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Mucolytic Therapy in COPD: Patient Usage and Preferences in Real-World Italian Settings

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Introduction: The Italian COPD Patient Association (Associazione Pazienti BPCO) conducted an online survey among its 2814 members with COPD to investigate the reasons for the widespread use of mucolytic therapies by patients, often including self-prescription using over the counter (OTC) alternatives.

Methods: After consulting with several respiratory specialists, the Association's steering committee developed a list of nine questions with possible answers that was posted on the website of the Association. The survey was open to all members of the Association, with responses to be e-mailed to the Association.

Results: Approximately 78% the 502 participants surveyed reported having used mucolytics in the previous six months, with 54.5% using prescribed medications and 23.5% opting for OTC medications. Usage patterns revealed that 43.4% utilized mucolytics during episodes of excessive mucus, while 35.5% used them regardless of the presence of mucus. In terms of formulation preferences, water-soluble granulated sachets (34.9%) and effervescent/dispersible tablets (22.8%) were the most preferred, followed by capsules (14.1%) and aerosol ampoules (11.2%). The factors influencing these preferences were the hydration benefits of sachets and tablets, the portability and taste advantages of capsules, and the swallowing difficulties of aerosol formulations. The data showed that 26.5% of survey participants consumed the entire contents of the prescribed or OTC package, while 19.9% utilised it for a minimum of 10 days, 31.5% for a period between 5 and 10 days, and 10.2% for less than 5 days. Cost was cited as a reason for discontinuation by 8.3% of participants. Notably, 29.5% of respondents believed that mucolytic efficacy was dependent on the amount of mucus. Most patients (66.3%) used mucolytics at home, and 57.4% took the medication once daily and 24.3% twice daily. Additionally, 41.8% were aware of the dual antioxidant and mucolytic properties of the medication.

Conclusion: These findings emphisise the need for a patient-centred approach, encouraging healthcare providers to consider individual preferences and offer personalised advice that has the potential to improve adherence and overall outcomes for COPD patients.

Keywords: adherence, antioxidants, COPD, formulation, mucolytics, preference

Introduction

The most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) report attributes minimal importance to the utilisation of mucolytic drugs in the management of chronic obstructive pulmonary disease (COPD). This is because the use of these drugs is associated with a reduction of 0.03 exacerbations of COPD (ECOPD) per patient per month,[1] which equates to an average reduction of one ECOPD every three years. The low emphasis placed by GOLD on mucolytics is fully supported by a systemic review conducted by the US Agency for Healthcare Research and Quality, through its Evidence-based Practice Centres in 2019, which concluded that mucolytics may have a negligible impact on the frequency of ECOPD and that the validity of their use during an ECOPD appears questionable.[2] Indeed, a recent study revealed that long-term treatment with high-dose N-acetylcysteine (NAC) did not result in a reduction in the annual rate of exacerbations or improve lung function. Despite this, the study observed a decrease in the annual rate of moderate or severe exacerbations relative to placebo among patients with COPD categorized as GOLD stage 1–2.[3]

However, a recent systematic review and meta-analysis of mucolytics in patients with stable COPD, incorporating 23 reports, concluded that these drugs reduce ECOPDs and hospitalizations in patients with stable COPD and have a safety

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profile comparable to that of placebo.[4] Moreover, a 2023 meta-analysis of 24 randomized controlled trials (RCTs) demonstrated moderate certainty that mucolytics could increase treatment success rates by 37% and significantly improve symptoms in people with ECOPDs.[5] Additionally, evidence suggests that nebulized NAC is efficacious in improving phlegm symptoms in COPD patients. The NEWEST study, for instance, revealed a substantial change in COPD assessment test phlegm score following 12 weeks of treatment, in comparison to the baseline, with over half of the participants expressing satisfaction with the effects of nebulized NAC therapy.[6]

Notwithstanding this compelling evidence, the GOLD report makes no mention of the use of inhaled mucolytics or their utilization in the treatment of ECOPD.[1] However, it does suggest the regular use of three thiol-containing agents, namely NAC and carbocysteine for COPD patients not taking inhaled corticosteroids (ICS) and erdosteine irrespective of ICS usage, with the objective of reducing the risk of ECOPD, although it emphasizes that this effect is modest but, to a certain extent, affects the quality of life.[1]

In Italy, mucolytics belong to category C. Category C drugs are defined as those used for less serious illnesses or those considered minor, with access to advertising and paid for entirely by the patient.[7] However, administrative data indicate that these drugs represent the categories with the largest increases in expenditure and consumption in 2022 compared to 2021, as reported by the Medicines Utilization Monitoring Centre of the Italian Medicines Agency (AIFA).[8]

To gain insight into the reasons for the high use of mucolytics by Italian COPD patients, despite the absence of tangible endorsement from scientific recommendations and regulatory authorities, the Italian COPD Patient Association (Associazione Pazienti BPCO) conducted a survey among its members suffering from COPD.

Patient-led surveys are instrumental in creating a more inclusive, responsive, and effective healthcare ecosystem by bridging the gap between clinical experiences and the lived realities of patients. Patient involvement in research leads to improvements in study design and the selection of relevant outcome measures, ensuring that healthcare research addresses the actual needs and concerns of patients.[9] However, we were unable to find any studies led by patients that specifically examine the use of mucolytics in the context of COPD.

In addressing this lacuna, the present article will examine the results of this survey, as we believe that these results can offer useful information to facilitate more effective and responsive health service choices that align with the needs of those directly affected by COPD.

Methods

The Italian COPD Patient Association aims to improve the understanding of the disease and its management among patients and their families, using the latest scientific knowledge. It acts as an interlocutor with the institutions to improve protection, promote campaigns, and support research. There are 2914 members with COPD living in different regions of Italy. To be considered for membership in the Association, patients must be diagnosed with COPD by a primary care physician or as a result of a specialist consultation. However, the specific details of the diagnosis are not required.

After consulting with specialists who, however, were not directly involved in the formulation of the study questions, the Association's Steering Committee, composed of members elected by the membership, developed a list of nine questions with possible answers (see Table 1). The questions and answers were deliberately simple, ensuring complete understanding even by individuals with limited cultural backgrounds. This list was then posted on the website of the Association at the end of May 2024. The survey was open to all members of the Association until the end of July 2024, with responses to be e-mailed to the Association.

The responses received were collated by the secretariat of the Association and forwarded anonymously to three specialists in respiratory diseases for scientific evaluation.

The study complied with the Declaration of Helsinki. In any case, according to current rules (such as those reported by the Italian Ministry of Health Decree of 30 November 2021 and related ethical guidelines), a study organized and conducted by patients themselves does not require the opinion of an ethics committee if all the following conditions are met: non-interventional nature, no collection of sensitive data beyond consent (Italian Legislative Decree n. 101 dated 10 August 2018 containing provisions for the alignment of the domestic legislation to the EU Regulation 2016/67), no

Table 1 Questions Asked During the Survey and Responses Received. Responses Were Collected From 502 Patients. The Relative Percentages for Each Answer are Given in Brackets

Question	Answers					
Have you used a mucolytic in the last 6 months?	Yes, the doctor prescribed it (54.5%)	Yes, I bought it myself (23.5%)	I did not (22.0%)			
If yes, when did you use it?	At a time when I had a lot of mucus (43.4%)	I often use it even when I do not have a lot of mucus (35.5%)	No answer (21.1%)			
Which formulation do you prefer?	Capsules (20.1%)	Water-soluble granulate sachets (34.9%)	Effervescent/ dispersible tablets (which dissolve in water) (22.8%)	Aerosol ampoules (11.2%)	No answer (11.2%)	
Why did you express this preference?	I prefer to dissolve the medicine in water, as this helps me to stay hydrated as recommended (55.0%)	I prefer capsules so there is no aftertaste of the solutions in my mouth (5.8%)	I prefer capsules to make sure the medicine is completely absorbed (2.6%)	I prefer capsules because they are more convenient to carry and take (14.1%)	I prefer aerosol because I cannot swallow (7.4%)	No answer (15.1%)
For how many days do you use these drugs?	Less than 5 (10.2%)	Between 5 and 10 (31.5%)	More than 10 days (19.9%)	I finish the packet (26.5%)	No answer (11.9%)	
If you answered "less than 5" or "between 5 and 10", why?	Because of the cost (8.3%)	Because I think it is only useful when I have a lot of mucus (56.2%)	Others (35.5%)			
Has it been explained to you that the effect of the drug is both antioxidant and mucolytic?	Yes (41.8%)	No (48.8%)	No answer (9.4%)			
Where do you usually take the drugs?	At home (66.3%)	Away from home (3.6%)	It is indifferent (18.3%)	No answer (11.8%)		
How many times a day do you take the drug?	1 (57.4%)	2 (24.3%)	More than 2 (4.8%)	No answer (13.5%)		

commercial sponsor, no additional risks to participants beyond those normally encountered in their daily lives or medical care, and a focus on patient-driven outcomes.

Results

The survey collected responses from 502 patients (Table 2). Before starting the response process, each patient was required to furnish demographic data, including age, sex, smoking status, and occupation. The demographic composition of the sample was as follows: 46.4% of subjects were male and 53.6% female. The mean age of the participants was 66 years, with males having a slightly higher mean age (see Table 2). Surprisingly, 11 members who responded to the survey reported having aged less than 30. It is also noteworthy that 21 males and 14 females did not disclose their age. The current smoking prevalence was 15%, while 65% of non-smokers reported a history of smoking. The largest demographic group comprised retired individuals, constituting 64% of the sample, followed by office workers and professionals (8%), and workers and housewives (5% each).

It must be pointed out that not all patients answered all the questions as shown in Table 1. Nevertheless, approximately 78% of respondents reported having utilized mucolytics within the last six months. Of these, 54.5% had used prescribed medications, while 23.5% had opted for over the counter (OTC) alternatives. Among the users, 55.1% reported taking mucolytics during episodes of excessive mucus, while 44.9% used them regardless of mucus presence.

Table 2 The Survey's Demographic

	Total (502)	Males (233)	Females (269)
Sex		46.4%	53.6%
Age (yrs)			
19 to 63	32%	28%	36%
64 to 73	31%	30%	32%
74 to 92.	30%	33%	27%
No answer	7%	9%	5%
Smokers			
No	78%	82%	75%
Yes	15%	13%	17%
No answer	7%	5%	8%
Ex smokers			
No	29%	27%	32%
Yes	65%	69%	61%
No answer	6%	4%	8%
Job description			
Student	1.5%	1.3%	1.9%
Freelance	7.9%	10.3%	5.9%
Housewife	5.3%		9.7%
Unemployed	1.6%	1.7%	1.5%
Office Worker	8.4%	5.1%	11.2%
Worker	5.6%	8.6%	3.0%
Manager	0.6%	0.9%	0.4%
Teacher	3.2%	1.3%	4.8%
Retired	64.1%	69.5%	59.5%
No Answer	1.8%	1.3%	2.12

A notable proportion of participants (34.9%) indicated a preference for mucolytics in the form of water-soluble granulated sachets, while 22.8% expressed a preference for water-soluble effervescent/dispersible tablets and 20.1% opted for capsules. A minority of respondents (11.2%) chose mucolytics formulated in aerosol ampoules. The preference for water-soluble granulated sachets or water-soluble effervescent/dispersible tablets was primarily due to their contribution to adequate hydration. Capsules were preferred over solutions for several reasons, including the absence of an aftertaste, the guarantee of complete drug consumption, and the greater portability and ease of use. The preference for the aerosol route was attributed to the difficulties encountered in swallowing.

The reported duration of mucolytic use varied considerably among patients, with 26.5% of people consuming the entire contents of the prescribed or OTC package, 19.8% continuing treatment for at least 10 days, 31.5% taking the drugs for between 5 and 10 days, and 10.2% of patients stopping treatment within 5 days. Among those who discontinued the treatment within 10 days, approximately 8.3% cited financial constraints as the primary reason for their decision, whilst 56.2% of respondents reported that the amount of mucus present did not necessitate additional mucolytic use, as they felt it was only beneficial in cases of excessive mucus production. The remaining 35.5% of respondents provided a wide range of answers, including: on doctor's orders, because I feel better, because it increases mucus production, I cycle 10 days every month, because it is sufficient, I try to limit the use of medication, etc.

An analysis of the data in Table 3 reveals notable distinctions between users of medical prescriptions (MP) and OTC mucolytics. MP users placed greater emphasis on symptom management, and reported a preference for medically supervised methods (eg, aerosol ampoules), and a propensity for longer use of mucolytics. In contrast, OTC users exhibited a preference for convenience, shorter-term use, and more casual or generalized methods of use, with a notable preference for capsules and use of the whole package.

Table 3 Disparities in the Responses of Users of Medical Prescriptions (MP) Versus Those Who Used Over the Counter (OTC) Mucolytics

Question	Answers					
When did you use it?	At a time when I had a lot of mucus	I often use it even when I do not have a lot of mucus	No answer			
	MP 55% OTC 48%	MP 44% OTC 48%	MP 2% OTC 1%			
Which formulation do you prefer	Capsules	Water-soluble granulate sachets	Effervescent/ dispersible tablets (which dissolve in water)	Aerosol ampoule	No answer	
	MP 18% OTC 30%	MP 38% OTC 41%	MP 30% OTC 21%	MP 12% OTC 8%	MP 1% OTC 0%	
Why did you express this preference?	I prefer to dissolve the medicine in water, as this helps me to stay hydrated as recommended	I prefer capsules so there is no aftertaste of the solutions in my mouth	I prefer capsules to make sure the medicine is completely absorbed	I prefer capsules because they are more convenient to carry and take	I prefer aerosol because I cannot swallow	No answer
	MP 66% OTC 58%	MP 5% OTC 8%	MP 2% OTC 4%	MP 14% OTC 22%	MP 9% OTC 3%	MP 4% OTC 3%
For how many days do you use these drugs?	Less than 5	Between 5 and 10	More than 10 days	I finish the packet		
	MP 9% OTC 14%	MP 34% OTC 37%	MP 28% OTC 16%	MP 29% OTC 33%		

A substantial percentage of participants, specifically 66.3%, consumed the medication within the domestic setting. Most respondents (57.4%) reported using the drug once daily, while 28.3% indicated that they took it twice daily.

As illustrated in Table 4, younger adults (19–63 years) were more likely to use mucolytics on a symptomatic basis, to prefer capsules, and to consume the full packet. They also expressed a preference for greater flexibility in the location of use. In contrast, middle-aged adults (64–73 years) reported using mucolytics even when there was no significant mucus, and preferred water-soluble sachets. They also were likely to use mucolytics for a longer period (5–10 days), with the majority using mucolytics at home. This finding suggests reduced mobility compared to younger adults. In contrast, older adults (74–92 years) exhibited a preference for effervescent/dispersible tablets and aerosol ampoules and demonstrated the highest rates of home usage and non-response in surveys, suggesting potential challenges with mobility or comprehension.

Surprisingly, 41.8% of the surveyed patients indicated that they were aware that the medication they were using had dual effects, specifically antioxidant and mucolytic properties.

Discussion

This patient-led survey provides valuable insights into the demographics, preferences, and behaviours of Italian COPD patients who use mucolytics/antioxidants. The findings highlight several important trends and considerations, providing valuable perspectives for medical research and helping to better tailor care to patients' needs.

The data confirm that COPD patients frequently use mucolytics/antioxidants, often by direct choice, regardless of prescription. More than half of those who took part in the survey used mucolytics mainly when they had excess mucus, while the rest used them regardless of whether they had mucus. Many patients preferred water-soluble granulate sachets and water-soluble effervescent/dispersible tablets, as these options could potentially contribute to hydration. The survey

Table 4 Effect of Age on the Use of Mucolytics. Patients Were Divided Into 4 Groups, Those Aged 19 to 63, Those Aged 64 to 73, Those Aged 74 to 92, and Those Who Did Not Answer the Question

	Answers				
When did you use it?	At a time when I had a lot of mucus	I often use it even when I do not have a lot of mucus	No answer		
	19 to 63 49%	19 to 63 36%	19 to 63 15%		
	64 to 73 40%	64 to 73 41%	64 to 73 19%		
	74 to 92 43%	74 to 92 30%	74 to 92 27%		
Which formulation do you prefer	Capsules	Water-soluble granulate sachets	Effervescent/dispersible tablets (which dissolve in water)	Aerosol ampoule	No answer
	19 to 63 28%	19 to 63 40%	19 to 63 23%	19 to 63 6%	19 to 63 3%
	64 to 73 19%	64 to 73 39%	64 to 73 18%	64 to 73 13%	64 to 73 11%
	74 to 92 17%	74 to 92 28%	74 to 92 26%	74 to 92 12%	74 to 92 17%
For how many days do you use these drugs?	Less than 5	Between 5 and 10	More than 10 days	I finish the packet	No answer
	19 to 63 7%	19 to 63 33%	19 to 63 22%	19 to 63 34%	19 to 63 4%
	64 to 73 9%	64 to 73 35%	64 to 73 18%	64 to 73 28%	64 to 73 10%
	74 to 92 14%	74 to 92 31%	74 to 92 19%	74 to 92 18%	74 to 92 18%
Where do you usually take the drugs?	At home	Away from home	It is indifferent	No answer	
	19 to 63 54%	19 to 63 10%	19 to 63 32%	19 to 63 4%	
	64 to 73 72%	64 to 73 1%	64 to 73 17%	64 to 73 10%	
	74 to 92 78%	74 to 92 5%	74 to 92 0%	74 to 92 17%	

revealed significant variation in the duration of use of mucolytics, with almost half of respondents discontinuing use within 10 days. The main reason for discontinuation was a perceived lack of need in the absence of mucus, while cost was a barrier cited by 8.3% of respondents. The majority of patients seemed to prefer the convenience of using mucolytics at home, and a single daily dose was generally considered sufficient. Finally, it is worth noting that almost half of the respondents said they were aware of the dual action of their medication, particularly its antioxidant and mucolytic properties.

We acknowledge that this survey, like the vast majority of studies conducted directly by patients, is characterised by a paucity of scientific rigour, stemming from a dearth of formal research expertise. This results in methodological deficiencies, an absence of statistical power, and the potential for personal biases among patients to predominate, potentially skewing results to reflect anecdotal evidence rather than broader trends. Furthermore, the survey is limited in scope, focusing on a specific condition in that those who participated were strictly members of the Italian COPD Patient Association. This may restrict the generalizability of the findings to other countries and societies. Nevertheless, the survey data offer some valuable insights.

Firstly, the results indicate a divergent perception of the necessity for and functionality of mucolytics, suggesting that a significant proportion of patients may be unaware of the potential benefits of their continued use or may harbor misconceptions about the role of mucolytics in the treatment of COPD.

The results of this survey demonstrate significant variation in the duration of mucolytic use reported by patients. This finding suggests a potential mismatch between patients' expectations and the recommended course of treatment. Indeed, the duration of mucolytic treatment should be contingent on whether the patient is experiencing stable COPD or an ECOPD. For the treatment of ECOPD, the duration generally averages 10 days, but ranges from 7 to 30 days,[5] whereas clinical studies suggest that a treatment duration of at least 2 months is beneficial for patients with stable COPD, with some studies extending up to 6–12 months.[10] This underscores the necessity to enhance patients' awareness regarding the optimal duration of therapy.

The responses from patients in this survey suggest that product development should prioritise ease of administration and specific patient needs, such as hydration but also swallowing difficulties, as one group reported a preference for taking mucolytics by aerosol due to their inability to swallow.

The frequency with which patients expressed a preference for taking the drug at home, and potentially once daily, is indicative of their predilection for more straightforward and manageable dosing schedules. This is likely to enhance compliance. However, the observation that approximately one third of patients reported taking the drug twice daily may indicate that this is the preferred intake frequency in cases of more severe symptoms or when following medical advice.

Research indicates that age has a significant impact on mucolytic usage patterns. Younger adults prioritize flexibility and convenience, middle-aged adults lean toward preventive habits with balanced treatment durations, and older adults prefer ease of use and exhibit greater reliance on home-based care. These insights underscore the importance of tailoring mucolytic formulations, packaging, and instructions to meet the specific needs of each age group.

The finding that almost half of the respondents expressed awareness of the dual antioxidant and mucolytic effects of their medications was somewhat unexpected. It suggests a moderate level of patient knowledge in this area, which could be further improved through targeted educational initiatives by healthcare providers to improve understanding of the action of mucolytics and adherence to treatment as prescribed by a physician.

Conclusion

The data from this patient-led survey are useful due to the paucity of information in the literature regarding the preferences and behaviours of COPD patients with regard to the use of mucolytics/antioxidants. The survey provides valuable insights, albeit with the limitations highlighted, that could be useful to practitioners and influence clinical practice. The preferences for specific formulations and administration routes, such as water-soluble sachets or effervescent/dispersible tablets due to their hydration benefits and ease of use, offer actionable insights for prescribing practices that align with patient preferences, potentially enhancing adherence to the prescribed mucolytic agent.

The utilisation of real-world evidence has the potential to facilitate discourse surrounding the role of mucolytics in the management of COPD, thereby potentially supporting the development of a RCT. Such an RCT could seek to investigate the efficacy of mucolytics in specific subgroups of COPD patients, particularly during exacerbations or for the management of specific symptoms such as excessive mucus production. The trial could compare mucolytic formulations (eg, granulated sachets vs capsules) to assess not only clinical outcomes but also patient satisfaction, adherence, and quality of life. Including a cost-effectiveness analysis would be critical, given that financial constraints were a limiting factor for some patients.

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All authors have made a substantial contribution to the work reported; have participated in drafting, revising, or critically reviewing the article; have given final approval of the version to be published; have agreed on the journal to which the article was submitted; and have agreed to accept responsibility for all scientific aspects of the work.

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