical information via the social media, even if scientifically uncontrolled [25]; the lower degree of doctor-to-patient relationship [26] and, consequently, the increasing role of defensive medicine.

Among the possible therapeutic options, the Italian general population expressed a large consensus in favour of presently available anti-tussive agents that still result the most preferred class of the over-the-counter (OTC) medications. Obviously, their relatively low cost and their easy accessibility likely contributes to explain this large consensus in favour of these OTC products, even if their efficacy and effectiveness still is debated in scientific terms.

From a general point of view, the general dissatisfaction versus the current therapeutic approach to L-LC is clearly suggested by the high willingness to pay “out-of-pocket” for obtaining any effective anti-tussive remedy in pharmacy. In particular, the proportion of patients with L-LC previously classified as suffering from the “so called refractory or unexplained cough”, but presently defined as suffering from the “Cough Hypersensitivity Syndrome” are particularly unsatisfied of present treatments and are anxiously waiting for oncoming specific therapeutic options that could minimize the impact of their long-lasting, invalidating conditions [27].

The present survey has same limitations. Persistent cough (lasting three-to-eight weeks) and chronic cough (lasting longer than eight weeks) were unified in the term “long-lasting cough” (L-LC) with the aim to minimize the role of subjects’ memory errors that are too

frequently biasing the traditional classification of cough, mainly only based on patients' claimed duration in clinical practice. The survey was not planned for classifying L-LC by its documented etiology, but it was only aimed to investigate the overall crude prevalence of L-LC in the general population. Individuals were investigated on voluntary basis by means of a self-administered anonymous questionnaire, and some voluntary mis-information were possible. Finally, the precise people's expenditure for L-LC was not exactly calculated, even if data obtained on the subjects' willingness to spend out-of-pocket for any reliever drug prove are clearly emphasizing that some crucial subjects' needs are still unmet. Further studies are needed and should be favoured for deeply investigating this particular issue.

Points of strength are: 1) the large sample size, pre-calculated for obtaining its statistical representativeness; 2) the multicentre design of the survey, based on the cooperation of thirty-two Centres evenly distributed across all Italian regions.

Conclusion

The prevalence of L-LC proves higher than presumed within the Italian general population. At present, L-LC is largely regarded as "a disease" and no longer as a spy symptom common to different diseases. This belief, that was progressively growing over the last decade, is curiously in agreement with the most recent scientific evidence on the Cough Hypersensitivity Syndrome.

The majority of Italians have a proper and restrictive position versus first-line "blind" prescriptions for treating L-LC, while anti-tussive agents are highly valued. Finally, the willingness to pay out-of-pocket for any reliever remedy is high.

Beliefs on L-LC are rapidly and substantially changing in present years, while anxiously waiting for innovative forthcoming therapeutic options in the near future.

Authors Contribution

All Authors contributed equally to the study. All Authors approved the final manuscript and consented for publication.

Competing Interests

The authors declare that they have no competing interests.

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Appendix 1

The questionnaire

Hi, how are you? We are carrying out a National survey, and your opinion is quite important. May I put some simple questions concerning your believes on cough? I'll take maximum 5 minute of your time. The interview will remain anonymous and data collection is conducted according to the present law on privacy. If you agree, we can start (If Yes, go on; if not, thank you, and have a good day).

Questions

- In your opinion, is cough a disease?
 Yes No Doubtful
- After when do you start to be worried of your cough?
 1 2 4 8 weeks
- Is cough merely a symptom of any disease?
 Yes No Doubtful
- When cough is long-lasting, what do you think about its cause?
.....
- Which specialist do you presume will be the best to refer to?
.....
- Should long-lasting cough only be effectively treated with antibiotics?
 Yes No Doubtful
- Are present anti-tussive drugs effective?
 Yes No Doubtful
- Are systemic steroids always needed in long-lasting cough?
 Yes No Doubtful
- Are domestic aerosols the right option against cough?
 Yes No Doubtful
- How much are you willing to pay in your pharmacy for receiving an effective anti-tussive drug?
 Up to 10€ 10 - 20€ More than 20 €

11. How many episodes of cough do you suffer over twelve months?
 Never 1-2 3-5 More than 5

(If “never”, skip to question # 14)
12. Which is the overall duration of these episodes?
 2-4 4-8 More than 8 weeks
13. In general, does your cough produce any sputum?

----- Yes No Doubtful
14. Age: _____ (years)
15. Gender: Male Female
16. Smoke: Active Never Ex-smoker
17. Job: Worker Employee Manager Professional/entrepreneur Student Retired Unemployed Housewife
18. Region where you live:

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