PHYSICIANS' PERCEPTION ON EFFICACY AND UTILITY OF MUCOLYTIC AGENTS IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RELATED CONDITIONS

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The IIHMR University, Jaipur

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in

Pharmaceutical Management

By

Sonika Tanwar

Under the Supervision and Guidance of

Dr. Sudhinder Singh Chowhan

2024

Cipla

Date: 14 June 2024

To Whom So Ever It May Concern

This is to certify that **Sonika Tanwar**, a student of **IIHMR University**, has successfully completed a **three-month internship** at **Cipla Ltd.** from **15 March 2024** to **14 June 2024.** This internship was undertaken as a part of her MBA dissertation requirement.

During this period, she worked on a market research project and demonstrated commendable dedication, hard work, and a keen interest in learning and contributing to our organization.

She has shown excellent analytical skills, the ability to work effectively within a team, and has contributed positively to the projects assigned. We appreciate her contributions and wish her all the best for future endeavours.

We hereby acknowledge Sonika Tanwar's successful completion of the internship program and extend our best wishes for her future career.

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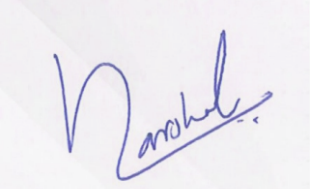

Mr. Harshal Gangurde
Marketing Head

Cipla Ltd.
Address: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai-400013, India. **Website:** www.Cipla.com

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This is to certify that the dissertation titled "Physicians' Perception on Efficacy and Utility of Mucolytic Agents in the Management of Chronic Obstructive Pulmonary Disease and Related Conditions" is a record of the research work undertaken by Sonika Tanwar in partial fulfilment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision. Her approach to the research study has been sincere, scientific, and analytical.

26/06/24

Dr. Sudhinder Singh Chowhan

Faculty Guide

IIHMR University, Jaipur

Date: 26-06-2024

26/6/2024

Dr. Saurabh Kumar Banerjee

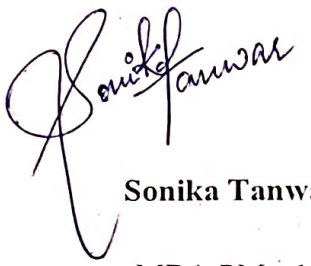
School Dean

IIHMR University, Jaipur

Date: 26-06-2024

DECLARATION BY STUDENT

At this moment, this dissertation titled "Physicians' Perception on Efficacy and Utility of Mucolytic Agents in the Management of Chronic Obstructive Pulmonary Disease and Related Conditions" is the bonafide record of my original researchwork. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished workof others has been duly acknowledged in the text.



Place: Jaipur

Date: 14-06-2024

Sonika Tanwar

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ABSTRACT

Purpose: The primary purpose of this market survey is to evaluate physicians' perceptions of the efficacy and utility of mucolytic agents in managing Chronic Obstructive Pulmonary Disease (COPD) and other related conditions. This survey aims to collect insights from medical professionals to understand their experiences and preferences associated with mucolytic treatments.

Objective: This study explores physicians' perceptions regarding the efficacy and utility of mucolytic agents in managing Chronic Obstructive Pulmonary Disease (COPD) and related respiratory conditions.

Methods: A survey was conducted among physicians, including pulmonologists and general practitioners, to gather insights on their clinical experiences with mucolytic agents. A survey is conducted, and a planned interaction with top Key Opinion Leaders is scheduled to discuss exploring the pivotal role of the mucolytic category in respiratory diseases like COPD and chronic bronchitis.

Results: Most COPD patients are on LAMA/ LABA and tend to dry up the secretions. In such patients, giving a mucolytic can help, but at the same time, adequate hydration is a must, and that should not be ignored. Doctors agreed that the antibacterial effect of Erdostyne is a farfetched thing, and it should first prove to be an effective mucolytic. However, MOA of decreased adhesiveness to bacteria induced by Erdostyne looks promising.

Conclusion: Doctors agreed that the best place in therapy would be in Bronchiectasis and COPD with hypersecretory phenotypes. They would also like to try it in post-tubercular COPD patients. Doctors said they would like to use it in asthmatic patients with excessive mucous, where patients get much choking due to mucous plugs. KOLs agreed that mucus clearance is essential as it predisposes to infection, leading to increased severity of disease and increased chances of exacerbation in COPD patients.

Keywords: Airway Mucus, Chronic Obstructive Pulmonary Disease, Discussion with KOLs, Management of mucus hypersecretion in COPD/CB, Quality of Life (QOL)

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Sonika Tanwar

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ABBREVIATIONS

S. No.	Abbreviation	Full Form
1	COPD	Chronic Obstructive Pulmonary Disorder
2	GBD	Global Burden of Disease
3	DALYs	Daily Adjusted Life Years
4	FEV	Forced Expiratory Volume
5	NAC	N-Acetylcysteine
6	DNA	Deoxyribonucleic Acid
7	Met	Metabolite
8	Cmax	The maximum (peak) plasma drug concentration attained after oral administration
9	Tmax	The time it takes for a drug to reach Cmax after administration
10	CB	Chronic Bronchitis
11	MWT	Minute Walk Test
12	ROS	Reactive Oxygen Species
13	ER	Erdosteine
14	AECOPD	Acute Exacerbations of Chronic Obstructive Pulmonary Disease
15	PO	Per Os – By Mouth/Orally
16	MCT	Mucociliary Transport
17	SE	Standard Error
18	AT	Antitrypsin
19	BAL	Bronchoalveolar
20	ERIC	Elastase Inhibitory Capacity
21	TB	Tuberculosis
22	KOLs	Key Opinion Leaders
23	KBLs	Key Business Leaders
24	GR	Growth Rate
25	CAGR	Compounded Annual Growth Rate
26	MS	Market Share
27	TSA	Total Sales Audit
28	MAT	Moving Annual Total
29	Crs	Crores
30	CVM	Covered Market
32	EI	Evolution Index
34	SPR	Strategic Prescription Research
35	Chest Phy	Chest Physicians
36	Cons Phy	Consultant Physicians
37	GPs	General Practitioners
39	ENTs	Ear, Nose, and Throat
40	Diabeto	Diabetologist
41	Cardio	Cardiologist
42	OAD	Obstructive Airways Disease

CHAPTER 1

INTRODUCTION

1.1 Chronic Obstructive Pulmonary Disease (COPD)

1.1.1 Definition and Overview of COPD: (1)

COPD is described as "a disease state characterised by airflow limitation that is not fully reversible" by the GOLD initiative. The airflow restriction is usually progressive and associated with an abnormal inflammatory response of the lungs to airborne particles or gases. Since asthma is characterized by airflow limitation, inflammation, and hyperresponsiveness of the airways to stimuli, it can be separated from COPD by the reversibility of functional deficits.

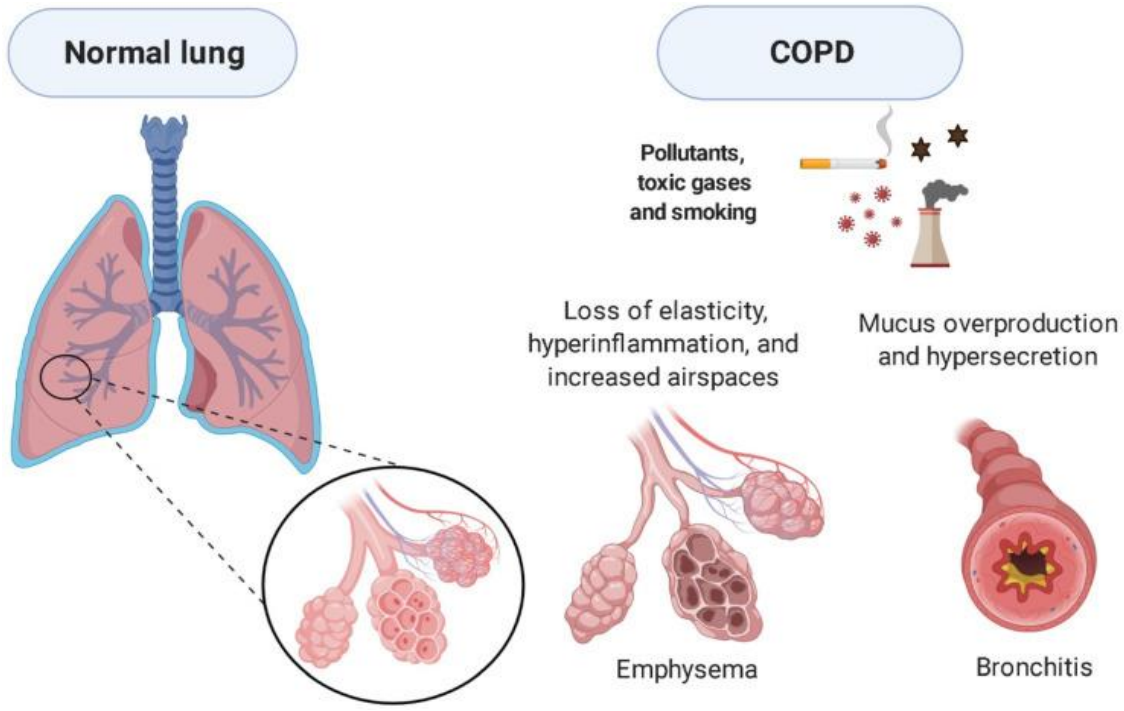

Figure 1.1: Normal Lung vs COPD (2)

1.1.2 Incidence and Prevalence of COPD:

Chronic obstructive pulmonary disease (COPD) is a widespread, curable, and preventable condition that affects 10.1% of persons 40 years of age and older worldwide. In 2019, COPD accounted for 3.23 million deaths globally, making it the third most frequent cause of death. Eighty percent of these fatalities occurred in countries with low and moderate incomes. Estimates of the number of COPD cases in the Southeast Asian nations covered by the World Health Organization rose by 68.8% between 1990 and 2010—from 44.5 million to 75.1 million, per a systematic review of the condition. (3)

Chronic obstructive pulmonary disease (COPD) is the second most prevalent cause of mortality and disability-adjusted life years (DALYs) in India, according to the Global Burden of Disease (GBD) study. According to the GBD 2019 Report, COPD accounts for more than 9.5% of all fatalities in India. In India, COPD is the primary cause of over 50% of chronic respiratory disorders and accounts for 70% of years spent disabled. (4)

1.1.3 Risks involved with COPD: (5)

Patients with COPD may experience a progressive decline in their lung function because of chronic airway mucus hypersecretion. After adjusting for age and cigarette smoking, a 12-year follow-up study involving 2,191 females and 1,757 males found a correlation between the decline in forced expiratory volume (FEV1) and chronic cough. Hospitalisation and acute exacerbation risk are significantly elevated in COPD patients with chronic airway mucus hypersecretion: The risk rose 2.6 times for women and 2.4 times for men. Speizer et al. observed 8,427 COPD patients over 12 years and discovered that persistent cough and phlegm substantially elevated the risk of death: The risk rose 3.75 times for men and 11.04 times for women.

1.1.4 The impact of COPD on patient quality of life: (6)

Patients with COPD may have a significantly reduced quality of life, which worsens as the disease progresses due to a faster reduction in lung function and a gradual degradation of the patient's physical performance. People are unable to socialise or indulge in their interests due to the illness, which causes frustration and rage in many. Patients struggle to be physically active and run the danger of dying young as they fight for oxygen while performing basic tasks.

1.1.5 Pathophysiology of COPD: (2)

Typical alveolar septa have elastic fibers that are mostly located in the subepithelial layer. These fibers resist connective tissue, allowing for passive recoil and deformability without the need for energy input. Collagen and elastic fibers are mechanically joined by proteoglycans and microfibrils. When lung volume approaches its maximum, collagen fibers stop breathing. Elastic fibers, on the other hand, often keep lung elasticity within a normal range of lung volume. Emphysema is a major disease that contributes to COPD and is characterized by elastolysis, or the destruction of elastic fibers. A gradual airflow restriction that is not fully reversible, associated with an abnormal inflammatory response of the lungs to foreign particles or gases, is the characteristic of COPD.

Emphysema is caused by reduced gas exchange, chronic airway expansion, lack of elastic recoil, hyperinflation, and limited expiratory flow, all of which are brought on by the collapse of alveolar walls. Fiber degradation by metalloproteinases results in modifications to the structure of collagen and elastic fibers. These traits affect the lung's mechanical and tissue stability, which hastens the disease's course and results in a progressive decline in lung function.

1.2. Mucolytics (7)

1.2.1 Definition of Mucolytics:

Medications classified as mucolytics are members of the mucoactive agent class. They work to improve the mucus layer that lines the respiratory system by exerting their influence on it. The numerous epithelia inside our bodies use mucus to defend against hazardous germs. Its duties also include shielding the epithelium from irritating substances that cause excoriation in the digestive system. Glycoproteins, immunoglobulins, and even some antibacterial enzymes like lysozyme are among the many proteins it includes. The biophysical properties of mucus are mostly determined by the cross-bridging of polymeric gel-forming mucins. This layer offers superior bacterial protection by thwarting the development of biofilms and bacterial growth. The mucus layer acts as a physical barrier against respiratory irritants in addition to preventing fluid loss. Expectorated mucus is sputum.

1.2.2 Types of Mucolytics:

Mucolytics are divided into two types:

1.2.2.1 Classic Mucolytics

Disulfide bonds are the building blocks of many complex proteins, including mucus. N-acetyl L-cysteine (NAC), the class's prototypical drug, works by means of the thiol-disulfide exchange mechanism while maintaining its reducing activity. The structure of the mucin polymers include cysteine residues. The disulfide bonds that cause the polymer to cross-link are anchored by these residues. The free thiol group in the NAC structure hydrolyzes the disulfide bonds attached to cysteine residues. The S-S bond is reduced to an S-H (sulfhydryl) bond in this reaction, disrupting the three-dimensional structure of mucus and making it unable to bind the complex protein structure.

- N – Acetylcysteine
- Carbocysteine
- Erdosteine and Fudosteine

1.2.2.2 Peptide Mucolytics

Unlike conventional mucolytics, peptide mucolytics preserve the protecting mucins. Peptide mucolytics target DNA polymers and F-actin links that tend to increase in purulent discharges. Therefore, peptide mucolytics are very beneficial in conditions such as cystic fibrosis because they depolymerise the DNA polymers or F-actin network that is often seen in purulent discharges, which lowers the viscosity of the mucus.

- Dornase Alfa
- Thymosin β4

1.3 Erdosteine

1.3.1 Background of Erdosteine: (8)

Erdosteine is a medication, sometimes called a mucolytic agent, that breaks down mucus. This thiol derivative is made to clinically treat infective exacerbations of chronic bronchitis and chronic obstructive bronchitis. Sulfhydryl groups are released from this medication when erdosteine passes through first-pass hepatic metabolism. This leads to three active metabolites that can scavenge free radicals and mucolytic activity. Erdosteine increases mucociliary transport while regulating mucus formation and viscosity. It also counteracts the harm done by free radicals that are produced by cigarette smoke. Clinical investigations have shown that erdosteine is safe and well-tolerated. More quickly and efficiently than a placebo, erdosteine 300 mg twice daily decreased cough (both frequency and severity), sputum viscosity, and sputum adhesivity. Ambroxol 30 mg twice daily did not have the same impact. When erdosteine and amoxicillin were given to individuals experiencing an acute infective exacerbation of chronic bronchitis, the antibiotic concentrations in the sputum increased. This, in turn, caused a more marked and early improvement in clinical symptoms compared to placebo. Adverse effects related to erdosteine are rare and often moderate, with a low prevalence of gastrointestinal problems.

1.3.2 Mechanism of Action of Erdosteine: (8)

Erdosteine is a mucolytic drug taken orally. It is made to treat the symptoms of chronic obstructive bronchitis and is categorised as a thiol derivative. Sulfhydryl groups found in erdosteine are liberated following hepatic first-pass metabolism in the liver. Its three active metabolites can scavenge free radicals and perform mucolytic action. Erdosteine improves mucociliary transport while controlling the amount and viscosity of mucus in the airways. Expectations rise because of this. Erdosteine exhibits suppression of the effects of cigarette smoke-produced free radicals. Research conducted on individuals suffering from chronic obstructive pulmonary disease (COPD) has demonstrated that this medication is generally well-tolerated and safe. More quickly and efficiently than a placebo, erdosteine 300 mg twice daily decreased cough (both frequency and severity), sputum viscosity, and sputum adhesivity. Ambroxol 30 mg twice daily did not have the same impact. When erdosteine and amoxicillin were given to individuals experiencing an acute infective exacerbation of chronic bronchitis, the antibiotic concentrations in the sputum increased. This, in turn, caused a more marked and early improvement in clinical symptoms compared to placebo. Adverse effects related to erdosteine are rare and often moderate, with a low prevalence of gastrointestinal problems.

1.3.3 Pharmacokinetics of Erdosteine: (9)

Adult volunteers receive single doses of erdosteine ranging from 150 mg to 1200 mg, and the drug exhibits a linear kinetic. In comparison, the Met I serum concentration of erdosteine is around 4-fold higher. Erdosteine and Met I do not accumulate or undergo metabolic activation after many administrations since their pharmacokinetic characteristics do not change after a single or multiple doses. Food has no appreciable effect on the absorption of erdosteine. When taken orally, erdosteine is rapidly absorbed in the gastrointestinal tract, reaching its plasmatic peak concentration (Cmax) 30–60 minutes (Tmax) after consumption. The chemical is rapidly transformed into Met I, a physiologically active metabolite. First-pass metabolism during oral pharmaceutical administration results in good drug bioavailability. The half-life is three hours, and the plasma binding protein is 65%. The pharmacokinetics of metformin and erdosteine were unaffected by moderate renal impairment in older adults.

1.3.4 Indication, Dosage, and Administration of Erdosteine: (10)

- As an Expectorant.
- For the symptomatic treatment of acute exacerbation of chronic bronchitis in adults for chronic obstructive bronchitis.
- For chronic obstructive bronchitis.
- Elderly and Adults (above 18 years of age): 300 mg 2-3 times a day for a maximum of 10 days.

Table 1.1: Dosage details of globally available products

S. No.	Recommended dosage as per the label of global products	Reference (Product details)
1	300 mg twice daily for a maximum of 10 days	ERDOTIN (Galen Ltd. UK)
2	300 mg capsule, 2-3 times a day	VECTRINE (Edmond Pharma s.r.l., Italy)
3	300 mg capsule, 2-3 times a day	ECTRIN (OEP Philippines, Inc., Philippines)
4	300 mg capsule, 2-3 times a day	ELDOTEINE (Korea United Pharma, Inc., Korea)
5	300 mg capsule, 2-3 times a day	ELSTEINE (Daewon Pharma, Korea)

CHAPTER 2

REVIEW OF LITERATURE

Cazzola M et al. (2010), In individuals with CB/COPD, erdosteine treatment is linked to a considerable improvement in symptom relief compared to placebo and mucolytics. This review supports the use of erdosteine in conjunction with standard therapy for respiratory disorders characterised by increased expectoration, such as acute CB/COPD exacerbations, despite certain limitations (such as incompletely validated ratings). (11)

Cazzola M et al. (2018), The data from ten studies, totalling 1278 patients, were incorporated into our findings, which demonstrate that erdosteine can lower the risk of at least one exacerbation as well as improve the clinical score of patients with COPD and chronic bronchitis. Additionally, our data indicate that erdosteine may decrease the duration of a COPD exacerbation, increase the time until the first exacerbation, and increase the likelihood of hospitalisation due to COPD. The fact that erdosteine has been shown to have a demonstrable impact on lowering the frequency and managing exacerbations of COPD is significant because it suggests that erdosteine should be included in the range of medications indicated for treating COPD. (12)

Moretti M et al. (2004), In addition to having fewer hospital days and exacerbations than the placebo group, the group of COPD patients receiving erdosteine for eight months continuously did not lose lung function. The quality of life connected to health improved significantly for patients in the erdosteine group. Throughout the research, the erdosteine group experienced a decrease in mean total COPD-related disease expenses per patient relative to the placebo group. According to the findings, erdosteine medication for eight months is beneficial in lowering hospitalisation and exacerbation rates and enhancing health. According to the study, erdosteine will probably play a significant role in helping people with symptomatic COPD receive treatment. (13)

Dal Negro RW et al. (2017), Erdosteine shortened the duration of the exacerbation by 24.6% (9.55 versus 12.63 days for erdosteine and placebo, respectively; $p=0.023$) regardless of the incident's severity. Erdosteine significantly improved the subjective severity levels of both participants and physicians ($p=0.022$ and $p=0.048$, respectively), and it significantly reduced the need of painkiller medication ($p<0.001$). Patients with COPD may experience fewer and shorter exacerbations when taking etosteine. Both the erdosteine and placebo therapy groups had similar rates of patients experiencing side events. (14)

Calverley PM et al. (2019) erdosteine to regular COPD maintenance medicine may reduce the frequency of mild exacerbations and the duration of all exacerbations in individuals with moderate COPD and a history of exacerbations. (15)

Dal Negro RW et al. (2016), Each group's mean ROS plasma levels grew significantly but comparably after the baseline 6MWT (p = ns). After the second 6MWT, there was a significant difference ($p < 0.025$) in the mean plasma ROS increase from baseline between the ER (+14.6% ± 2.7) and the placebo group (+24.4% ± 3.8). A significant trend was also observed in the mean 8-isoprostane rise, which varied from baseline by +14.1% ± 2.6 in the ER and by +26.3 ± 2.9 in the placebo group during the second 6MWT ($p < 0.006$). Data from this experiment indicate that ER reduces the quantity of inflammatory mediators generated by exercise-induced oxidative stress, which benefits patients with severe COPD. (16)

Dal Negro RW et al. (2015) Results show that erdosteine is a valuable component of the therapeutic approach for oxidative stress-induced inflammation prevention and therapy, which is often the first step toward the beginning of AECOPD. They also support the time- and dose-dependent actions of the antioxidant. (17)

Moretti M et al. (2015), The results show that in patients with AECOPD, adding ER (900 mg/d) to conventional treatment improves patient outcomes. AECOPD symptoms were reduced, the time until the first exacerbation was postponed, and airway inflammation was markedly reduced with ER. The authors suggest that patients who have severe, prolonged, or frequent exacerbations of their COPD may benefit most from ER visits. (18)

Dal Negro R et al. (2008), This impact appears to be more associated with the unique defence against lipid peroxidation than with the scavenging action, which is found to be on par with NAC. By "re-sensitizing" β 2-adrenoceptors, E produces a form of indirect bronchodilation. When verified by more controlled research, it might be helpful in the long-term management of COPD. (19)

Dal Negro RW et al. (2008), Erdosteine has a considerable effect on a few pro-inflammatory cytokines that are mostly related to oxidative stress in current smokers with moderate COPD. The impacts showed themselves in varied ways throughout time. To confirm these pilot findings and ascertain their long-term therapeutic value, more thorough investigation is needed. (20)

Crisafulli E et al. (2007), This pilot study found that administering PO erdosteine 225 mg twice in addition to conventional chest physical therapy to these elderly patients with bronchiectasis and chronic mucus hyper-secretion had some positive physiological and clinical effects. (21)

Dal Negro RW et al. (2011), 1) Scavenging and anti-inflammatory properties of erdosteine were both validated. 2) It was shown that erdosteine has a significant impact on eicosanoids. 3) This new result highlights the medication's significant anti-inflammatory capabilities in COPD. 4) More research is required to determine whether Erdosteine can effectively manage persistent inflammation in long-term respiratory conditions. (22)

Marchioni CF et al. (1995), Of the nineteen side effects of erdosteine, three were epigastralgia, three were nausea, one was diarrhoea, one was a tasting loss, and one was bleeding. Three of the 13/17 associated placebo-related events were epigastralgia, four were nauseated, four were diarrhoea, one was pyrosis, and one was dry mouth. They've all been classified as low or moderate degrees of severity. Additionally, there are no notable distinctions in terms of safety between the two treatments that are being evaluated from a qualitative standpoint. An especially intriguing conclusion drawn from the efficacy/safety evaluation is that the synergistic activity between erdosteine and the antibiotic alters the clinical picture earlier and more profoundly without raising the incidence of adverse effects. (23)

Olivieri D et al. (1991), MCT was unaffected by the placebo, but it was greatly enhanced by the erdosteine therapy (mean percentage variation ± SE vs baseline values of +60.4 ± 18.4 and -3.0 ± 5.9, respectively). The distinct mucus transport activity of erdosteine may be therapeutically beneficial in patients suffering from chronic bronchitis. It can be utilized to reverse the drop in MCT when used with β2-agonists. (24)

Marchioni CF et al. (1990), Finally, following two weeks of erdosteine therapy, patients with chronic bronchitis had a decrease in the marker for mucus glycoproteins (fucose). Nevertheless, the pharmacokinetics of xanthine derivatives were unaffected by this medicine. We further suggest that there might be other local consequences linked to the significant rise in the IgA/albumin ratio, such as the inhibition of inflammation and the strengthening of the humoral defense system. (25)

Vagliasindi M et al. (1989), Finally, patients with chronic bronchitis showed a decrease in the marker for mucus glycoproteins (fucose) after two weeks of erdosteine therapy. However, this medication had no effect on the pharmacokinetics of xanthine derivatives. We also propose that the substantial increase in the IgA/albumin ratio may have other local effects, such as suppressing inflammation and bolstering the humoral defenses. (26)

Ricevuti GI et al. (1988), Erdosteine significantly increased the concentrations of antibiotics in sputum but not in serum. Along with a faster decrease in body temperature and viscosity, the combination treatment accelerated the sterilization of sputum. These results show that in patients with acute exacerbations of chronic bronchitis, erdosteine increases the amount of amoxicillin in sputum. This may be due to the fact that erdosteine thins the secretions in the bronchi. (27)

Rogliani P et al. (2019), Antibiotic concentrations in sputum were considerably elevated by etosteine, but not in serum. The combined treatment not only caused a faster decrease in body temperature and viscosity, but it also sped up the process of sterilising sputum. These findings demonstrate that in patients experiencing acute exacerbations of chronic bronchitis, erdosteine raises the concentration of amoxicillin in sputum. This could be because erdosteine reduces the viscosity of bronchial secretions. (28)

CHAPTER 3

METHODOLOGY

3.1. Research Design

This study aims to explore physicians' perceptions regarding the efficacy and utility of mucolytic agents in managing Chronic Obstructive Pulmonary Disease (COPD) and related conditions.

3.2. Research Type

Exploratory and Descriptive research design

3.3 Research Questions:

1. How do physicians perceive mucolytic agents' efficacy in managing chronic obstructive pulmonary disease (COPD)?

2. How do physicians perceive the clinical utility of mucolytic agents in the overall management strategy for COPD and related conditions?

3. What has been the physicians' experience regarding patient outcomes when using mucolytic agents for COPD management?

4. How can educational interventions improve physicians' knowledge and use of mucolytic agents for COPD?

3.4 Research Objective:

To explore physicians' perception of mucolytic agents concerning their effectiveness and safety in COPD treatment.

3.5. Sample Selection

3.5.1. Target Population

Chest Physicians and Consultant Physicians at Jaipur District

3.5.2. Inclusion Criteria

Top KOLs & KBLs in respiratory medicine.

3.5.3. Sampling Method

Stratified and Cluster Sampling Method

3.5.4. Sample Size

217 Chest Physicians and Consultant Physicians

3.6. Data Collection

3.6.1. Survey Instrument

Data was collected using a structured questionnaire developed specifically for this study.

3.6.2. Pilot testing

The questionnaire was pilot tested with a small group of physicians (n=10) to ensure clarity, relevance, and comprehensiveness. Feedback from the pilot test was used to refine the survey instrument.

3.6.3. Data Collection Procedure

The survey was done by personally meeting the doctors and getting the survey forms filled out by them.

3.7. Data Analysis

- Descriptive statistics was used to analyse and summarise the data.
- Microsoft Excel was used to summarise the data.
- Pivot tables were used to analyse the data.
- Graphs, including bar charts and column charts, were used to visualise the data.

3.8. Ethical Considerations

No experiments were done on humans or animals, and therefore, it didn’t cause any harm to them.

3.8.1. Informed Consent

Participation in the survey was voluntary, and informed consent was obtained from all respondents. The purpose of the study and the confidentiality of responses were explained in the survey introduction.

3.8.2. Confidentiality and Anonymity

All data collected were kept confidential. Responses were stored securely, with access limited to the research team.

3.8.3. Conflict of Interest

None

CHAPTER 4

RESULTS

4.1 Market Analysis

Table 4.1: NAC Market Category: Solid, Liquid, and Injection

		Total	Solids	Injections	Liquids
Value (In Crs)		212.0	177.0	35.0	0.1
Units ('000)		153,89	85,31	68,47	11
Growth %	Value GR%	29%	30%	23%	528%
	Unit GR%	21%	20%	22%	522%
CAGR% (5 Yrs.)	Value CAGR%	20%	20%	19%	104%
	Unit CAGR%	14%	11%	17%	102%
No. of Brands			44	11	2
Top Brands			Mucinac (Cipla) 74% MS Mucomix (Samarth) 5% MS Viscojoy (JB Pharma) 4% MS	Mucomix (Samarth) 54% MS Mucyst (Neo Pharma) 19% MS Mucinac (Cipla) 18% MS	Mucomix (Samarth) 54% MS Nacfil (Fourrts) 0% MS

Data Source: IQVIA TSA sales audit for the period of MAT-Dec'23

Interpretation:

- From the above table, we can see that the NAC market is growing with a 20% CAGR in the solids category.
- Also, we can see that Mucinac is the leading player with a 74% market share in the solids category.

Table 4.2: Mucolytics market overview: Top brands and market value with growth

Brands	Product Launch	Company	Value (MAT-Dec'23)				Units (MAT-Dec'23)			
			IN Crs	GR %	CAGR %	MS %	IN '000	Gr %	CAGR %	MS %
ALL India			**177**	**30 %**	**20%**	**100 %**	**8531**	**20 %**	**11%**	**100 %**
Mucinac	2005/4	Cipla	130.6	35%	24%	74%	5835	23 %	13%	68%
Mucomix	2005/1	Samarth Pharma	8.6	38%	19%	5%	596	35 %	15%	7%
Viscojoy	2021/2	JB Pharma*	6.6	68%	…	4%	363	59 %	…	4%
Lumenac	2009/4	Lupin Limited	6.6	-2%	9%	4%	303	-6%	1%	4%
Quicnac	2021/12	Alkem*	5.4	103 %	…	3%	330	94 %	…	4%
Mucotab ET	2014/4	Zydus Cadila*	3.8	45%	19%	2%	174	34 %	10%	2%
Nacfil	2004/4	Fourrts India	2.1	1%	-3%	1%	159	-4%	-7%	2%
Fluimucil	2014/9	Modi Mundi Pharma	1.9	-21%	24%	1%	87	-28 %	11%	1%
Mucotab	2010/10	Zydus Cadila*	1.1	7%	-4%	1%	45	-5%	-11%	1%
Mucaryl	2016/7	Glenmark Pharma	1.1	-7%	-18%	1%	57	-14 %	-22%	1%

Data Source: IQVIA TSA sales audit for the period of MAT-Dec'23

Interpretation:

- Mucinac leading the category with 13% Unit CAGR
- The category is well dominated by one brand, and we can see that Mucinac has 74 % MS in terms of value and 68% MS in terms of units.
- Price-led growth for the category & Mucinac both.
- Out of the total market in India, 177 Cr, Mucinac has 130.6 Cr.
- Two new entrants (Vicojoy & Quicnac) have also started gaining market share.

Table 4.3: Market: Demography wise

	CVM		Music				
	Value (In Crs)	**GR%**	**Value** (In Crs)	**GR%**	**EI**	**MS%**	**Δ MS%**
All India	**176.9**	**30%**	**130.6**	**35%**	**104**	**74%**	**3%**
West Bengal	22.9	48%	17.2	56%	105	75%	4%
Uttar Pradesh	18.1	24%	13.5	24%	99	75%	0%
Delhi	10.8	58%	9.4	69%	107	87%	6%
Rajasthan	7.1	17%	4.9	23%	105	69%	3%
Assam	6.2	25%	4.5	35%	108	72%	5%
Orissa	4.7	39%	3.8	51%	109	81%	7%
Punjab	4.6	15%	3.4	15%	100	74%	0%
Haryana	4.2	9%	3.0	18%	109	71%	6%
Bihar	3.3	13%	2.4	27%	113	70%	8%
Madhya Pradesh	3.1	6%	1.9	15%	108	62%	4%
Uttarakhand	2.8	36%	1.8	31%	96	66%	-3%
Jammu & Kashmir	2.0	22%	1.2	20%	99	58%	-1%
Himachal Pradesh	1.0	7%	0.8	5%	99	77%	-1%
Chhattisgarh	0.8	-7%	0.4	-15%	92	50%	-5%

Data Source: IQVIA TSA sales audit for the period of MAT-Dec'23

Interpretation:

- West Bengal is the leading state with a 48% growth rate.
- All the markets are growing with double-digit growth.

Table 4.4: Target customer and prescription contribution

N-Acetyl Cysteine (NAC)						
	MAT			Prescription Contribution		
	MAT Dec'22	MAT Dec'23	Gr%	MAT Dec'22	MAT Dec'23	Δ Contri.
SPR	**4354**	**5240**	**20%**	**100%**	**100%**	**---**
GPs	894	1293	45%	21%	25%	4%
ENTs	787	1040	32%	18%	20%	2%
Cons Phy	638	761	19%	15%	15%	0%
Chest Phy	718	656	-9%	16%	13%	-4%
Diabeto	177	281	59%	4%	5%	1%
Cardio	186	238	28%	4%	5%	0%

Data Source: IQVIA TSA sales audit for the period of MAT-Dec'23

Interpretation:

- Chest Physicians' prescriptions are declining.
- Consultant Physicians' prescriptions continue to grow.
- Consultant Physicians & Chest Physicians are the 3rd & 4th largest contributing specialties of doctors.
- Declining prescriptions for NAC at Chest Physicians

4.2 Survey Analysis

Table 4.5: Use of mucolytics in different types of patient profiles

Patient Profile	No. of Doctors	% of Doctors
All the above	166	77
Bronchiectasis	7	3
Chronic Bronchitis	13	6
COPD	22	10
Patients with a persistent cough	9	4

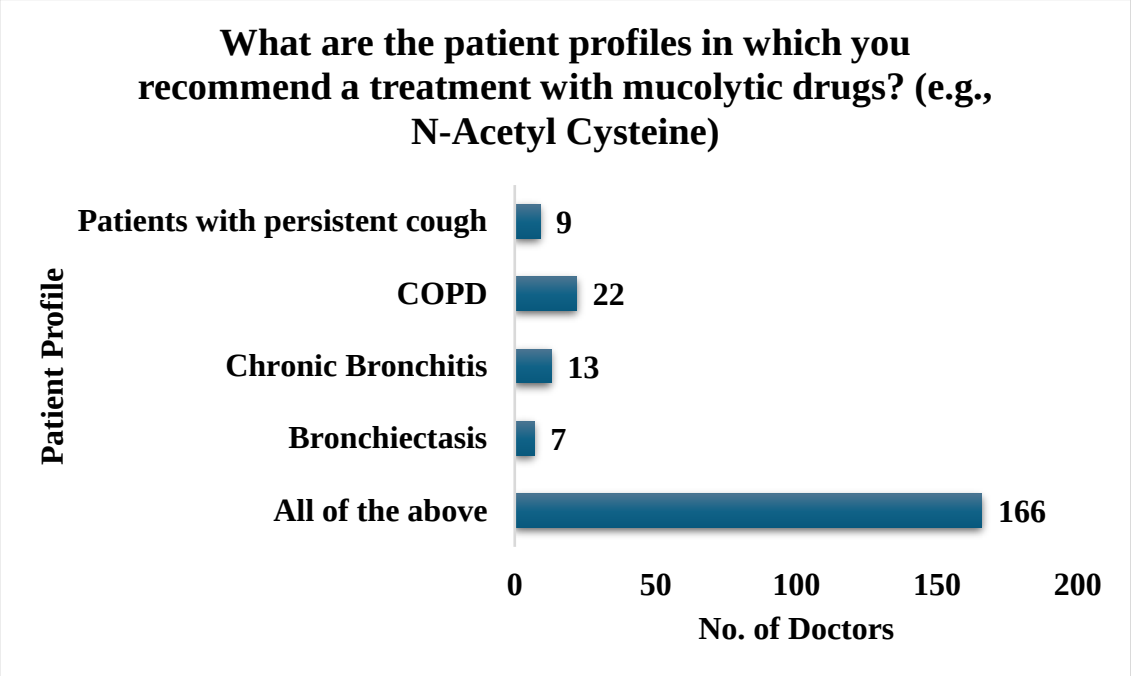

Figure 4.1: Use of mucolytics in different types of patient profiles

Interpretation:

This graph shows that 77% of the doctors recommend treatment with mucolytic agents in all patient profiles (i.e. Patients with persistent cough, COPD patients, Chronic Bronchitis, and Bronchiectasis). So, we can say that mucolytic drugs are used in various respiratory diseases.

Table 4.6: % of patients who need add-on treatment with NAC

% of Patients	No. of Doctors	% of Doctors
20% - 40%	109	50
<20%	44	20
>60%	8	4
41%- 60%	56	26

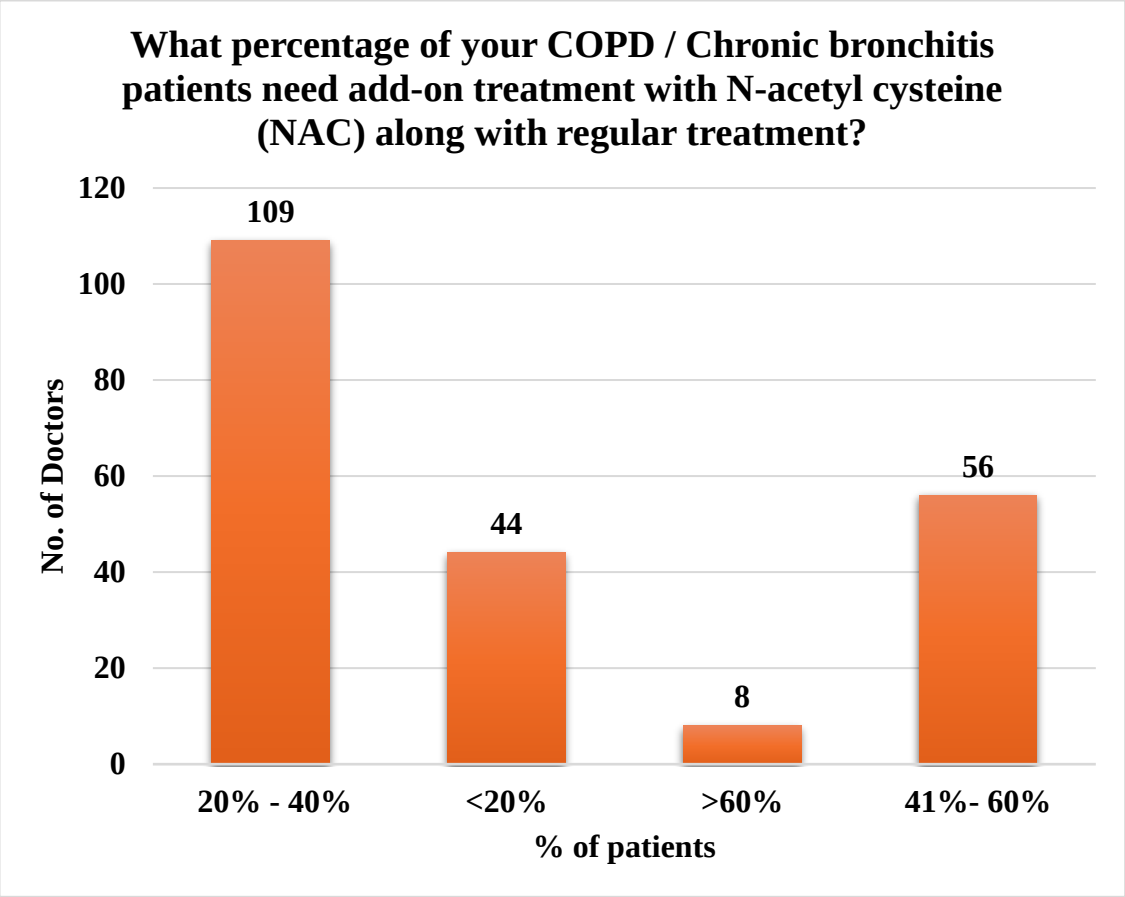

Figure 4.2: % of patients who need add-on treatment with NAC

Interpretation:

We can see that maximum doctors have a 20-60 % inflow of patients who require add-on treatment with N-Acetyl cysteine. So, we can undoubtedly see that mucolytics are in high demand.

Table 4.7: Recommended time for treatment with mucolytic agents

Time Duration	No. of Doctors	% of Doctors
A short course of 1-2 weeks	57	26
15 days	82	38
2-3 months	19	9
More than a month	59	27

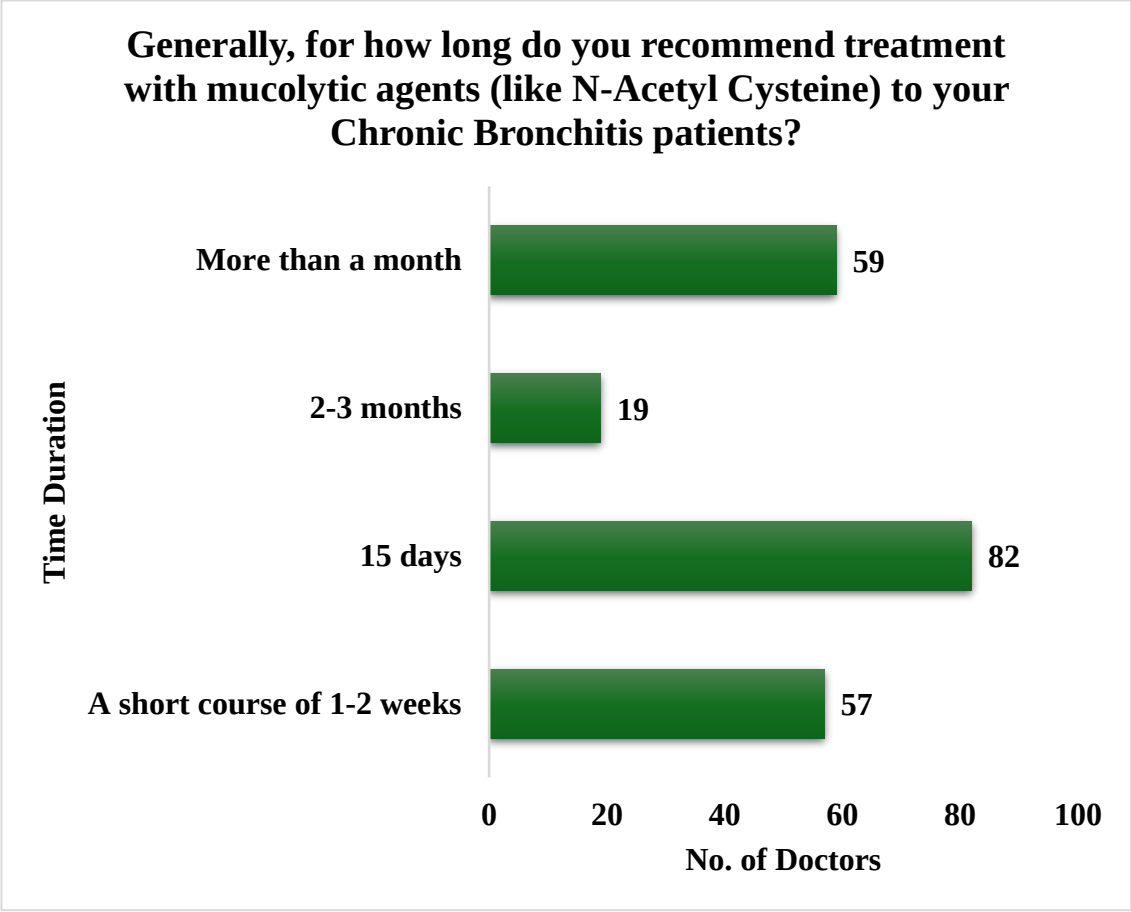

Figure 4.3: Recommended time for treatment with mucolytic agents

Interpretation:

We can see that most doctors recommend treatment with mucolytic agents for a minimum of 1-2 weeks and even for a month. So, if we calculate the total units required for one patient, it will be only on the higher side.

Table 4.8: NAC helps to reduce exacerbations or not

Yes/No	No. of Doctors	% of Doctors
No	47	22
Yes	170	78

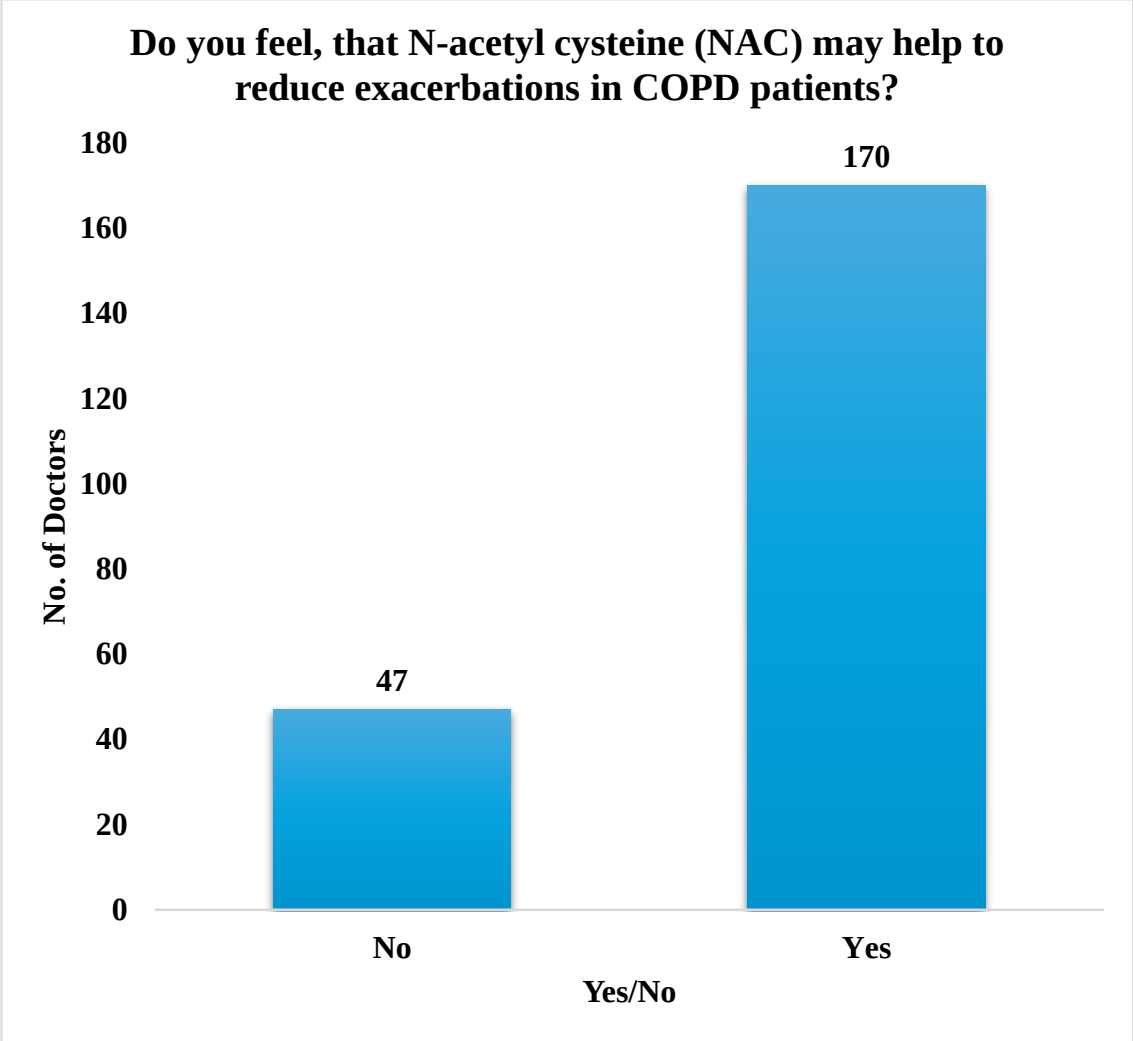

Figure 4.4: NAC helps to reduce exacerbations or not

Interpretation:

We can see that 78% of doctors say that NAC helps reduce COPD exacerbations. So, we see mucolytics also have another use apart from just showing the main mucolytic effect, i.e., to manage mucus hypersecretion. However, 22% of the doctors still do not agree with reducing exacerbations, so we can work on this.

Table 4.9: Satisfaction level with antioxidant properties of NAC

Level of Satisfaction	No. of Doctors	% of Doctors
Neutral	108	50
Not much	21	10
Very much	88	40

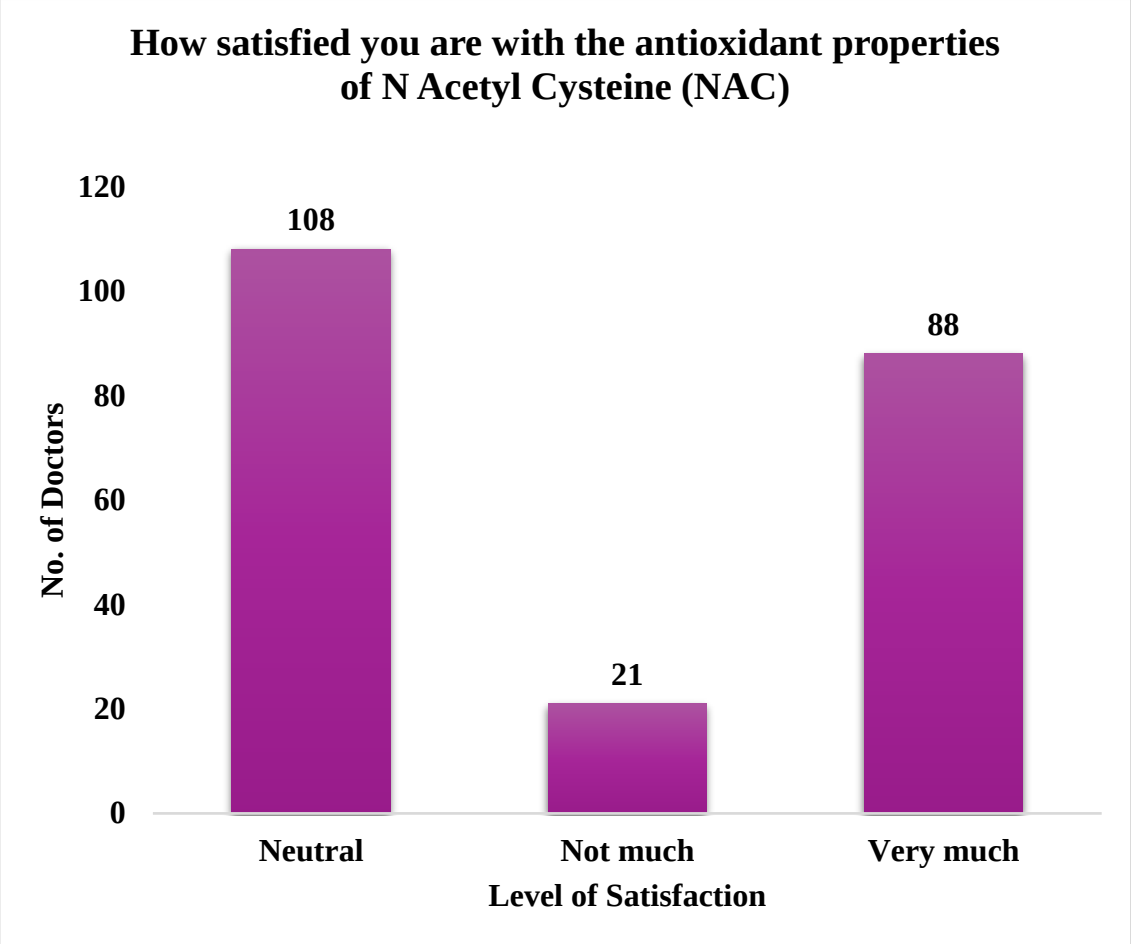

Figure 4.5: Satisfaction level with antioxidant properties of NAC

Interpretation:

We can see that 50% of doctors didn't prefer to speak about the antioxidant properties of NAC. So, we can say that the doctors are unaware of the antioxidant properties of mucolytic agents because we can also see that 40% of doctors are aware of it and are satisfied with the same.

Table 4.10: NAC helps to reduce hospitalisation or not

Yes/No	No of Doctors	% of Doctors
No	50	23
Yes	167	77

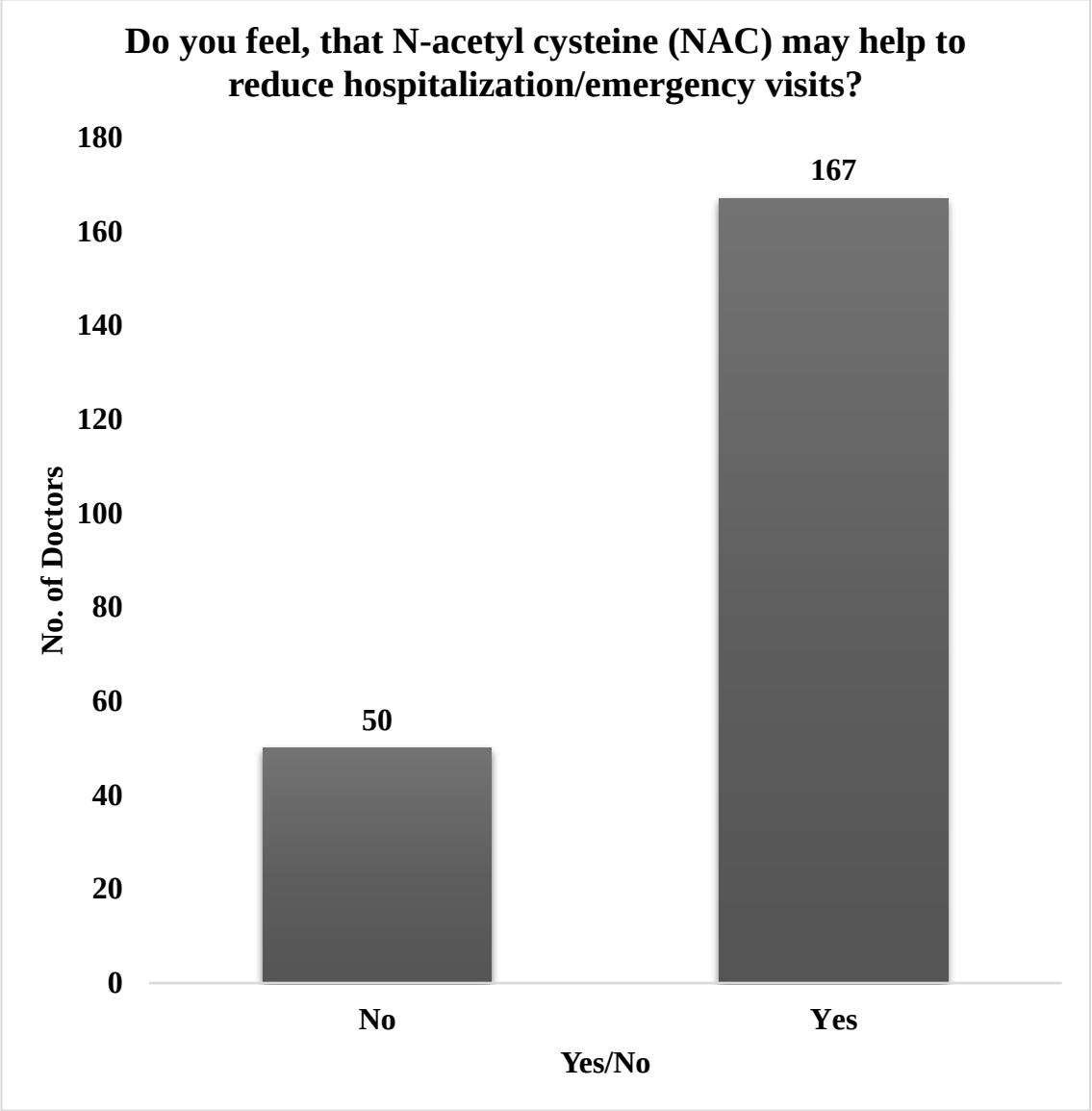

Figure 4.6: NAC helps to reduce hospitalisation or not

Interpretation:

We can see that 77% of the doctors say that NAC helps to reduce hospitalisation/ emergency visits. So, it's an added advantage of mucolytic agents.

Table 4.11: Type of OAD patients recommended for combination drugs

Type of OAD Patients	No of Doctors	% of Doctors
All the above	129	59
Bronchiectasis	14	6
Chronic Bronchitis	25	12
COPD	34	16
Patients with persistent cough of more than three months	15	7

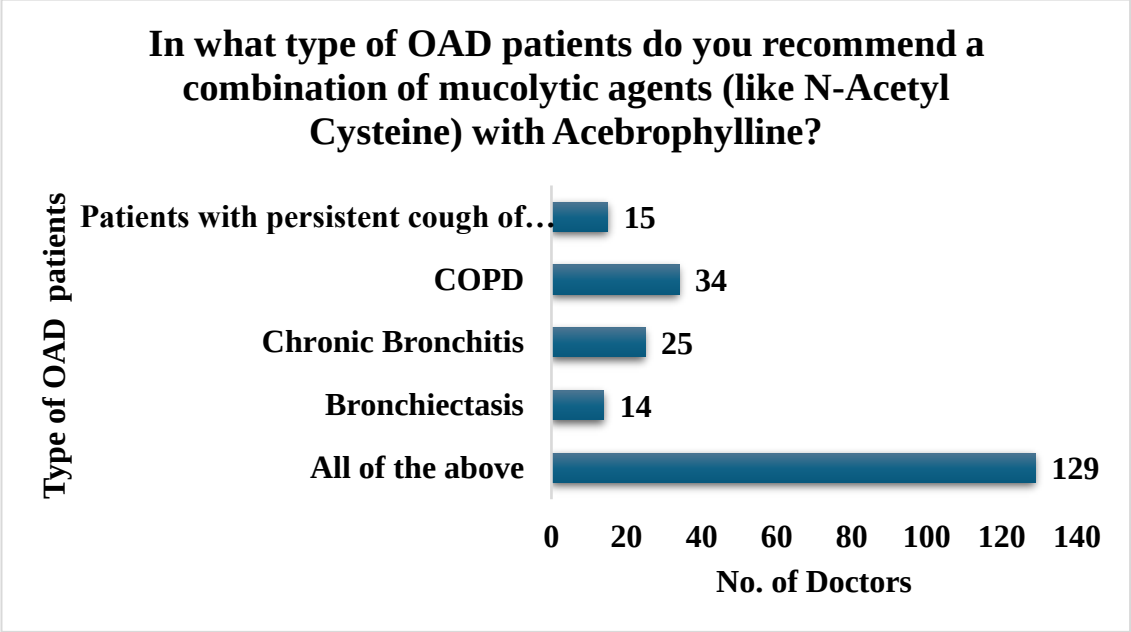

Figure 4.7: Type of OAD patients recommended for combination drugs

Interpretation:

We can see that 59% of doctors say that they recommend mucolytic agents in combination with Acebrophylline in all types of Obstructive airway diseases (OAD), i.e. COPD, Chronic Bronchitis, Bronchiectasis, and Patients with persistent coughs of than three months. So, we can say that mucolytic agents can also be combined with Acebrophylline, which is used as a bronchodilator for COPD and other respiratory diseases.

Table 4.12: Treatment with NAC outweighs its cost or not

Level of Belief	No of Doctors	% of Doctors
No, I don't believe.	36	17
Some, I believe.	120	55
Yes, I firmly believe.	61	28

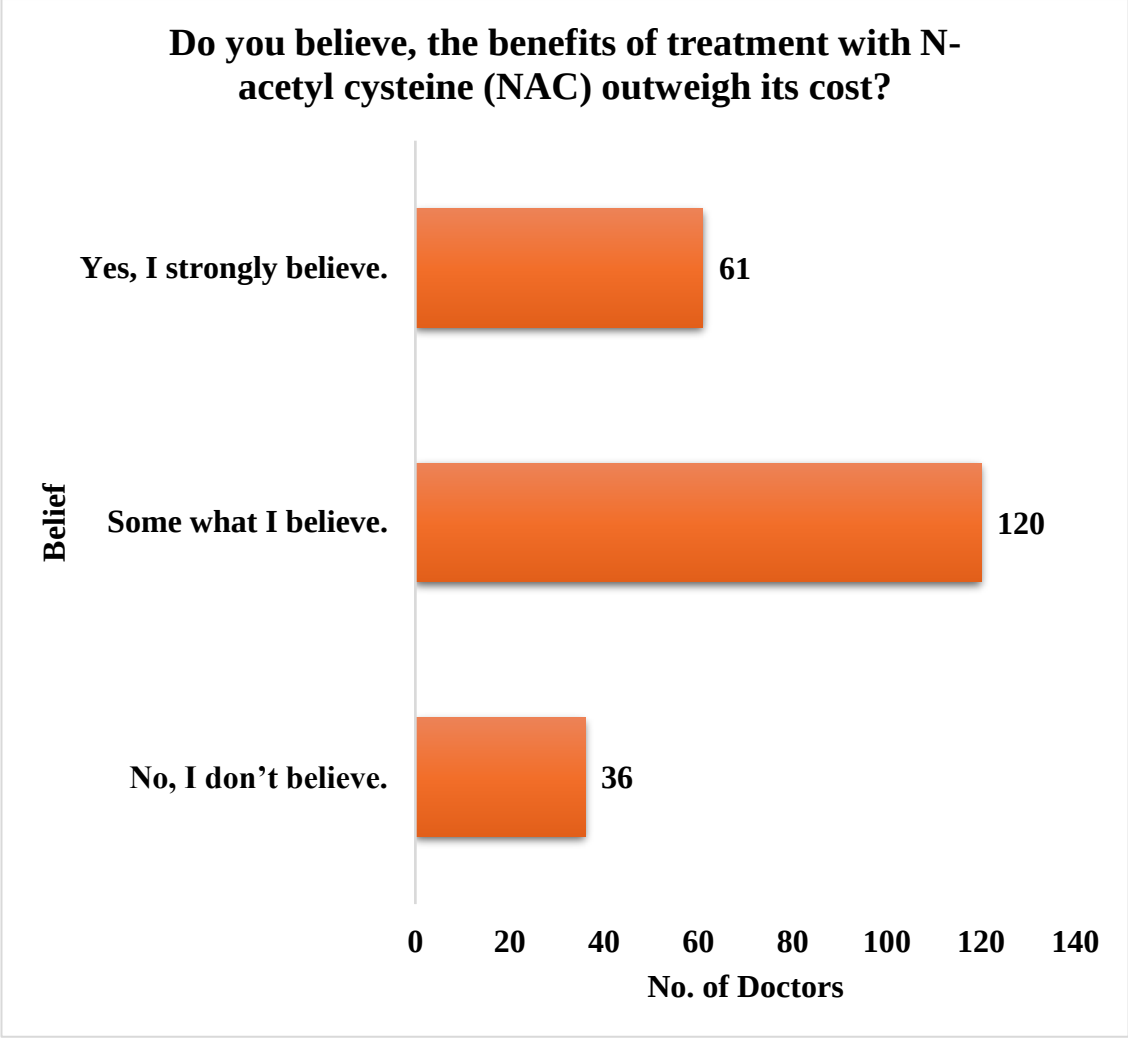

Figure 4.8: Treatment with NAC outweighs its cost or not

Interpretation:

We can see that only 28% of doctors firmly believe that treatment with NAC outweighs its cost, and 55% do not fully agree with this as they think the treatment is a bit costlier.

Table 4.13: There is a reduction in the use of reliever medications or not

Yes/No	No. of Doctors	% of Doctors
No	44	20
Yes	173	80

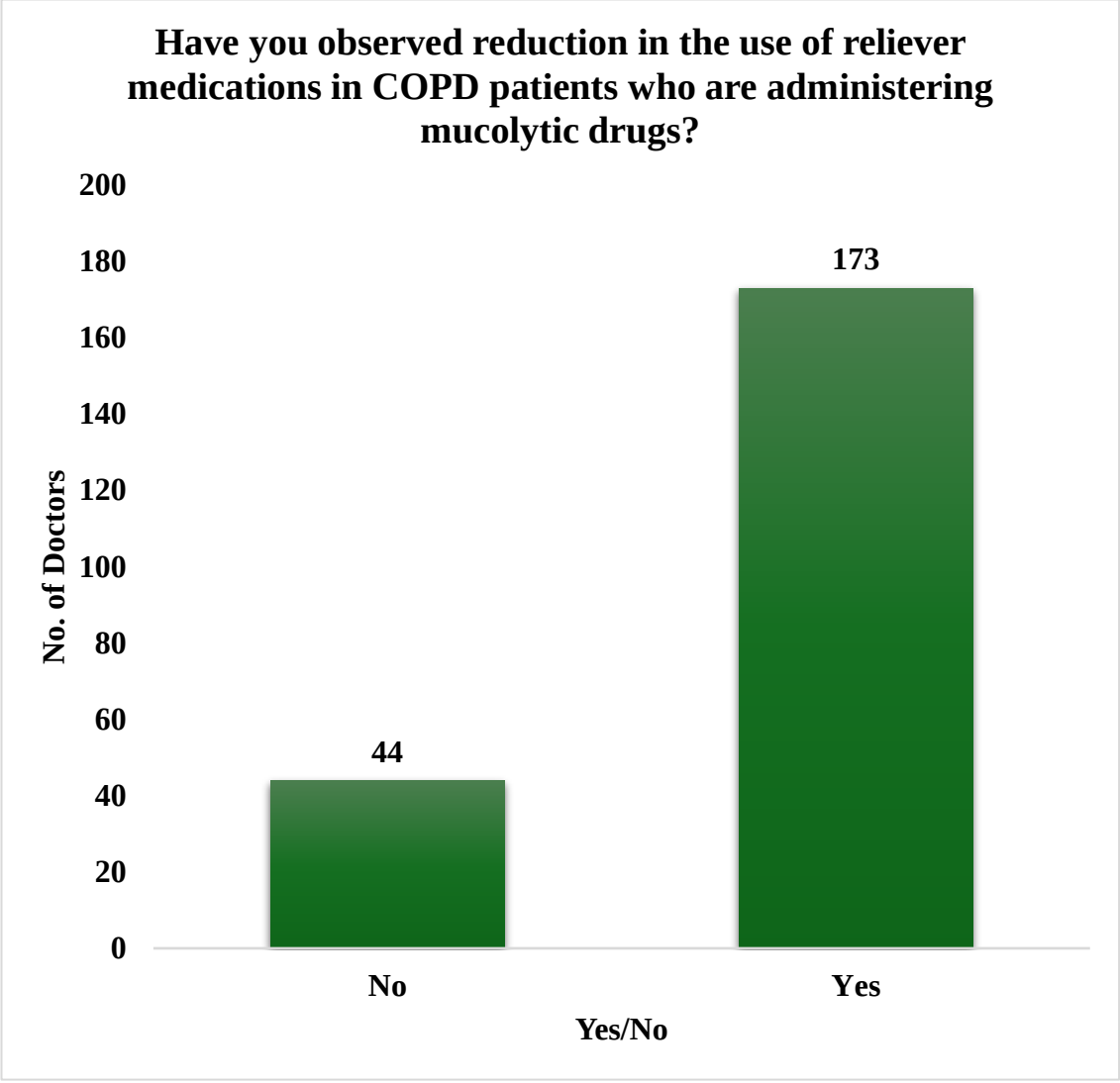

Figure 4.9: There is a reduction in the use of reliever medications or not

Interpretation:

We can see that 80 % of the doctors believe there is a reduction in the reliever medications in COPD patients who are administering mucolytic drugs. So, we can say that it can help reduce the overall cost of the treatment, and the patient has to take fewer medications.

Table 4.14: Clinical experience regarding synergism

Clinical Experience	No of Doctors	% of Doctors
Increased adverse effects	70	32
Improved patient outcomes	108	50
No noticeable difference	39	18

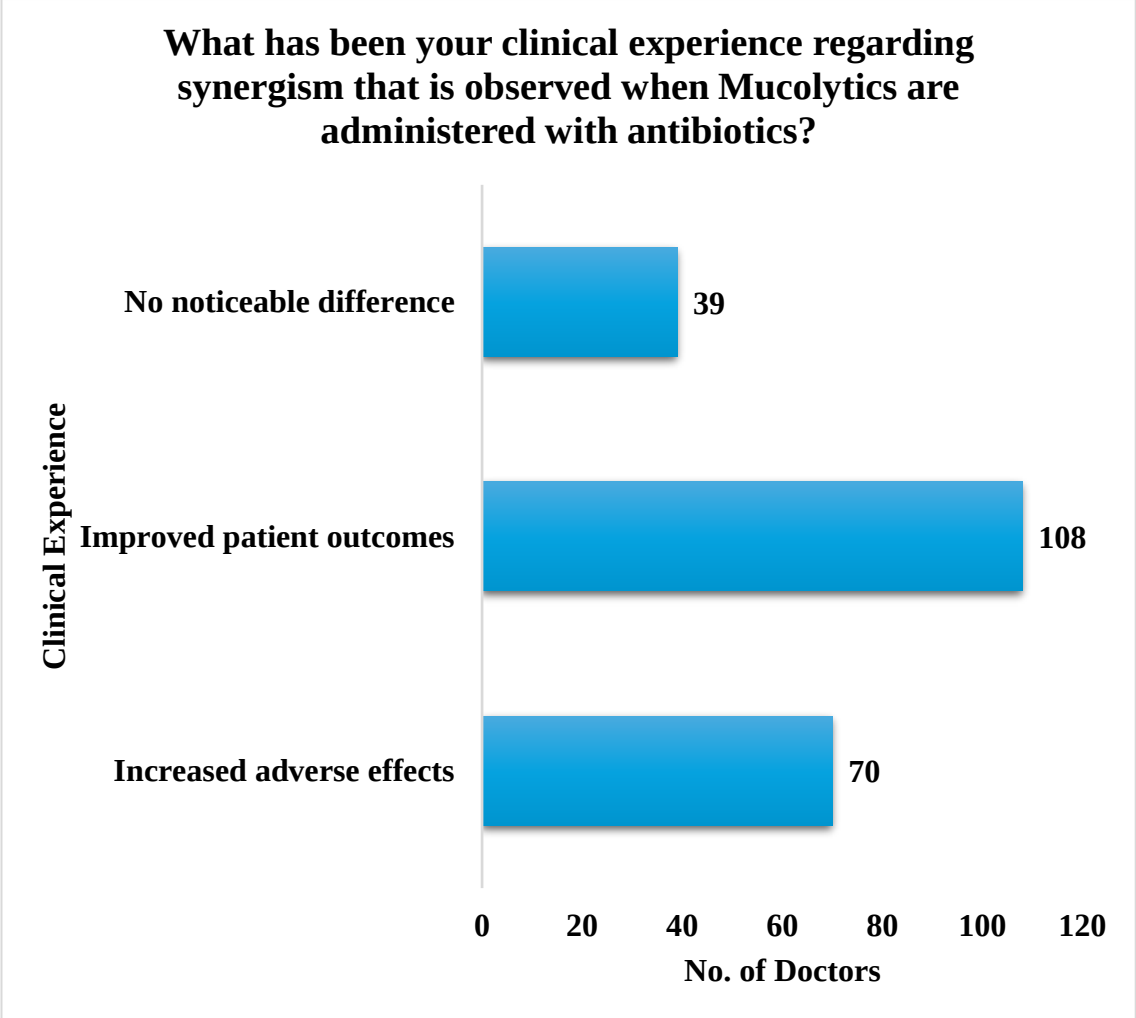

Figure 4.10: Clinical experience regarding synergism

Interpretation:

We can see that 50% of the doctors say that when mucolytics are administered with antibiotics, they show a synergistic effect; hence, patient outcomes are improved. So, there is an added advantage of prescribing mucolytics with antibiotics.

Table 4.15: Mucolytics are recommended for recurrent exacerbators or not

Yes/No	No of Doctors	% of Doctors
No	34	16
Yes	183	84

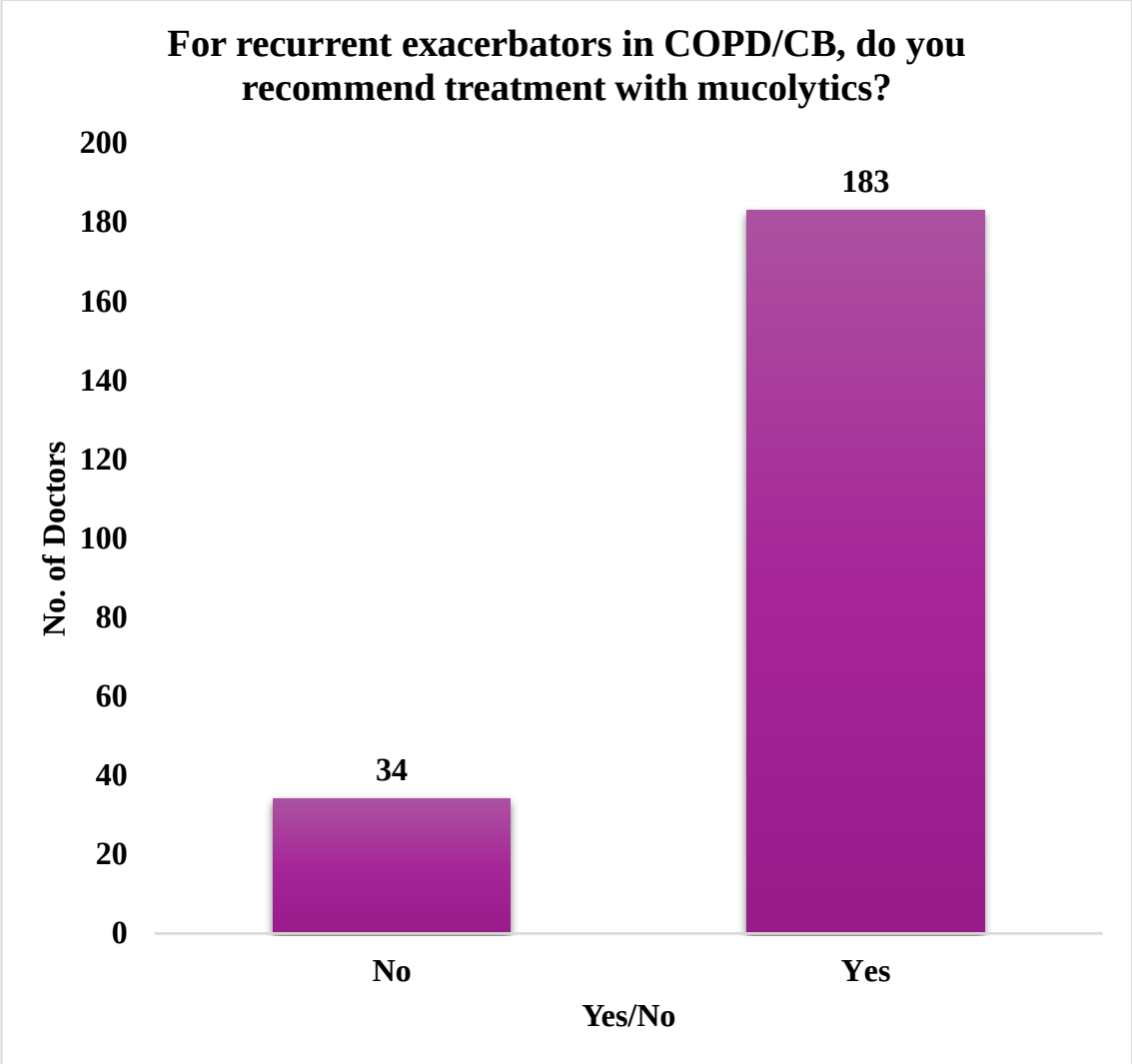

Figure 4.11: Mucolytics are recommended for recurrent exacerbators or not

Interpretation:

We can see that 84% of the doctors recommend treatment with mucolytics for recurrent exacerbators in COPD/CB. So, we can say that mucolytics also help treat recurrent exacerbations.

Table 4.16: Effect of pleiotropic effects on choice of mucolytics

Yes/No	No of Doctors	% of Doctors
No	38	18
Yes	179	82

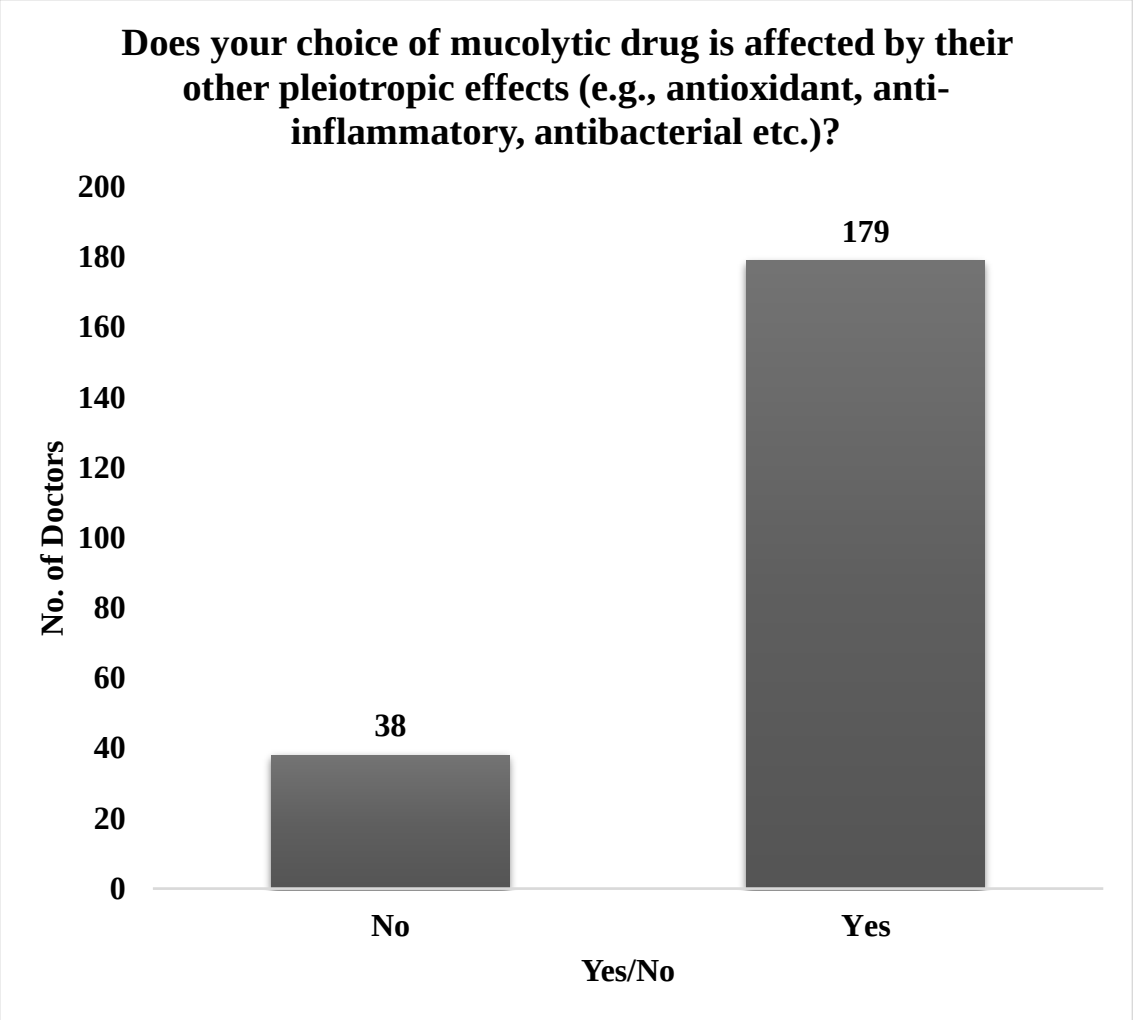

Figure 4.12: Effect of pleiotropic effects on choice of mucolytics

Interpretation:

We can see that 82% of the doctors say that the choice of mucolytic drugs is affected by their other pleiotropic effects (e.g., antioxidant, anti-inflammatory, antibacterial, etc.). Here, we can talk about the difference between the two different mucolytics, i.e. NAC and Erdosteine, because Erdosteine is superior in this case.

Table 4.17: % of patients characterised with increased airway sputum

% of Patients	No of Doctors	% of Doctors
<20%	62	29
>60%	8	4
20% – 40%	118	54
41% – 60%	29	13

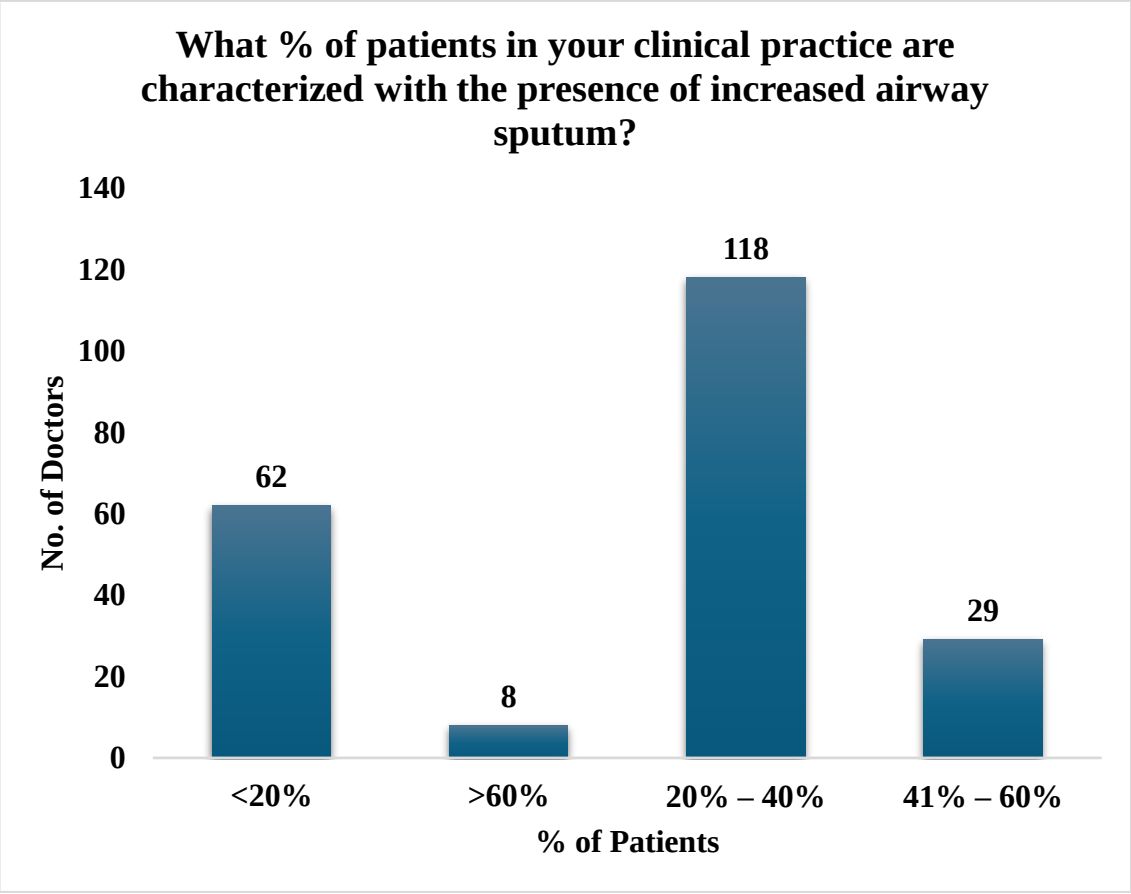

Figure 4.13: % of patients characterised with increased airway sputum

Interpretation:

We can see that 54% of the doctors say that increased airway sputum characterises 20-40% of patients in their clinical practice. So, we can say these patients will require mucolytics in their treatment.

CHAPTER 5

DISCUSSION

5.1 Summary of Findings

The physician survey provided important new information about how doctors see mucolytic drugs in the treatment of Chronic Obstructive Pulmonary Disease (COPD) and associated illnesses. The statistics, which take into account both clinical experiences and evidence-based procedures, point to an agreement about the advantages and drawbacks of these agents.

5.2 Perceived Efficacy of Mucolytic Agents

According to the majority of responses, mucolytic medications like carbocisteine and N-acetylcysteine (NAC) efficiently lower sputum viscosity and enhance expectoration. This is consistent with research that has been done and supports the use of mucolytics to improve mucus clearance and lessen exacerbations in COPD patients. Physicians inquired about the medication's safety profile. It was made clear that using Erdostyne in patients with severe liver failure or creatinine clearance less than 25 ml/min is not advised because there is no data in these populations. But we have safety studies that go up to 52 weeks published.

5.3 Utility in Clinical Practice

Most people gave mucolytic drugs high ratings for their usefulness, especially those with chronic bronchitis and recurrent exacerbations. For patients with mucus hypersecretory syndrome, many physicians have been utilizing acebrophylline or NAC + acebrophylline; however, some people are intolerant to these combinations and should be switched to Erdostyne.

5.4 NAC Vs Erdosteine

- Erdosteine is an effective mucolytic and possesses antioxidants, anti-inflammatory and anti-bacterial activity
- Erdosteine and anti-biotic, when co-administered, act synergistically
- The safety profile reported in multiple clinical trials shows that erdosteine is well tolerated than NAC

5.5 Challenges and Limitations

Erdosteine is the first launched in India in the mucolytic category, where CIPLA is the market leader with the brand Mucinac. Building this category and establishing the

molecule amongst the medical fraternity is crucial. If we look towards the supporting study for the molecule, it is limited as of now.

5.6 Implications for Clinical Practice

It has been demonstrated that etorhine is useful in extending the time interval between COPD exacerbations, lowering the risk of acute exacerbations, Cutting the length of AECOPD, lowering the chance of hospitalization because of AECOPD, Enhancing the cumulative global efficacy index (cGEI), which is the total of all respiratory symptom scores that have been evaluated, including dyspnea, difficulty expectorating, viscosity, and purulence of the sputum. lowering the hurdle to expectoration, Enhancing the symptoms on the Breathlessness, Sputum, and Cough (BSC) scale

5.7 Recommendations for Future Research

- Doctors suggested that once they use it for six months, there should be a review meeting, and only then can they give the correct feedback on how it works in patients.
- The doctors also suggested that Cipla form a study group to see how Erdostyne fairs in efficacy and safety and determine which profile suits them most.
- The effective dissemination of the role of mucolytic agents in respiratory diseases should be done via informative inputs.
- The evidence on pidotimod should be shared with experts to help them understand the potential role of such molecules.

5.8 Limitations of the Study

Erdosteine is a new molecule category that needs to develop a consensus statement and a new study to develop this brand in the mucolytic category of the market. Tremendous opportunities for the molecule in the market just need various types of new research papers to establish the molecule in targeted patient profiles.

5.9 Conclusion

When and where is long-term care indicated?

- One important treatment characteristic of COPD is hypersecretion of airway mucus; as the illness progresses, exacerbations occur more frequently, reducing patient quality of life and raising medical expenses.

- Mucolytics can reduce exacerbations by up to 0.8 exacerbations annually, with a more notable impact in individuals with more severe COPD, according to data from 26 RCTs. This impact is similar to the decrease in exacerbations observed with inhaled corticosteroids (ICS) and tiotropium.

Long-term mucolytic treatment should be considered in:

- Individuals with more severe COPD;
- Individuals experiencing extended or frequent exacerbations;
- Individuals requiring repeated hospital admissions
- Individuals who experience exacerbations frequently and are unable to take ICS or tiotropium

CHAPTER 6

RECOMMENDATIONS & STRATEGIES

6.1 Recommendations

We are establishing the role of Erdosteine as a superior Mucolytic agent in managing COPD and Chronic bronchitis cases and sharing KOLs' opinions to demonstrate the molecule's efficacy.

6.1.1 Personalized Treatment Plans:

Regular Monitoring: Implement regular follow-up appointments to monitor patient response to mucolytic therapy and adjust treatment plans as necessary.

6.1.2 Clinical Guidelines and Protocols:

Standardized Protocols: Encourage the adoption of standardised protocols for initiating, dosing, and monitoring mucolytic therapy to ensure consistency and improve patient outcomes.

6.1.3 Education and Training:

Continuous Medical Education/Round Table Meet (CME/RTM): Conducting the departmental meeting to create awareness about the molecule and discuss its efficacy and superiority.

Patient Awareness: Sharing leaflets and prescriptions to the patients about precautions they should take during disease episodes.

6.1.4 Research and Development:

Comparative Studies: Conduct comparative effectiveness research to evaluate the benefits of mucolytic agents relative to other COPD treatments, such as bronchodilators and corticosteroids.

6.1.5 Multidisciplinary Approach:

Holistic Management: Incorporate mucolytic therapy into a broader COPD management plan, including lifestyle modifications, pulmonary rehabilitation, and other pharmacological treatments.

6.2 Strategies & Tactics to Drive:

6.2.1 Enhance Physician Engagement:

Workshops and Seminars: Organize workshops and seminars to discuss the latest research on mucolytic agents and share best practices among healthcare providers.

Online Platforms: Utilize online platforms and forums to facilitate discussions and knowledge exchange among physicians regarding using mucolytic agents in COPD management.

6.2.2 Improve Patient Outcomes:

Patient Support Groups: Establish support groups for COPD patients where they can share experiences, receive encouragement, and learn about managing their condition effectively.

6.2.3 Promote Research Collaboration:

Research Networks: Create networks of researchers and healthcare institutions to collaborate on studies investigating the efficacy and safety of mucolytic agents.

Grant Opportunities: Identify and promote grant opportunities for research on COPD and mucolytic therapies.

6.2.4 Optimize Resource Utilization:

Data Analytics: Data analytics can track treatment outcomes and identify patterns that can inform better clinical decision-making and resource allocation.

CHAPTER 7

CONCLUSION

As a result, mucolytic drugs are generally thought to be effective and useful in the treatment of chronic obstructive pulmonary disease and associated disorders by physicians since they offer numerous advantages beyond simply decreasing mucus hypersecretion. We can use the most recent mucolytic agent, Erdosteine, as an example.

- Having antioxidant, anti-inflammatory, and antibacterial properties, ergotoxine is a potent mucolytic.
- When taken together, erdosteine and antibiotics have a synergistic effect.
- Several clinical trials' safety profiles indicate that erdosteine is more tolerable than NAC.
- After a 4-day treatment, erythropoietin significantly reduces the levels of cytokines and ROS.
- By day seven of treatment, there was a noticeable drop in the lipid peroxidation product 8-isoprostane.

Erdosteine has also been proven to be effective in:

- Lowering the likelihood of COPD acute exacerbations;
- Delaying the onset of a COPD exacerbation; and Shortening the AECOPD duration
- Reducing the chance of hospitalization because of AECOPD
- Increasing the cumulative global efficacy index (GCI), which is the total of all respiratory symptom scores that have been evaluated, including dyspnea, catarrh Ronchi at auscultation, viscosity, and purulence in the sputum.
- Reducing expectoration difficulty and improving the symptoms on the BSC (breathlessness-sputum-cough) scale

CHAPTER 8

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ANNEXURE - A

QUESTIONNAIRE FOR PRESCRIBERS

Name: _____

Specialty: _____

Location: _____

1. What is the patient's profile in which you usually recommend treatment with mucolytic drugs (e.g., N-Acetyl Cysteine)?

a) COPD
b) Chronic Bronchitis
c) Bronchiectasis
d) Patients with a persistent cough
e) All the above

2. What percentage of your COPD / Chronic bronchitis patients need add-on treatment with N- Acetyl Cysteine (NAC) and regular treatment?

a) <20%
b) 20%-40%
c) 41%-60%
d) 60%

3. Usually, for how long do you recommend treatment with mucolytic agents (like N-Acetyl Cysteine) to your Chronic Bronchitis patients?

a) A short course of 1-2 weeks
b) 15 days
c) More than a month
d) 2-3 months

4. Do you feel that N-acetyl cysteine (NAC) may help to reduce exacerbations in COPD patients?

a) Yes
b) No

5. How satisfied are you with the antioxidant properties of N-acetyl cysteine (NAC)?

a) Very much
b) Neutral
c) Not much

6. Do you feel that N-acetyl cysteine (NAC) may help to reduce hospitalisation/emergency visits?

a) Yes
b) No

7. In what type of OAD patients do you recommend combining mucolytic agents (like N- Acetyl Cysteine) with Acebrophylline?

a) COPD
b) Chronic Bronchitis
c) Bronchiectasis
d) Patients with persistent cough of more than three months
e) All the above

8. Do you believe the benefits of treatment with N-acetyl cysteine (NAC) outweigh its cost?

a) Yes, I firmly believe.
b) To some extent, I believe.
c) No, I don't believe.

9. Have you observed a reduction in the use of reliever medications in COPD patients who are administering mucolytic drugs?

a) Yes
b) No

10. What has been your clinical experience regarding synergism observed when Mucolytics are administered with antibiotics?

a) Improved patient outcomes
b) No noticeable difference
c) Increased adverse effects

11. For recurrent exacerbators in COPD/CB, do you recommend treatment with mucolytics?

a) Yes
b) No

12. Is your choice of mucolytic drug affected by its other pleiotropic effects (e.g., antioxidant, anti-inflammatory, antibacterial, etc.)?

a) Yes
b) No

13. What % of patients in your clinical practice are characterised by increased airway sputum?

a) <20%
b) 20%-40%
c) 41%-60%
d) >60%