



**UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE**  
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**THE UNIVERSITY OF MEDICINE AND PHARMACY**  
**"CAROL DAVILA", BUCHAREST**  
**DOCTORAL SCHOOL**  
**THE FIELD OF MEDICINE**

**FACTORS INFLUENCING THE COMPLIANCE OF**  
**ASTHMATICS, PATIENTS WITH COPD AND**  
**OVERLAP SYNDROME IN ROMANIA**  
**- PRELIMINARY STUDY -**

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**2022**

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## Introduction

Modern management of chronic respiratory diseases requires medication for long periods of time to prevent symptoms and limit airflow. An important issue in the proper management of asthma, COPD and asthma-COPD is compliance with treatment.

Poor adherence to prescribed medication increases morbidity and mortality, and it is increasingly documented that long-term adherence to prescribed therapy is difficult to achieve. It is known that the non-compliance of patients with asthma, COPD and asthma-COPD to medication is high and can lead to the worsening of the disease, to the change of regular therapy, to the increase in the number of hospitalizations as well as to the increase in the costs of care services.

It is estimated that the incidence of treatment non-compliance in Romania is 13.6% [1]. The World Health Organization (WHO) estimates that non-adherence to treatment is 50% in developed countries and even lower in developing countries. [2] At the same time, it classifies the reasons for non-compliance with treatment according to: patient category, health status, medication, socio-economic conditions, low level of education, the health system or the medical team and the treatment itself [3].

Anxiety and chronic respiratory diseases do not appear to be related at first sight, however, anxiety is a comorbidity among these patients.

Studies to date have shown low compliance with treatment in patients with chronic respiratory diseases due to the fact that they do not take their treatment regularly.

The aim of the thesis is to identify and correct the factors that cause treatment non-compliance in children, adolescents and adults with asthma, COPD and COPD-asthma in Romania. The better the noncompliance factors are corrected, the more disease control is achieved and "reliever" drugs are not used. Providing help in using the device is related to improving inhalation technique.

The study evaluates the compliance rate to the medication received in patients with chronic respiratory diseases, both before and after the intervention of doctors, an intervention carried out by periodic follow-up of patients, using several tools (planned visits, good doctor-patient relationship, feedback at each visit, highlighting the triggering factors, explaining the

inhalation technique and the treatment scheme, explaining the importance of administering the treatment and highlighting the adverse effects).

The research method is a complex one, with clinical and paraclinical evaluation of patients. The study aimed to follow up patients every 3 months for a period of one year. Study participants completed questionnaires at each visit. The ACT questionnaire was used to assess asthma control and the CAT questionnaire to monitor COPD [4]. COPD-asthma patients completed both questionnaires, the CAT questionnaire and the ACT questionnaire [5]. All patients underwent an anxiety assessment using the ASQ questionnaire.

The general part of the thesis is structured in three chapters. In the first chapter, the pathologies are established according to the clinical and paraclinical diagnosis. In the second chapter we addressed the specific strategies for correcting non-compliance, and in the third chapter we framed the aspects of medical economy in these patients. In the special part, 595 patients were evaluated, of whom 57% were men and 43% were women. Compliance was monitored from the perspective of the visits, depending on the need to administer the "treatment as needed", by evaluating the clinical examination, by counting the doses used and the correctness of the inhaler technique. The non-compliance rate in terms of visits was 88%. The highest percentage of compliance is in the 41-60 year old category (4.2%), and the lowest percentage of compliance is in the 19-40 year old group (2%).

The high cost of drugs, poor counseling, care for other family members, lack of immediate treatment efficacy, chronic nature of the disease, fear of adverse effects, comorbidities, forgetfulness and lack of knowledge of how to use the device are the main factors of non-compliance.

In the case of evaluating compliance from the perspective of the "treatment as needed" administration requirement, an improvement in compliance is observed, with a decrease in the use of "reliever" treatment from the time of visit 1 (5.7%) to the time of visit 5 (1.4%). The presence of sibilant rales indicates a lack of treatment administration and is associated with poor compliance. From the compliance analysis according to the clinical examination, it was identified that 1.4% of the patients are non-compliant.

Based on the results obtained from the evaluation of the inhalation technique we can consider that 8% of the patients had a defective technique at visit 2. This non-compliance

factor is improved during the visits (1.1% at visit 4), following as at visit 5 all patients to present a correct technique.

In the case of evaluating compliance from the perspective of checking the doses used, it was identified that 36.8% have unused doses at visit 2 and 10.3% at visit 4, and a total compliance with the correct use of all doses in those who presented 5 visits.

The advanced measures of explanations from specialists and complex monitoring led to the correction of the non-compliance factors related to the medical team and patients (the factor related to antipathy to drugs was corrected by 10.6%, the factor related to the chronic nature of the disease, with 6.3% the self-interruption factor was corrected, with 6.9% the inhalation technique was corrected, with 4.8% the forgetfulness factor was corrected, the fear of adverse effects with 2.6% and the factor regarding well-being by 6%).

With respiratory symptom control achieved, a controlled total ACT score predominates and is associated with a low score on anxiety dimensions. Anxiety was 1.4 times more common in people with severe asthma compared to non-severe asthma.

In the period March-December 2020, no spirometry was performed due to infection with the SARS COV 2 virus. Given that I work as an allergist, the number of patients who address this field is mostly asthmatics, hence the number large number of asthmatic patients included in the study. The sample of patients with COPD is low because a small number of people present to the allergology specialty, however their addressability to the pneumology specialty is high.

It is important in the future to continue studies on the detection of non-compliance factors to better understand the educational possibilities of patients each time they contact the health system. Correcting non-compliance factors is made easier by introducing validated and standardized questionnaires.

## I. The general part

### 1. Evaluation of patients with chronic respiratory diseases: asthma, COPD and COPD-asthma. Anxiety assessment

Asthma, COPD and COPD-asthma are defined as chronic respiratory diseases, characterized by symptoms such as wheezing, shortness of breath, tightness in the chest (chest constriction), dyspnea and cough, along with limitation of expiratory airflow. Asthma attacks are a constant threat. This anticipated real threat is accompanied by a general feeling of tension and activation, which is known as anxiety [6].

#### 1.1. Clinical and paraclinical expression of asthma

The diagnosis of bronchial asthma is based on clinical (wheezing, shortness of breath, tightness in the chest and coughing that varies in time and intensity) and paraclinical (spirometry) criteria. Spirometry reveals variable expiratory airflow limitation [reversibility after performing the bronchodilator test (BD): increase in FEV1 > 12% and > 200 ml from baseline 10-15 minutes after administration of SABA (short-acting beta2-agonist) 200-400mcg]. The Asthma Control Test (ACT) is used to assess asthma control [10], [11], [12].

Table I.1. Clinical significance of the ACT score

ACT Score	Clinical Significance
5-15	well uncontrolled
16-19	Not well controlled, in which case it is necessary to change the treatment to achieve total control
20-25	Very poorly controlled

#### 1.2. Clinical and paraclinical expression of COPD

The diagnosis of chronic obstructive pulmonary disease (COPD) is made on the basis of clinical (persistent respiratory symptoms - dyspnea, chronic cough or sputum production, wheezing and chest pressure) and paraclinical (spirometry) criteria. COPD patients have a post-bronchodilator forced expiratory volume ratio of 1 s/forced vital capacity (FEV1/FVC)

<0.7 without reversibility after bronchodilator (SABA). The COPD Assessment Test [CAT] is used to assess the health status and symptomatic impact of COPD [4].

Table I.2. Clinical significance of the CAT score

<b>Scor CAT</b>	<b>LEVEL</b>	<b>LEVEL OF CLINICAL SIGNIFICANCE</b>
>30	Very high	Daily activities are affected
>20	high	Dyspnea occurs even when doing the smallest things or even when talking. All activities require a great deal of effort.
10-20	Medium	Just a few days a week is fine. It presents one or two exacerbations per year. Activities are done very slowly, with frequent breaks.
<10	low	Most days are good, and the symptoms worsen with intense physical activities.

### **1.3. Clinical and paraclinical expression of COPD-asthma**

COPD-asthma patients present with persistent airflow limitation with several features; it is identified in clinical practice by the characteristics it shares with both asthma and COPD. COPD-asthma patients completed both questionnaires, the CAT questionnaire and the ACT questionnaire [5].

### **1.4. Anxiety assessment**

Anxiety is characterized by excessive fearful features of patients associated with behavioral disorders. Anxiety is an emotional state defined by both cognitive and somatic symptoms, such as feelings of tension, worried thoughts, palpitations, and fear of ongoing danger [15].

Anxiety was assessed using the ASQ questionnaire. A score is calculated for each cognitive, somatic, behavioral dimension and a global score for anxiety by summing the partial scores [16]. The cognitive dimension highlights aspects of anxiety related to thoughts (eg - difficulty concentrating, worry and intrusive thoughts), while the behavioral dimension highlights the person's behavior and the somatic dimension captures features that relate directly to physical experiences (eg - sweating, muscle tension and palpitations) [15].



## **2. Specific strategies for correcting non-compliance in patients with asthma, COPD and COPD-asthma**

Compliance is a health care process involving asthma control, COPD and COPD-asthma.

### **2.1. Basic definitions: compliance, adherence, noncompliance**

**Compliance** is defined as "agreeing" or "doing as you are asked" [19]. Adherence is "an intentional and responsible process of care in which patients and physicians, through collaboration, strive to achieve each other's health goals." [20].

**Adherence** is described by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [23].

Failure to follow recommended treatment defines noncompliance. It can be interpreted as an inability to follow instructions. Identifying the reasons for non-compliance is essential for determining the appropriate intervention strategy [10].

Both in the literature data and in our paper, compliance referred to how patients comply with medical visits and follow recommended treatment. From the point of view of compliance with visits, patients were classified as compliant (those who had 5 visits within a year), partially compliant (those who did not respect the control periods and had between 2-4 visits) or non-compliant ( those who did not subsequently present themselves at any control) [15,25]. The presence of sibilant rales indicates the lack of administration of the treatment according to the indications received suggesting low compliance. Considering that the control of symptoms is associated with compliance with the treatment, and the need for "treatment as needed" increases when the disease is not well controlled, from here we deduce an absence of compliance in this category of patients. Compliance was also tracked according to the inhalation technique and the number of doses consumed [15,25]. The number of doses was also tracked with the help of the family doctor. Although treatment noncompliance is multifactorial, I focused on the factors related to the doctor and the patient, not from the perspective of the fact that the others are not important, but due to the ability to track and intervene where appropriate [15,25].

## **2.2. Factors influencing compliance**

The World Health Organization classifies the reasons for non-compliance with treatment depending on the patient category, health status, medication, socio-economic conditions, low level of education, the health system or the medical team and the treatment itself [3,25].

### **2.2.1 Non-compliance factors in asthmatics**

There are various nonadherence factors, i.e., patient-related factors, regimen-related factors, and physician-related factors [21],[25],[26],[27].

A study by COCHRANE et al identified two categories of non-adherence factors, namely unintentional non-adherence and intentional (or 'smart') non-adherence [19],[28],[29],[30].

#### **Noncompliance factors in COPD [2,25].**

- Patient compliance: Psychosocial problems, socio-economic, cultural and religious status, Simple forgetfulness or neglect, stigmatization, self-discontinuation, fears about side effects, inappropriate expectations, underestimation of severity and antipathy to drugs;
- Social barriers: complicated work schedules, complexity of therapeutic regimen and drug costs;
- Nature of the Disease: genetic deficiency of alpha-1-antitrypsin, bronchial hyperreactivity;
- Medication: combination of several medications;
- Inhalation technique;
- The medical team: the cooperation between the doctor and the patient, the lack of communication with the patient and the lack of explanations of the use of the device

Many factors contribute to a lack of therapeutic compliance, most of which can be addressed by the physician. [25].

## **2.3. Successful contributions to achieve the compliance of patients with asthma, COPD and COPD-asthma**

Communication between patients and the doctor or pharmacist is essential for optimizing patient adherence [25]. Successful goals for improving patient compliance require a number of important contributions from the medical community, the patient, and the authorities.

### **2.3.1. Compliance through the lens of patient education**

Informing patients about their disease state and the consequences of non-compliance with treatment, the causes of their disease should increase the patient's knowledge and clarify misconceptions about his medical condition, integrating information about diagnosis, risk factors, consequences, treatments and prognosis [7],[31 ],[32],[33]. Identifying and supporting patients who do not know how to read basic health materials and are unable to understand the instructions for using the device. [25]. In Romania there is the INSPIRO program, which addresses all patients diagnosed with bronchial asthma or chronic obstructive pulmonary disease and aims to increase treatment adherence [34].

### **2.3.2. Compliance through the lens of physician education**

Appropriately consulting patients and providing frequent feedback increases their confidence. [25]. A long-term relationship of trust with patients promotes the improvement of doctor-patient communication, but also the patient's trust in the doctor's recommendations [25].

### **2.3.3. Compliance through the lens of the authorities ensuring the medication**

Since there are many people who cannot economically afford the necessary treatment to keep the disease under control, the authorities should come to their aid, reduce the cost of the treatment so that it can be easily purchased by all the sick.

### **2.3.4. Noncompliance Monitoring Tools in COPD and Asthma**

- Self-reporting;
- Periodic evaluation and verification of inhalation technique with different devices, counting of therapeutic units;
- Verification of knowledge of medication and administration schedule;
- Assessment of compliance with inhaler treatment - CAT Questionnaire;
- Assessment of compliance with inhaler treatment - ACT Questionnaire;
- Spirometric assessment of patients;
- Checking the therapeutic response and highlighting some adverse effects;
- Tracking the number of exacerbations;
- communication between the doctor and the patient.

### **3. Medical economic aspects in people with asthma, COPD and asthma-COPD**

#### **3.1. Generalities about the prevalence of costs in asthma**

Illness-related costs are usually classified into direct, indirect and intangible costs. Direct costs include asthma management, additional investigations or treatments, and other costs. Indirect costs include work-related losses and early mortality. Finally, intangible costs are those related to unquantifiable losses, such as decreased quality of life, increased suffering, and limitation of physical activities [45].

Average annual per capita expenditures increased significantly between 1996–1998 and 2004–2006 (\$3802 versus \$5322), annual drug expenditures doubled from \$974 to \$2010 per person, and hospital visit expenditures outpatient costs increased from \$861 to \$1174, while inpatient and emergency department visit costs were similar over the same period [45].

#### **3.2. Direct and indirect costs in COPD**

The most important costs are generated by frequent hospitalizations due to exacerbations and the absence of continuous treatment for this chronic condition. The Centers for Disease Control and Prevention estimates costs attributable to COPD of \$32.1 billion in 2010, with a projected increase to \$49.0 billion by 2020. The total costs of absenteeism were \$3.9 billion in 2010, with 16.4 million workdays lost due to COPD [48]. The United States is the world's largest consumer of health care, with total health care costs reaching \$1.6 trillion in 2002 [33]. In helping with these huge costs, universal use of pulmonary rehabilitation could result in savings of \$1 to \$1.25 billion annually [53]. COPD is the most important cause of absenteeism and it is estimated that productivity losses at the European level caused by COPD reach the sum of 28.5 billion EURO annually. With a percentage of 62.4% of lost working days, COPD ranks first in this category [8].

#### **3.3. Healthcare costs related to noncompliance and nonadherence.**

Patient noncompliance with chronic respiratory disease treatments compromises treatment success and patient quality of life, while increasing medical costs. The World Health

Organization (WHO) estimates that treatment non-adherence is 50% in developed countries and even lower in developing countries [55].

The average cost of health care expenditures for each person in the US in 2002 was \$5,440, resulting in a total of more than 880 million physician visits. DeMatteo estimated that the costs may be more than \$300 billion per year in patients who do not follow their doctor's advice[55]. Using national health statistics, Iskedjian et al. estimated that hospitalization costs attributable to patient noncompliance with controller therapy in Canada exceeded \$1.6 billion [33], and Morgan's study suggests that a portion of all prescribed medications are wasted or thrown away, at a cost of 30, \$47 [55].

#### **3.4. Data about Romania**

Non-compliance with treatment represents 13.6% [1]. It is estimated that the prevalence of COPD in Romania is 9.3% [57]/ (8.3% in 2018 versus 8.13% in 2012) [58] and 5-7% of subjects with asthma and it is still increasing [59]. The INSPIRO study estimates that approximately 200,000 people in Romania have COPD [7]. In Romania, patients with COPD have at least 2 exacerbations requiring hospitalization per year. Romania ranks 3rd in Europe in terms of COPD mortality rate in men [7],[8].

## II. PERSONAL CONTRIBUTIONS

### 4. Research hypothesis and general objectives

Studies to date have demonstrated low compliance to treatment in patients with chronic respiratory disease. These results are because people with asthma, COPD and COPD-asthma do not regularly take treatment due to non-compliance factors.

Providing help in using the device is related to improving inhalation technique. Clinical and paraclinical investigations should allow the detection of respiratory diseases in the early stages and thus facilitate the necessary therapy. On the therapeutic level, the transition from "reliever" treatment to "controller" drugs (long-acting beta 2 agonists + inhaled corticosteroids and antileukotrienes) was achieved, a fact that reduced presentations to the emergency room and allowed the disease to be controlled. The training of the medical staff in order to periodically follow up the patients increases the identification of the factors of non-compliance with the treatment.

Our goal is to identify the factors that cause treatment non-compliance in children, adolescents and adults with asthma, COPD and COPD-asthma in Romania, and how the problems can be assessed and corrected, allowing disease control in these categories of people. To demonstrate long-term compliance, patients with chronic respiratory diseases were followed for a period of one year. All patients received a questionnaire with questions regarding noncompliance factors in order to identify and correct them.

I highlighted the stated goal by evaluating the following objectives:

- Specifying the prevalence of remote compliance in patients with respiratory diseases according to:

- The visits made
- Age of the patient and associated conditions;
- Clinical and paraclinical condition;
- Follow-up of consumed doses and "as needed" treatment requirements

- Highlighting and correcting non-compliance factors;

- Ensuring patient-centered medical assistance with monitoring symptoms by evaluating the ACT score for asthma, the CAT score for COPD and performing spirometry;

- Improving the inhaler technique (checking the inhalation technique with different devices and repeating the device administration gestures).
- Addressing the interdependence between asthma, COPD and COPD-bronchial asthma and the 4 dimensions of anxiety.

## 5. General methodology

The approach to the patients in the study was complex. This included:

### 5.1. Comprehensive medical measures

#### 5.1.1 Principles of approach to patients with asthma, COPD and asthma-COPD

During each visit, we assessed the patient's condition and the assessment of the effectiveness of the treatment. Lifestyle and personal medical history data were retrieved. Associated pathological personal antecedents and allergological evaluation were followed.

**a. Patients with asthma.** Clinical and paraclinical examination was performed in all asthmatic patients.

**b. COPD patients.** Patients with COPD have symptoms such as dyspnoea, chronic cough or sputum production and/or a history of exposure to risk factors (smoking, cooking smoke and biomass, dusts, vapours, gases, toxic substances and other chemicals) and various physical signs [60],[61].

**c. Patients with asthma-COPD syndrome** Patients with asthma-COPD syndrome may have manifestations similar to both asthma and COPD. Respiratory symptoms include persistent but more variable dyspnea on exertion.

#### 5.1.2 Monitoring patients through spirometry

Pulmonary function was assessed using spirometry [15,25]. Likewise, spirometry is the most recommended and reproducible method of highlighting airflow limitation and measuring severity [62], [63], [64].

In the period March 2020-December 2020, no spirometry was performed due to the SARS COV 2 virus infection [9], [15].

##### a. Patients with COPD

FEV1/FVC ratio < 0.70 post-short-acting inhaled bronchodilator confirms the presence of persistent airflow limitation.

Table V.2. Obstruction severities according to FEV1

	FEV 1	
GOLD 1	Mild	≥80%



GOLD 2	Moderat	50-79%
GOLD 3	Severe	30-49%
GOLD 4	Very severe	<30%

**a. Patients with asthma**

Bronchial obstruction is defined by a decrease in the FEV1/FVC ratio  $< 0.7$  [65]. The severity of the obstruction is determined by the FEV1 value [68],[69]. A bronchodilator reversibility test was performed in all patients with suspected asthma and spirometrically confirmed bronchial obstruction, with FEV1 measurement before and after bronchodilator administration [15,25].

**c. Patients with asthma-COPD syndrome** Spirometry reveals airflow limitation not fully reversible but often with variable history

**5.1.3 Patient monitoring using questionnaires**

**a. Patients with COPD**

Assessment of symptoms using questionnaires such as the COPD Assessment Test (CAT). (Fig. 5.1). Your test score helps improve your COPD management.

**b. Patients with asthma**

The ACT questionnaire helps in the assessment of asthma [15, 25]. The points given to the answer to each question are added up. The total score indicates asthma control.

**c. Patients with asthma-COPD**

COPD-asthma patients present with persistent airflow limitation with several features; it is identified in clinical practice by the characteristics it shares with both asthma and COPD. COPD-asthma patients completed both questionnaires, the CAT questionnaire and the ACT questionnaire [73].

**d. Anxiety assessment**

All patients solved the ASQ Questionnaire which captures the cognitive, somatic and behavioral dimensions of anxiety. A score for each cognitive, somatic, behavioral dimension and a global anxiety score are calculated by summing the **partial scores**.

**5.2 Therapeutic measures depending on the stage of the disease.**

**a. Patients with asthma**

In asthmatics, we used the therapeutic schemes in steps according to GINA, both in children aged 6-11 years and in adults and adolescents over 12 years old [74].

The route of administration of antiasthmatic drugs can be inhaled or systemic (oral or parenteral). The advantage of the inhalation route consists in the direct administration of the drug at the level of the airways, with a lower risk of systemic side effects. The choice of inhaler for stable asthma was made according to: patient preferences, cost, patient's ability to use it correctly. Patients were instructed in a satisfactory inhalation technique.

#### **b. COPD patients**

Patients with COPD received treatment according to GOLD.

#### **c. Patients with COPD-asthma**

There is little evidence from randomized clinical trials about how such patients should be treated. However, given the risk associated with bronchodilator monotherapy in patients with asthma, patients with COPD should be treated with at least low-dose CSI if they have a history or diagnosis of asthma.

### **5.3. Statistical tools**

Data organization and statistical processing was carried out using the SPSS v.26 application.

1. For descriptive analysis, frequency analysis and comparison analysis of distributions obtained with equal probability distribution (uniform distribution) and association analysis were used. For the two analyzes comparing frequency distributions, the Chi-square test was used for which the test value, the degree of freedom and the level of significance  $p$  associated with the obtained value were reported. NS (statistically insignificant) was noted for values of  $p \geq 0.05$ .

2. For analyzes of the probability of presenting a certain level of the dependent variable, depending on the category of the independent variable, ordinal logistic regression analysis was used. The following were reported from the results obtained:

- B - the estimate of the coefficient  $\beta$  from the regression equation and indicates the increase in OR (odds ratio) with  $e^\beta$  for an increase of one unit of the independent variable;
- the standard error of estimate B;

- The value of the Wald test in the null hypothesis ( $B=0$ ,  $eB=1$ ),  $df$  – the degree of freedom,  $p$  – the level of statistical significance

- the value of  $\exp(B)$  and the confidence interval of this value (CI 95%).

Friedman and Kendall W non-parametric tests were used for the comparative analysis with repeated measurements. For these tests, the test value and the level of statistical significance  $p$  were reported. In the case of obtaining statistical significance, the multiple comparison test was also applied to identify significantly different pairs.

## **6. Factors that influence the compliance of asthmatic patients, patients with copd and overlap syndrome in romania - preliminary study -**

### **6.1. Introduction**

Non-compliance negatively affects treatment outcome and wastes resources. This study addresses how to know remote compliance related to chronic respiratory diseases by periodically following up patients and assessing symptom control.

#### **Guidelines for the correction of noncompliance factors in asthma**

The therapeutic strategy in asthma is undoubtedly individualized in each country, it is carried out according to socio-economic conditions, national strategy and health policy.

Currently, we have resorted to the following strategies to correct compliance factors: planned asthma visits. At each visit we provided feedback to increase patient confidence and we observed the appointment schedule.

Triggers (allergens, smoking) were revealed and their avoidance was recommended. They have been evaluated to prevent exacerbations and loss of asthma control.

The treatment plan was developed and a written plan was made. The importance of using the medication, even in the absence of symptoms, was discussed with the patient and the therapeutic response was verified. Patients were informed about the status of the disease and the consequences of not observing the treatment

The inhalation technique was theoretically and practically explained to each patient. Subsequently, each patient received a demo device which they could practice the inhalation technique with in order to better master it.

Regarding the concrete strategy for asthma control, the Asthma Control Test (ACT) and The CAT questionnaire – the COPD assessment, questionnaire was used, which provides a standardized way to capture the necessary information about the disease. In parallel, spirometry was also performed.

A good doctor-patient relationship was maintained. The physician's communication skills were used to motivate patients and strengthen progress.

Leaflets with information on asthma and inhalation techniques were provided. It was recommended to avoid the administration of beta-blockers, the administration of aspirin to those with the Samter's triad (aspirin sensitivity) and sulphites in patients with a previous history.

A gastroenterologist visit was recommended for the treatment of gastrointestinal disorders: gastroesophageal reflux and gastritis.

## **6.2. Subjects included in the study**

This is a prospective randomized clinical study conducted in 3 centres in 2 towns (Tg Jiu and Timisoara), on the compliance of patients with asthma, COPD and ACO in the Romanian population. This study was conducted after the written consent of the participating patients, 595 subjects from rural and urban settings. Enrolment started in January 2017- December 2020, were invited to participate in the study. The study envisaged patient follow-up over the course of one year every 3 months.

### **Patients included in the study:**

- Age >6 and under 80
- Patients with an initial and previous diagnosis of asthma, COPD or ACO were included.

### **Exclusion criteria include:**

- Age below 6 and above 80
- Any acute or chronic condition that would have limited patients' ability to fill in the questionnaires

At the study visit, doctors collected the following information: socio-demographic, comorbidities, current COPD treatment, asthma and ACO syndrome, spirometry, number of exacerbations and self-report questionnaires. Information was collected during patient interviews. CAT and ACT questionnaire scores and FEV1 assessment using spirometry were calculated. The study and the informed consent form were approved by the ethics committee. All patients provided written informed consent before enrollment.

## **6.3. Result**

### **Patient characteristics**

The research group consisted of 595 patients, men and women with diagnoses of breathing difficulties: asthma, COPD and asthma-COPD. The large asthma batch is due to the fact that a large number of people with asthma present to the allergology. Comparative

analysis of the structure of gender, age and environment determined on the three diagnostic groups.

Table VII.1. Presentation of distribution of sex, age, environment of origin compared according to diagnosis

Factor		Astm		COPD		astm- COPD		Total		$\chi^2$	p
		N	%	N	%	N	%	N	%		
Sex	Masculin	171	32,8	48	88,9	15	78,9	234	39,3	77,5	0,00
	Feminin	351	67,2	6	11,1	4	21,1	361	60,7	3	1
Mediu	Urban	336	64,4	15	27,8	7	36,8	358	60,2	31,7	0,00
	Rural	186	36,6	39	72,2	12	63,2	237	39,8	9	1
Age	< 18 years	93	17,8	0	0	0	0	93	15,6	61,2	0,00
	19 – 40 years	115	22,0	0	0	1	5,3	116	19,5	1	1
	41 – 60 yers	221	42,3	25	46,3	14	73,7	260	43,7		
	> 60years	93	17,9	29	53,7	4	21	126	21,2		
Total		522	87,7	54	9,1	19	3,2	595	100	795,	0,00
										4	1

Note:  $\chi^2$  – the value of the Chi-square test applied to the resulting contingency tables, p – the level of statistical significance corresponding to the test value.

A high prevalence of the diagnosis of breathing difficulties is identified in the case of women (60.7%). The comparison test with an equiprobability distribution of gender categories indicates a statistically significant difference for a test value  $\chi^2 = 27.11$  and  $p < 0.001$ .

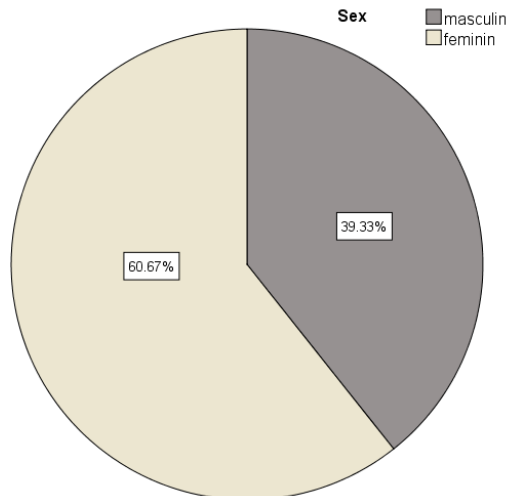


Fig. 8.1. Distribution of patients according to sex

From the point of view of the environment of origin, a very low proportion of patients from the urban environment was identified in the case of patients with COPD (4.1%) and asthma-COPD (2.0%). Statistically significant difference from the environmental distribution in the case of asthma diagnosis for a test value  $\chi^2=31.79$  and  $p<0.001$ .

In the case of the diagnosis of asthma, approximately 60% of patients are over 41 years old, while patients with a diagnosis of COPD present similar proportions (46.3% aged between 41 and 60 years and 53.7% aged over 60 years). In the case of patients diagnosed with asthma-COPD, the largest share belongs to those between the ages of 41 and 60 (73.7%). The difference in trend between the three distributions is statistically significant for a test  $\chi^2=61.2179$  and  $p<0.001$ .

**Specifying the prevalence of remote compliance in patients with respiratory diseases according to:**

**1. Analysis of compliance by number of visits and symptom control.**

Evolution during the 5 visits.

Table VIII.31. Analysis of the characteristics of the groups formed during the visits.

	Asthma		COPD		asthma-COPD		$\chi^2$	p
	N	%	N	%	N	%		
Visit 1	522	87,7	54	9,1	19	3,2		

Visit 2	314	90,5	25	7,2	8	2,3	5,99	0,05
Visit 3	169	93,4	8	4,4	4	2,2	7,94	0,02
Visit 4	110	93,2	4	3,4	4	3,4	5,77	0,06
Visit 5	70	95,9	2	2,7	1	1,4	5,18	0,08

A very strong reduction in the weights with COPD and asthma-COPD diagnoses is observed, starting with the 3rd visit, the number of patients with these conditions no longer allows their use in statistical analyses. That is why the global analysis will only be applied to patients diagnosed with asthma.

Table VIII.34. Characteristics of the groups at each visit according to the independent factors.

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
	N	%	N	%	N	%	N	%	N	%
<b>Spirometri</b>	323	69,0	202	68,5	109	66,1	74	67,9	46	66,7
normal										
mild	107	22,9	70	23,7	40	24,2	27	24,8	<b>19</b>	27,5
Moderat	21	4,5	13	4,4	9	5,5	4	3,7	3	4,3
Severe	17	3,6	10	3,4	7	4,2	4	3,7	1	1,4
Poorly	248	47,5	167	53,2	90	53,3	55	50,0	<b>38</b>	54,3
controlled										
Not well	174	33,3	104	33,1	56	33,1	41	37,3	25	35,7
controlled										
Well controled	100	19,2	43	13,7	23	13,6	14	12,7	7	10,0
<b>Clinic</b> normal	445	87,3	266	87,2	142	85,5	91	85,0	<b>56</b>	83,6
Sibilant	65	12,7	39	12,8	24	14,5	16	15,0	11	16,4

Patients who presented 5 visits were included in the well compliant group (12.2%), and those with 2-4 visits were included in the partially compliant group (46%) and 41.6% were noncompliant (did not present no visit except study visit). For symptom control we used the CAT and ACT questionnaire.



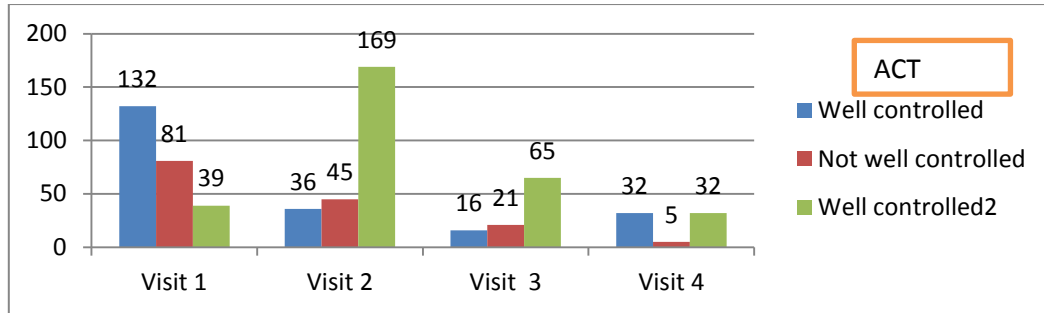


Fig. 7.13. Evolution of compliance (ACT) from the 2-4 visit batch at each visit

In the group of patients with COPD, the CAT level is probably not significant on the following visits.

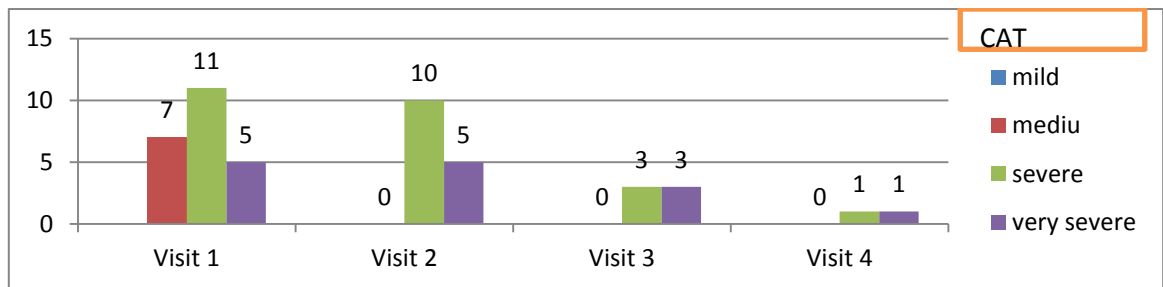


Fig. 7.14 Evolution of compliance (CAT) from the batch with 2-4 visits at each visit

In the group of asthmatics, the ACT improved and remained controlled during the visits.

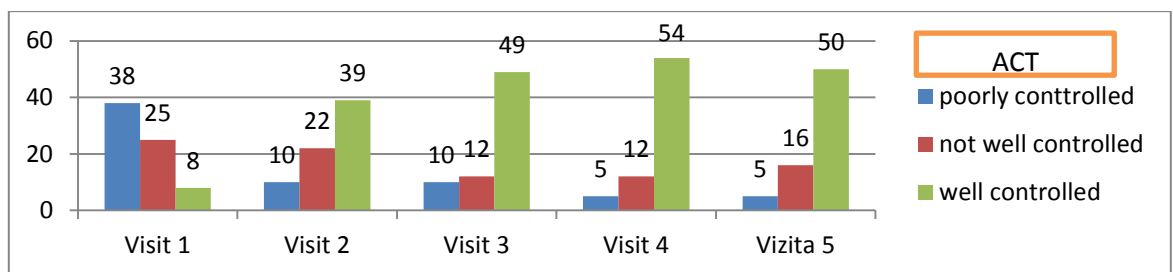


Fig. 7.15. Assessment of compliance (ACT) at each visit in the 5-visit batch

## 2. Assessment of compliance in each age category

Table VIII.8. Compliance at every age range.

Factor	Compliance (ACT)	$\chi^2$	P
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		Poorly controlled		Not well controlled		Well controlled			
		N	%	N	%	N	%		
age	<19 years	33	35,5	37	39,8	23	24,7	16,80	0,010
range	19 – 40 years	55	47,8	32	27,8	28	24,4		
	41 – 60 years	103	46,6	81	36,7	37	16,7		
	> 60 years	57	61,3	24	25,8	12	12,9		
Total		248	47,5	174	33,3	100	19,2		

A high proportion of at least partial control (approximately 65%) was identified in the case of patients aged up to 19 years and a low proportion in the case of patients over 60 years of age (approximately 39%). For patients between the ages of 19 and 60, the shares of those with no control and those with at least one partial control are approximately equal (50%). The trend of differentiation is statistically significant for a test value  $\chi^2=16.80$  and  $p<0.01$ .

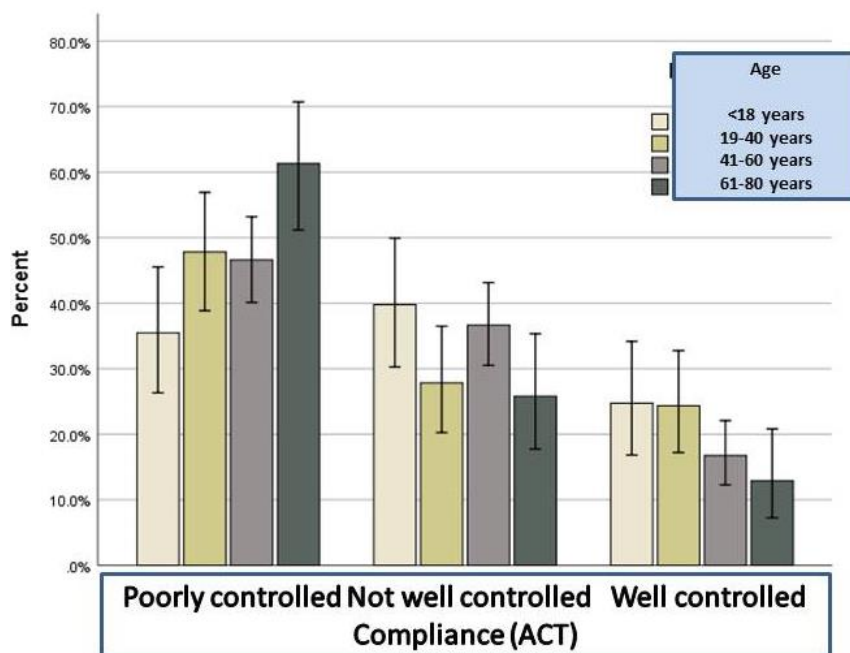


Fig. 8.6. ACT assessment at each age group

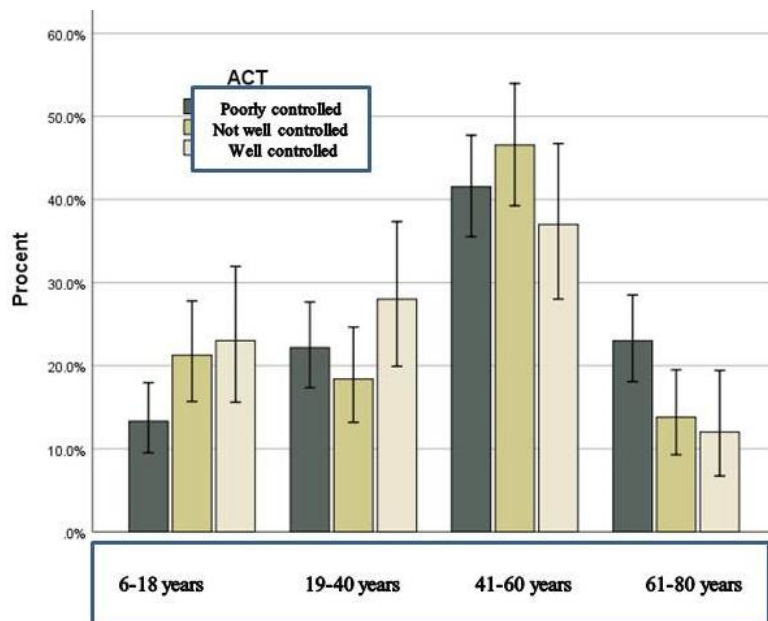


Fig. 8.7. ACT assessment for each age category

### 3. Clinical and paraclinical condition.

Table VIII.13. Compliance according to the clinical and paraclinical examination.

Factor		Compliance (ACT)						$\chi^2$	P
		Poorly controlled		Not well controlled		Well controlled			
		N	%	N	%	N	%		
Examen clini	Normal	197	44,3	155	34,8	93	20,9	12,19	0,001
	Sibilant	43	66,2	17	26,2	5	7,6		
Spirometry	Normal	148	45,8	115	35,6	60	18,6	7,72	0,103
	Mild	62	57,9	29	27,1	16	15,0		
	Moderat	23	60,5	12	31,6	3	7,9		
	Severe								
Total		233	49,8	156	33,3	79	16,9		

From the contingency table above, it can be seen that, in the case of the sibilant type clinical examination, the share of patients with very low compliance (uncontrolled) is significantly higher (approximately 66%) than in the case of those with a normal clinical

examination (approximately 44%) . The identified trend difference is statistically significant for a test value  $\chi^2=12,19$  și  $p<0,001$ .

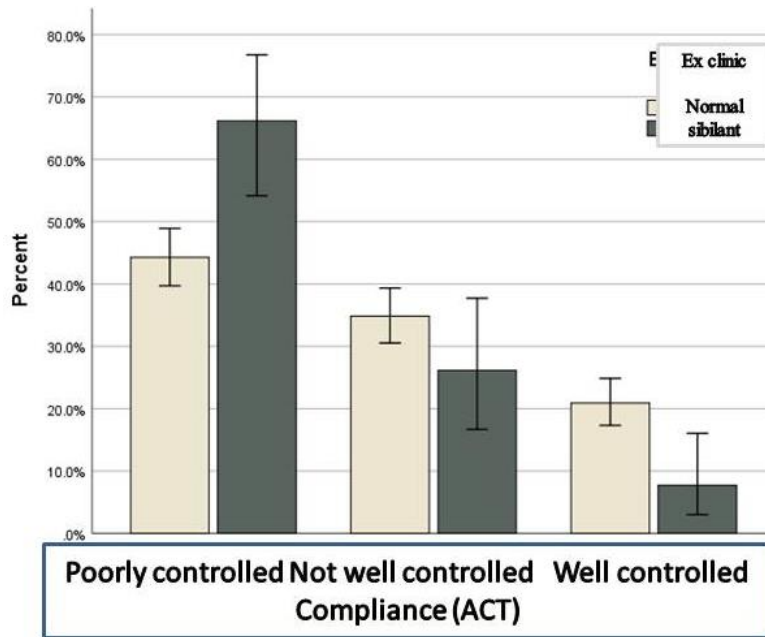


Fig. 8.8. ACT assessment based on clinical examination

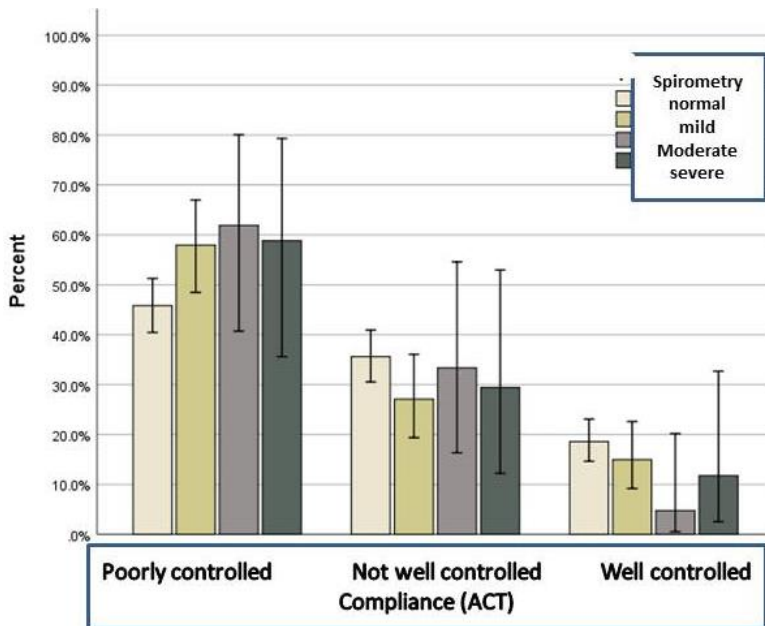


Fig. 8.9. ACT assessment and spirometry

The presence of sibilant rales indicates an absence of treatment use and implicitly poor compliance. During the visits, the presence of sibilant rales is preserved in the group with 5 visits.

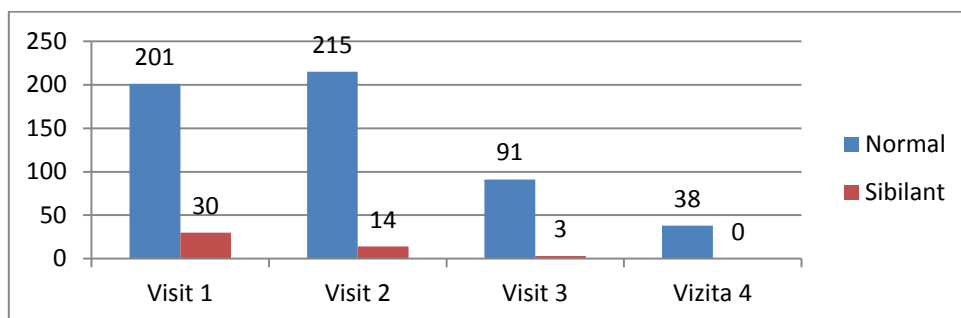


Fig. 7.21. Assessment of compliance by means of clinical pulmonary examination, at each visit in the group of patients with 5 visits.

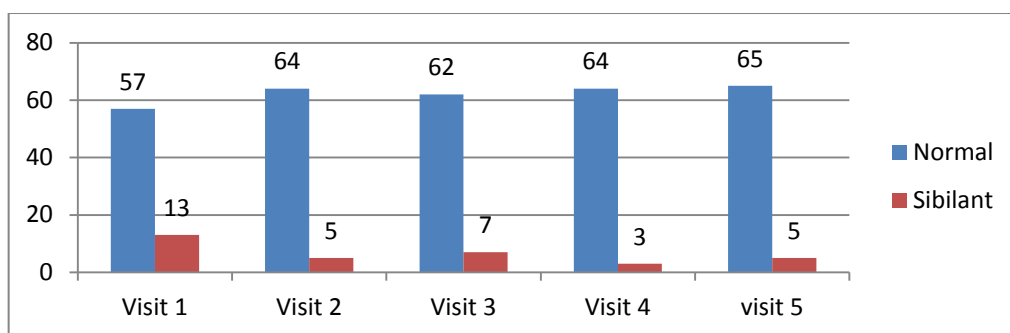


Fig. 7.21.

Assessment of compliance by means of clinical pulmonary examination, at each visit in the group of patients with 2-4 visits.

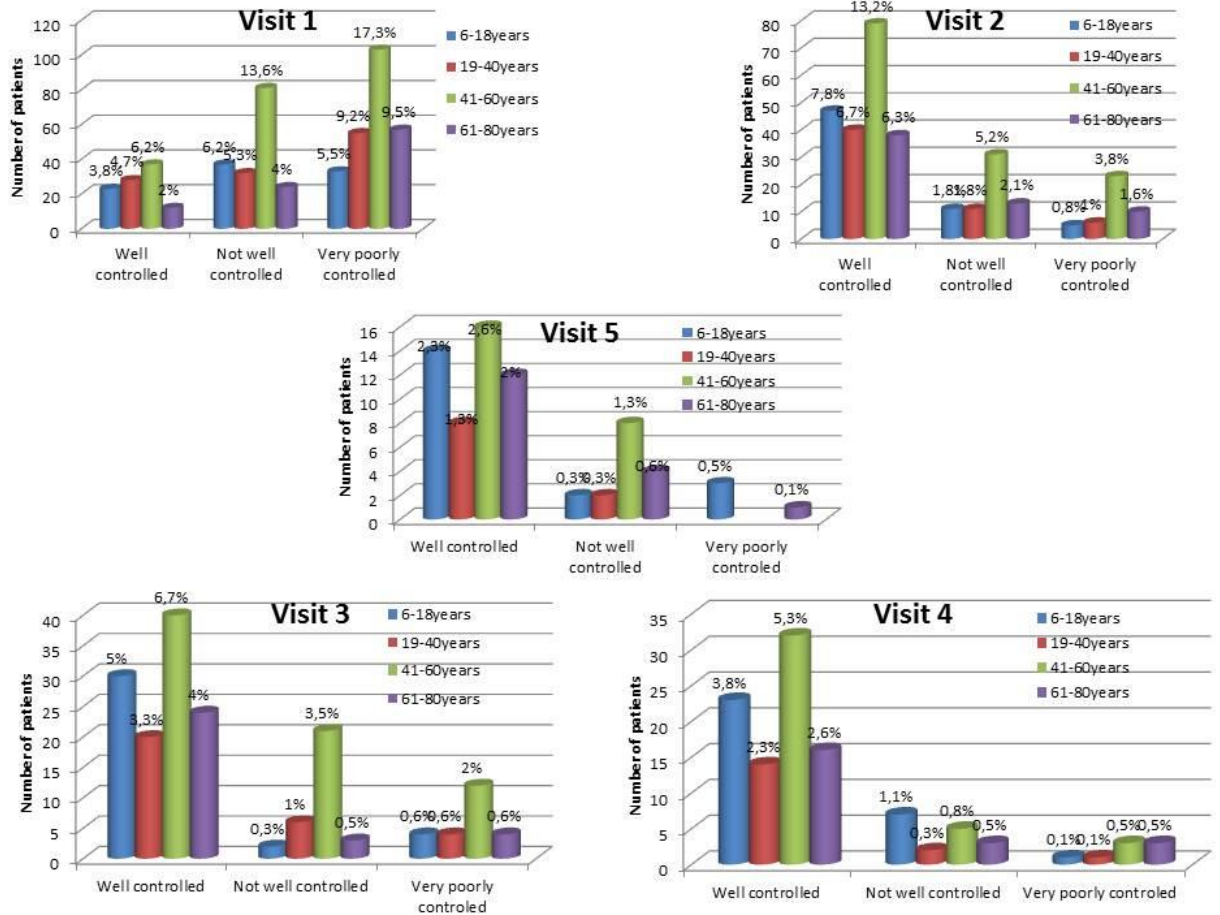


Fig. 6 Prevalence of respiratory symptoms of patients with asthma and its severity assessed with the ACT questionnaire at each visit

We evaluated 49 patients with COPD from the categories 41-60 years and 61-80 years where we observed a high initial CAT score of 4.3%, and at visit 5 of 0.3%. Initially, 0.3% patients were observed with low CAT, 2.6% had medium CAT and 1.6% had very high CAT. At visit 2 1.1% have medium CAT, 1.8% high and 1% very high. At visit 3 high and very high CAT of 0.6% each are observed with the predominance of high in group 3 and very high in group 4. At visit 4 high CAT predominates (0.5%) with a frequency of 0.3% in the 41-60 years group; only 0.1% have a very high score in the 61-80 years group. (Fig. 7.7.)

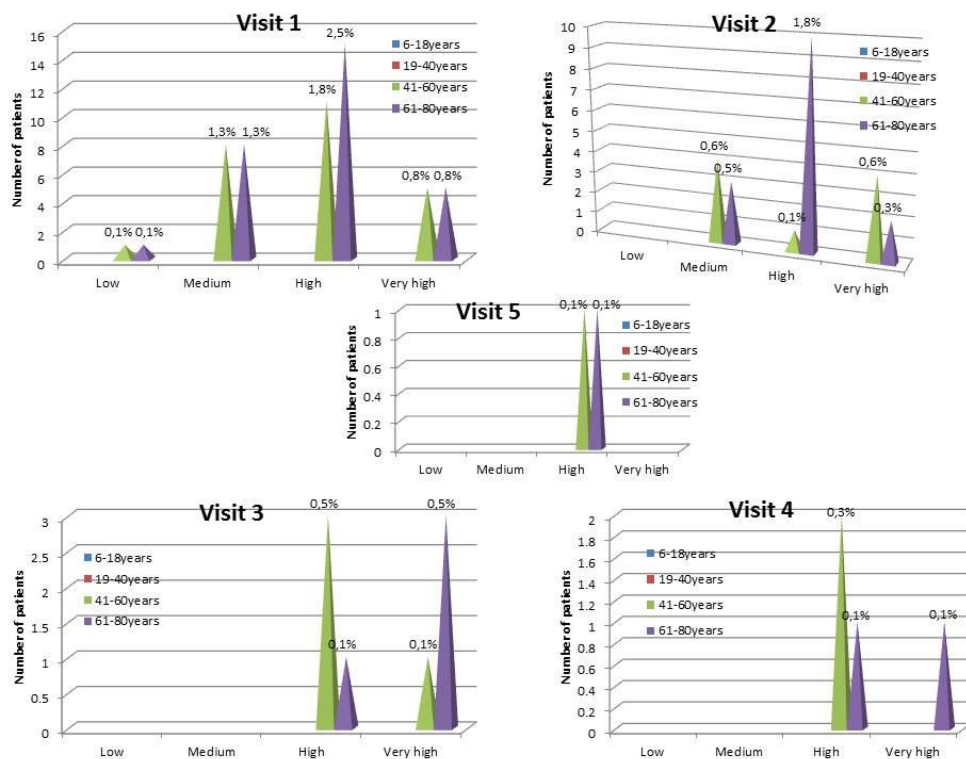


Fig. 7.7. Prevalence of individual respiratory symptoms of COPD patients and their severity assessed with the CAT questionnaire at each visit

COPD-asthma patients completed both questionnaires. In the 41-60 years category, it is observed that at the first visit uncontrolled asthma predominates (1.1%) in the ACT questionnaire and the average score (0.8%) in the CAT score. Only one patient (0.1%) is compliant with uncontrolled ACT score and average CAT score. In these patients uncontrolled ACT (1.3%) and average CAT (1.1%) prevailed at the first visit; also at the first visit there were people who presented symptoms classified as fully controlled ACT (1%), partially controlled ACT (0.6%) and low CAT of 0.6%, high CAT 0.5% and very high CAT of 0.6%.

Overall, there were 49 (8.2%) **exacerbations/hospitalizations** in patients with asthma, COPD and COPD-bronchial asthma during the study period.

#### 4. Assessment of compliance according to the need to use emergency treatment

The use of emergency treatment is an indicator of low compliance. During the visits, there is improvement in compliance from the perspective of emergency treatment use in both groups.

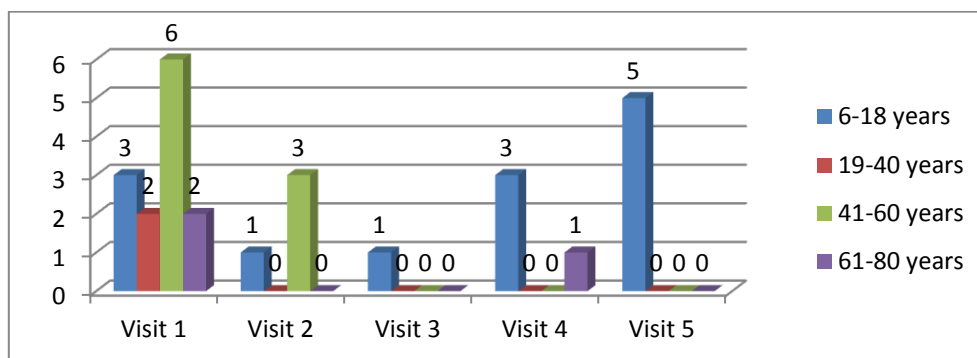


Fig. 7.20. Evaluation of compliance (emergency treatment) in the group of patients with 5 presentations in each age category

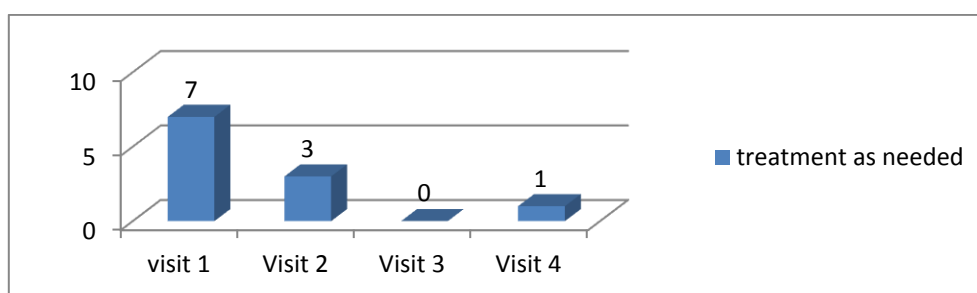


Fig. 7.21. Assessment of compliance according to the need for emergency treatment in the group of patients with 2-4 visits

### 5. Evaluation of compliance according to the technique of using the device

Initially, the inhalation technique was explained to all patients, and at the following visits the technique performed by them was checked, the results being described in figure 7.16. All patients in the fully compliant group show correct technique at visit 5, having a 16% improvement. (Fig. 7.17.)



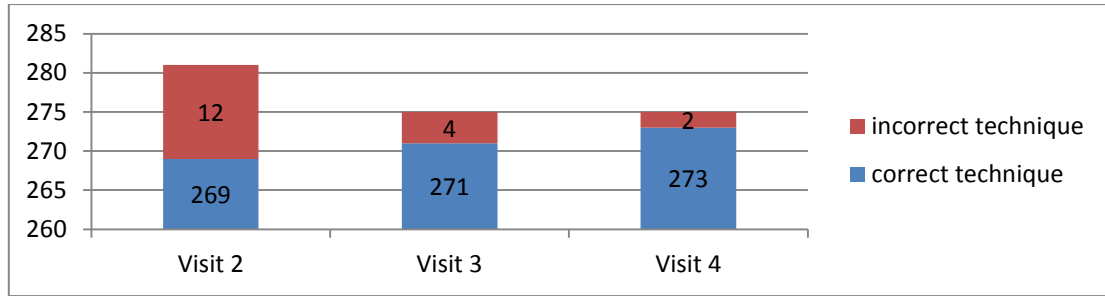


Fig. 7.16. Evaluation of the inhaler technique in the group of patients with 2-4 visits

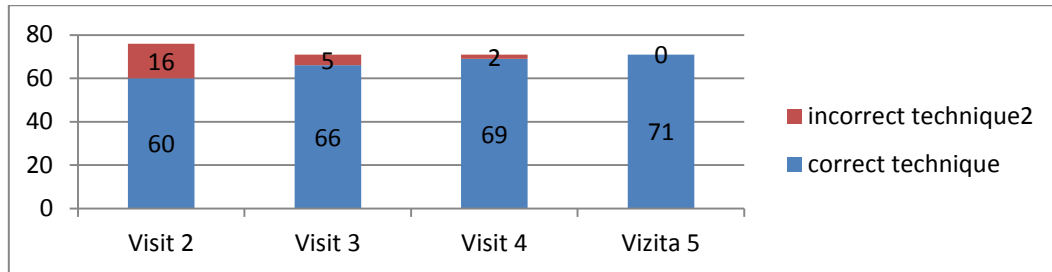


Fig. 7.17. Evaluation of the inhaler technique in the group with 5 visits

## 6. Assessment of compliance according to the number of doses consumed

Inhaler treatment allowed compliance monitoring depending on the doses consumed. A large number of patients do not use all doses from the inhaler due to numerous non-compliance factors. This has been partially corrected according to Fig. 7.18 and Fig 7.19. In the 5-visit group, a 54% improvement in regular medication administration was achieved

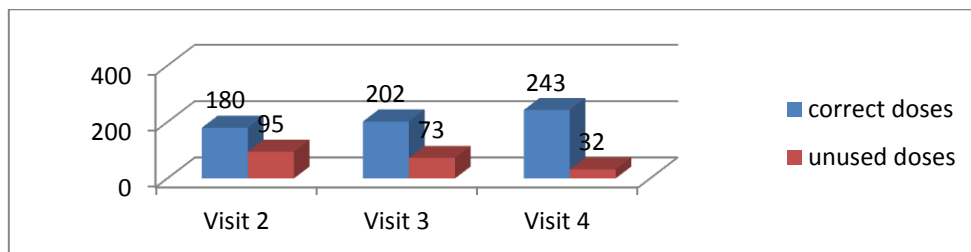


Fig. 7.18. Tracking the number of doses consumed from the inhaler in the batch with 2-4 visits

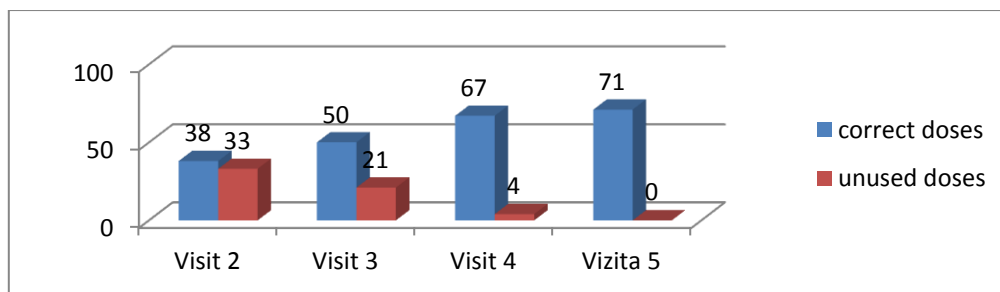


Fig. 7.19. Assessment of compliance according to the doses used in the 5-visit batch

## 7. Analysis of psychological dimensions (anxiety)

This analysis was performed only on male subjects aged over 41 years.

Table VIII.28. Analysis of anxiety type by diagnosis.

		Anxiety global						$\chi^2$	<i>p</i>
		Low score		Medium score		High score			
		N	%	N	%	N	%		
Diagnostics	Asthma	55	<b>74,3</b>	12	16,2	7	9,5	16,96	0,002
	COPD	20	41,7	10	<b>20,8</b>	18	<b>37,5</b>		
	astm-COPD	7	50,0	3	<b>21,4</b>	4	<b>28,6</b>		
		Anxietate somatică				$\chi^2$	<i>p</i>		
		Low score		Medium score+high					
		N	%	N	%				
Diagnostics	Asthma	62	<b>83,8</b>	12	16,2	11,43	0,003		
	COPD	27	56,3	21	<b>43,2</b>				
	astm-COPD	9	64,3	5	<b>35,7</b>				
		Anxietate comportamentală				$\chi^2$	<i>p</i>		
		Low score		Medium score+high					
		N	%	N	%				
Diagnostics	Asthma	66	<b>89,2</b>	8	10,8	13,06	0,001		

	COPD	30	62,5	18	<b>37,5</b>		
	astm-COPD	12	85,7	2	14,3		
Anxietate cognitive							
		Low score		Medium score+ high		$\chi^2$	<i>p</i>
		N	%	N	%		
Diagnostics	asthma	64	<b>86,5</b>	10	13,5	7,51	0,023
	COPD	35	72,9	13	27,1		
	asthma- COPD	8	57,1	6	<b>42,9</b>		

Analysis of the relationship between anxiety and compliance.

Analysis will be done separately according to ACT/CAT.

Table VIII. 29. Analysis of the relationship between anxiety and compliance (ACT Analysis)

ACT analysis

Anxiety	B	Eroarea std.	Test values			Exp(B)	CI 95% Exp(B)		
			Wald	Hi-pătrat	df		p	Inf.	Sup.
Global	-0,092	0,05	4,1		1	0,043	0,91	0,83	0,99
Somatic	-0,176	0,08	5,27		1	0,022	0,84	0,72	0,98
behavioural	0,016	0,09	0,03		1	0,853	1,02	0,86	1,21
Cognitive	-0,061	0,08	0,62		1	0,430	0,94	0,81	1,09

Table VIII. 30. Analysis of the relationship between anxiety and compliance (CAT Analysis)

Anxiety	B	Eroarea std.	Test value			Exp(B)	CI 95% Exp(B)		
			Wald	Hi-pătrat	df		p	Inf.	Sup.
Global	0,225	0,11	4,30		1	0,05	1,25	1,01	1,55

Anxiety	B	Eroarea std.	Test value			Exp(B)	CI 95% Exp(B)		
			Wald	Hi-pătrat	df		p	Inf.	Sup.
Somatic	0,189	0,16	1,37		1	0,242	1,21	0,88	1,66
behavioural	0,144	0,18	0,60		1	0,437	1,16	0,80	1,66
Cognitive	-0,065	0,17	0,15		1	0,699	0,94	0,67	1,30

Based on the results obtained from the ordinal logistic regression analyses, we can consider the fact that a high level of global anxiety will be associated with a high level of compliance, the odds ratio  $\exp(B)=1.25$  allows us to say that patients with medium and high anxiety are 1.25 times more likely to show high compliance than those with low anxiety.

To analyze the evolution of the three parameters during the visits, the Kendall test of concordances for repeated measurements was applied.

Table VIII.35. Kendall's test and analysis of the evolution of spirometry parameters, clinical examination, ACT

Parametr	N	Kendall W	$\chi^2$	Df	P
Spirometry	54	0,015	3,18	4	0,559
clinic test	70	0,033	8,93	4	0,063
ACT	70	0,398	111,52	4	0,001

The obtained results indicate the lack of statistically significant differentiation of the level of the clinical test and spirometry during the 5 visits. The statistical significance associated with the values of the Kendal W test is below the critical significance level  $p<0,05$ .

**Related-Samples Friedman's Two-Way Analysis of Variance by Ranks**

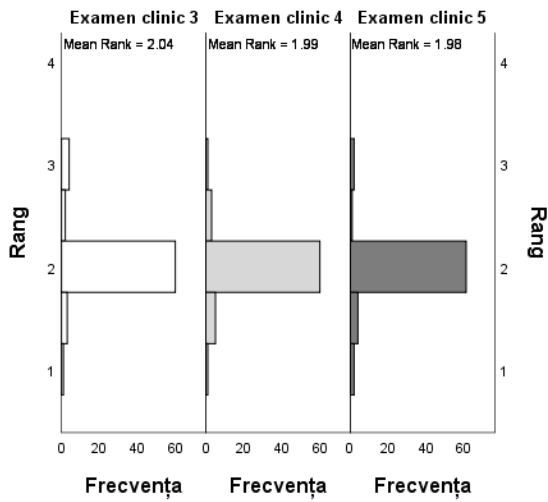


Fig. 8.10. Clinical test level and statistical significance associated with Kendal W test values

**Related-Samples Kendall's Coefficient of Concordance**

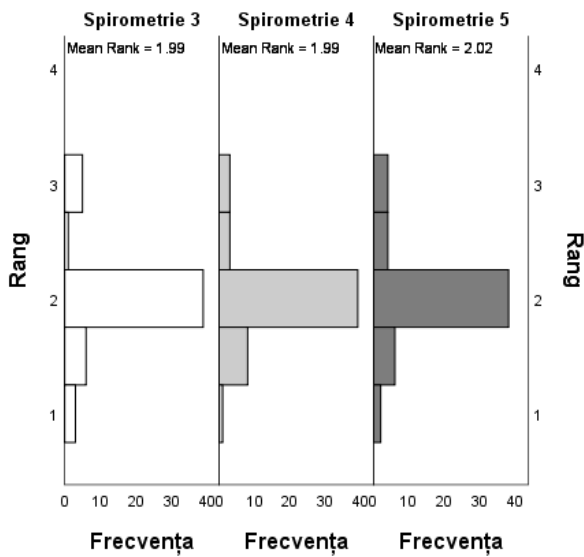
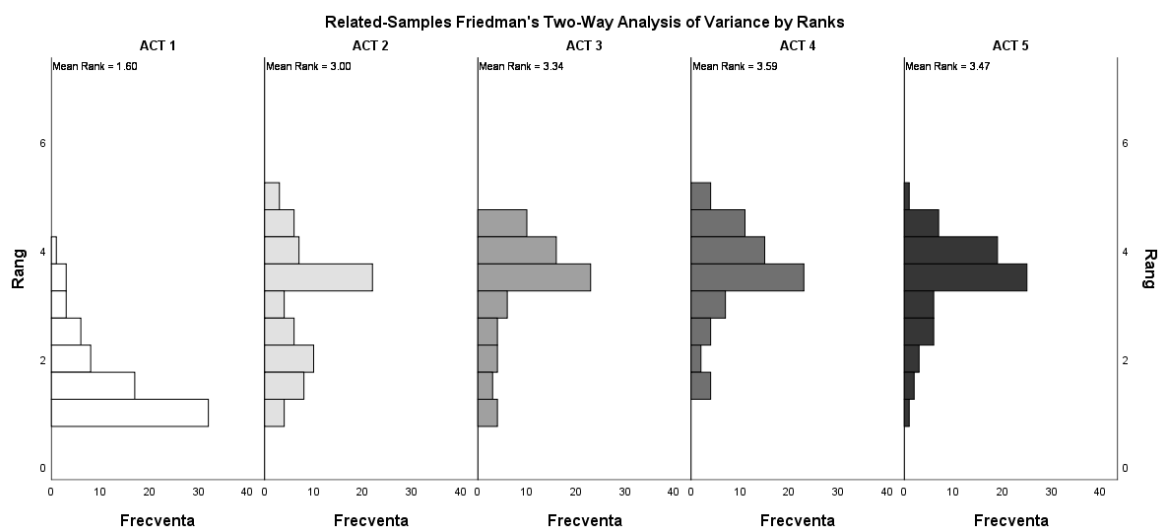


Fig. 8.11. Level of spirometry and statistical significance associated with Kendal W test values

In the case of the level of compliance, a strong increase can be observed from the graph below from the time of visit 1 to the time of visit 2, the average rank increases from 1.6 - which corresponds to a partial control, to 3.0 which corresponds to a control total. But from the time of visit 2, the evolution no longer determines statistically significant differences.

Overall, we can consider an evolution of the compliance level for a value of the Kendal test  $W=0.398$  and  $p<0,001$ .



The multiple comparison test indicates statistically significant differences only between the time of the initial visit and all other visits, no statistically significant differences are observed between subsequent visits.

### **Non-compliance factors identified in each age category**

In the analyzed time interval, several non-compliance factors related to the patient were identified in which the doctor could intervene to correct them, they are represented in Fig. 6.8 ..(Țircă și colectivul, *Internal Medicine*, 2021)(25).

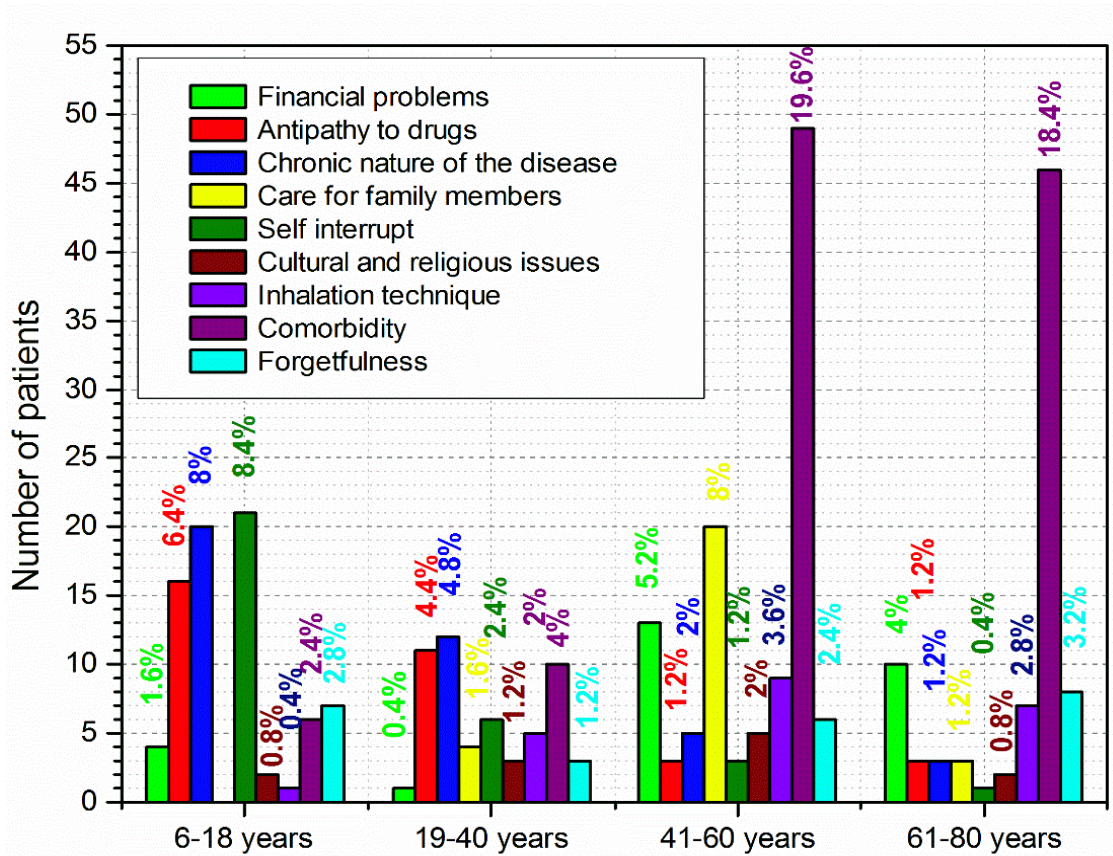


Fig 6.9. Non-compliance factors identified in each age category

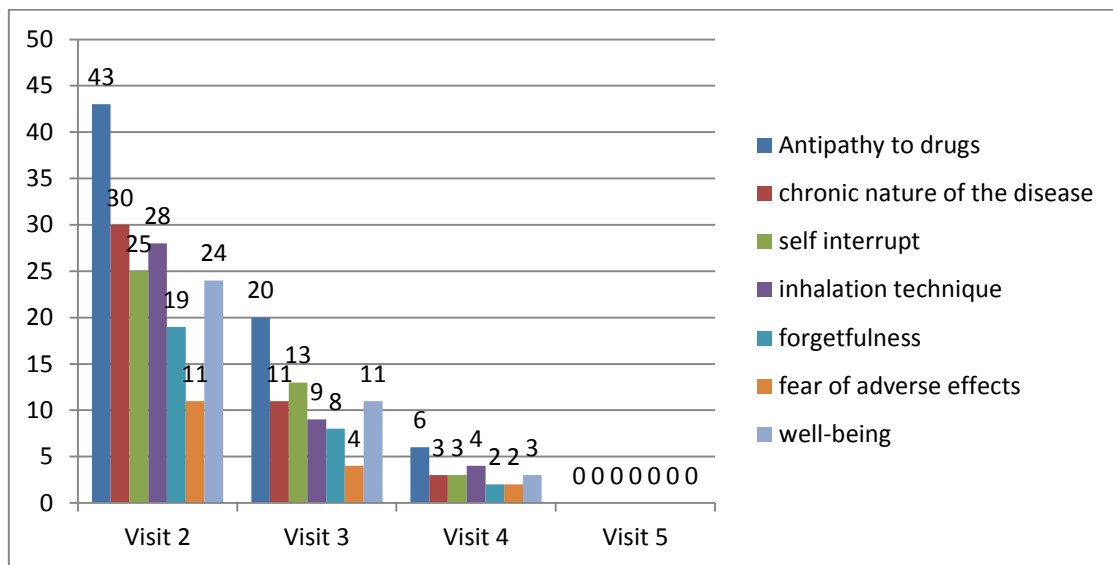


Fig. 6.10. Correctable factors at each visit

### The group of compliant patients

Demographic data on gender distribution indicate the predominance of males (2.3%) in the first age category. In groups 2, 3 and 4, the female gender predominates (1.1%, 2.8% and 2%, respectively). The distribution of patients according to the area of origin showed that at the age of 6-18 years, 41-60 years and 61-80 years, urban patients predominate (2%, 2.6% and 1.6%), and in the group 19-40 years old we have an identical incidence of 0.8% (Fig.7.12.)

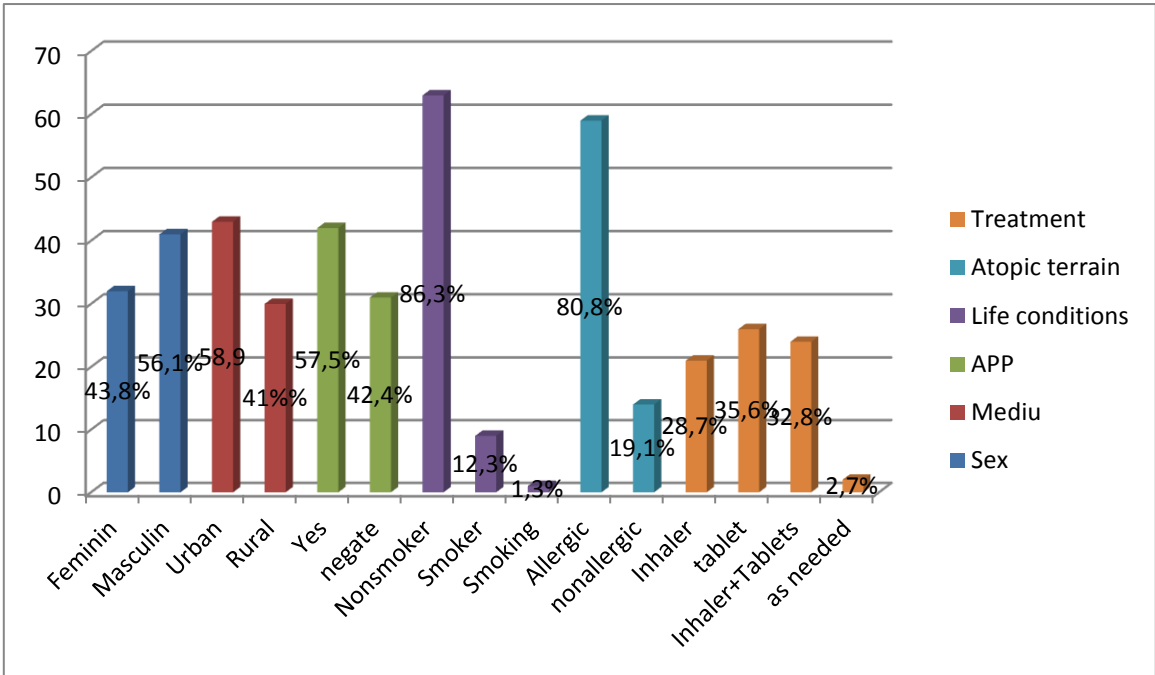


Fig. 7.12. Clinical and demographic characterization of compliant patients

Compliant patients who correctly administered the treatment achieved disease control (ACT-asthma total controlled 8.4%). (Fig. 7.13.)



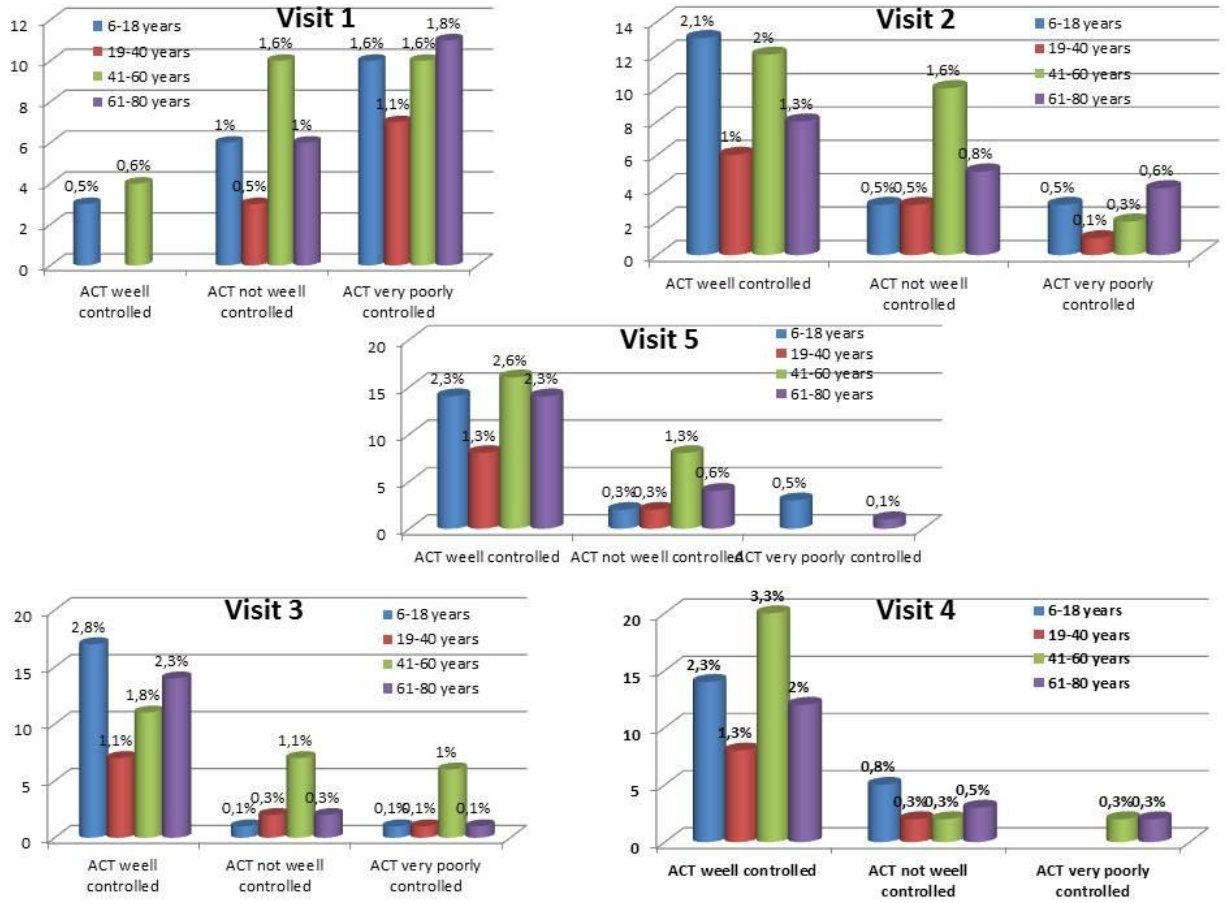


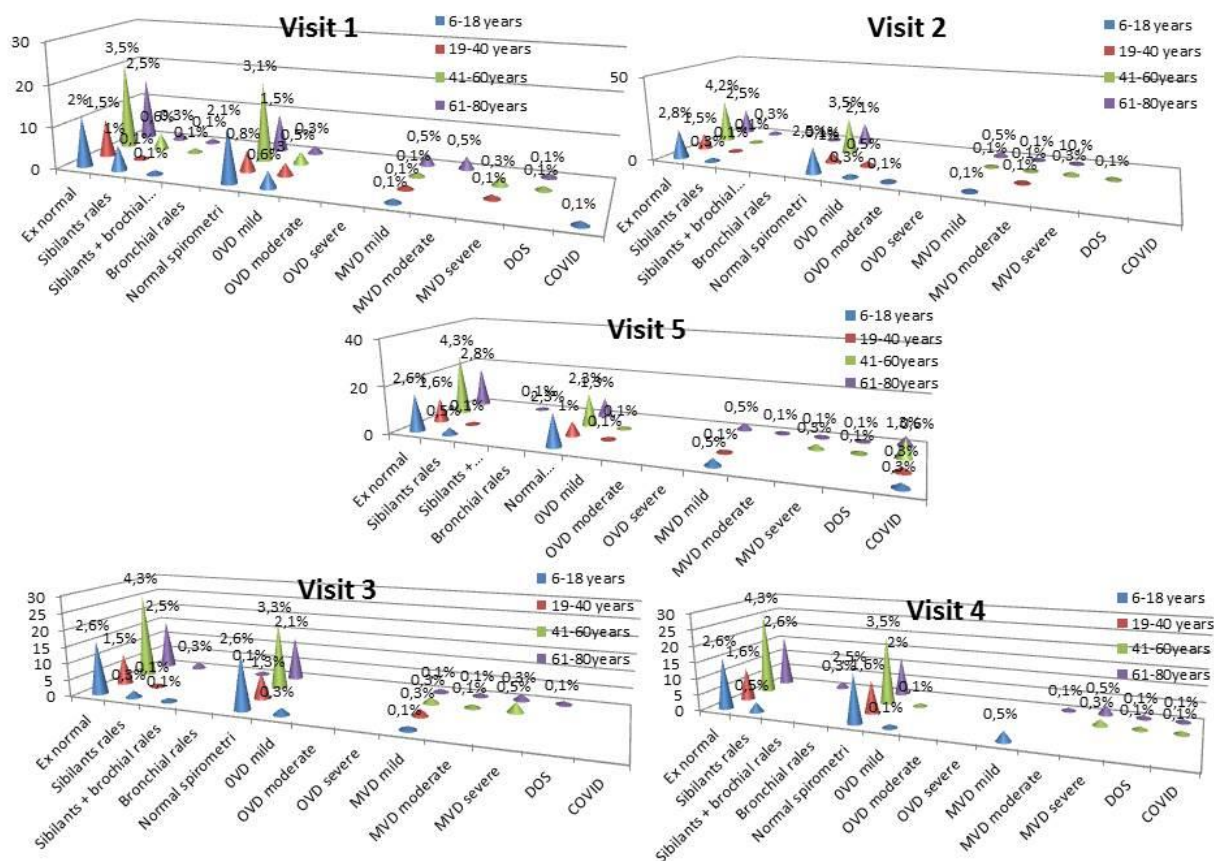
Fig. 7.13. Prevalence of respiratory symptoms of patients with asthma and its severity assessed with the ACT questionnaire at each visit in the group of compliant patients

A number of 2 patients have COPD, 0.1% of the age group 41-60 years and 0.1% of the age group 61-80 years. Both at the first visit and during the 5 visits they present high and very high CAT.

In this group, of the compliant patients, 1 patient in the age group 41-60 years presented COPD-bronchial asthma. He showed several variations in symptom control (initially ACT-fully controlled and medium CAT, at visit 2 he has partially controlled ACT and high CAT, but at subsequent visits uncontrolled ACT and CAT is very high, high and medium.)

The assessment of respiratory function performed with the help of spirometry is shown in Fig 14. This had a very good evolution in compliant patients, with its normalization in most patients (7%). Very few patients experienced mild obstructive ventilatory dysfunction (0.3%). The clinical examination of the patients, shown in Fig. 7.14., was normal at most of the

control visits (11.5%), but there were people who presented pulmonary stataacoustic sibilant rales (0.5%).



The assessment of anxiety showed that at the age of 6-18 years and 19-40 years all patients, 3.1% and 1.6%, respectively, have a low global score. At the age of 41-60 years, 3.5% of patients have a low global score, 0.3% an average score and 0.5% a high score. At the age of 61-80 years, 2% have a low score, 0.8% have an average score and only 0.1% have a high score. Analyzing the somatic dimension, it can be seen that the low score predominates, 3.1%, 1.6%, 3.8% and 2.3% in order of age categories. Only the 41-60 and 61-80 years old categories show an average score of 0.5% and 0.6%, respectively. No patient has a high score. Even in the behavioral and cognitive dimensions, the high score is not observed in compliant patients. In the first age category, 3.1% have a low score in both the behavioral and the somatic dimension. In group 2, all 1.6% have a low score in both the behavioral and the somatic dimension. In age category 3, 4% have a low score and 0.3% an average score in the behavioral dimension and 3.5% a low score and 0.8% an average score in the cognitive

dimension. In age group 4, 2.8% had a low score and 0.1% an average score in the behavioral dimension and 2% a low score and 1% an average score in the cognitive dimension. Fig. 7.15., 7.16.

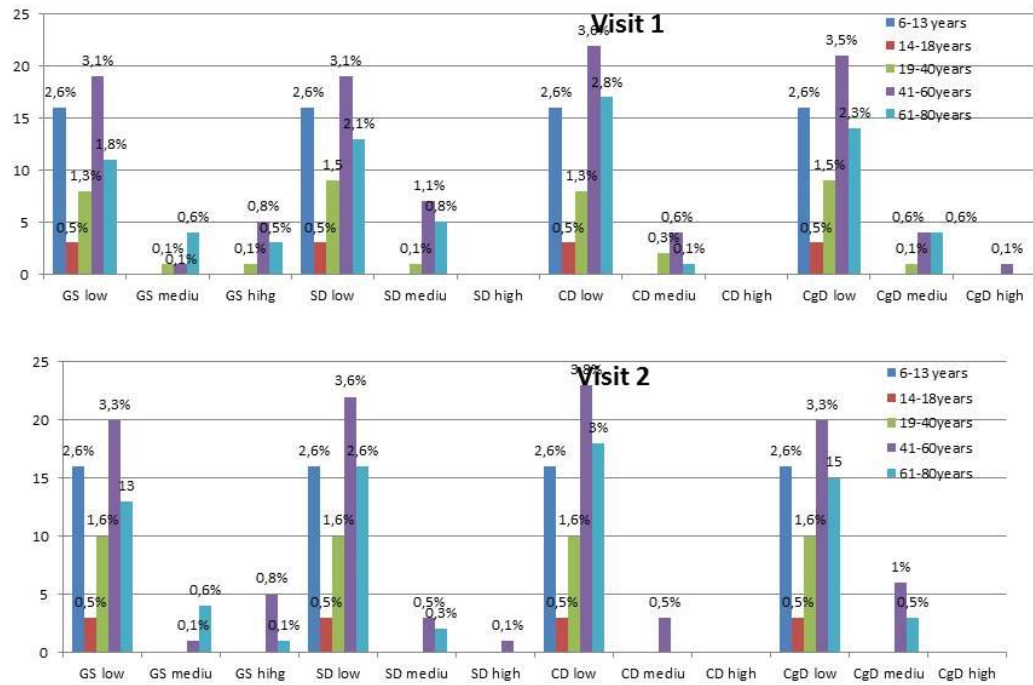


Fig. 7.15. Assessment of anxiety dimensions at visits 1 and 2 in the group of compliant patients

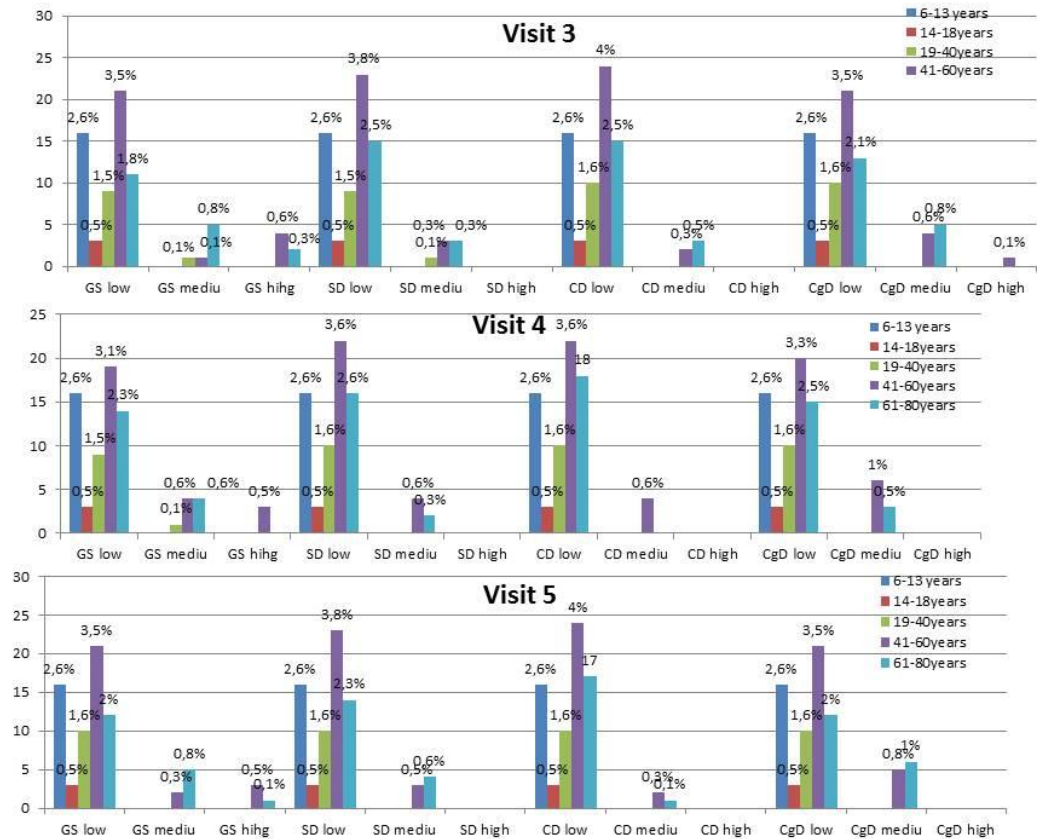


Fig. 18 Assessment of anxiety dimensions at visits 3, 4 and 5 in the group of compliant patients

The anxiety assessment showed that at the age of 41-60 years and 61-80 years, 0.1% of patients have a high global score and 0.1% an average global score. Analyzing the somatic dimension, it can be seen that the average score of 0.3% prevails. In the behavioral dimension, 0.1% have an average score and the same number have a low score. Both patients present a low score in the cognitive dimension. In the behavioral and cognitive somatic dimensions, the high score is not observed in compliant patients.

### The group of patients with asthma

In this group, the female gender predominates, 58.9%, and the distribution of patients according to the environment of origin showed that the urban environment predominates, 56.4%.

Looking at the analysis of the atopic terrain status, 32.6% are allergic.

In this group, most patients presented other associated pathologies: rhinitis (2.1%), osteoporosis (1.3%), digestive disorders (4.5%), thyroiditis (1.5%), hypertension (15.7%), urticaria (1.6%), DM (2.6%), and other comorbidities.

Asthma severity was assessed using the ACT questionnaire. 11.7% are compliant patients. At the first visit, uncontrolled asthma predominates with 41.6% or partially controlled with 29.2%, during the visits the asthma is better controlled, reaching that in compliant patients the total controlled ACT of 8.4% prevails, followed by partially controlled asthma 2.6% and uncontrolled asthma is found in only 0.6%. Despite treatment some continued to have partially controlled (2.6%) or poorly controlled (0.6%) asthma, but in a much lower percentage. (Fig. 7.17.)

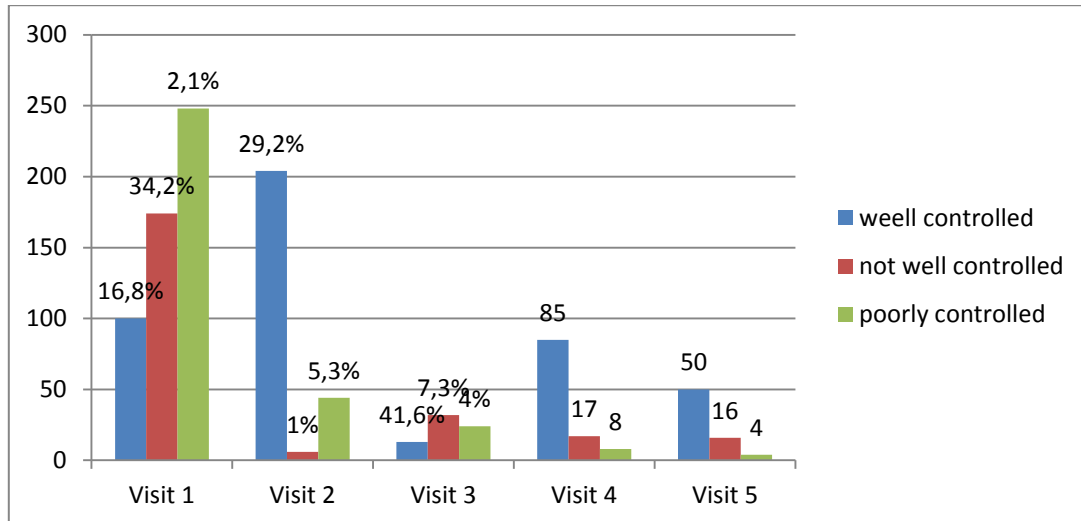


Fig. 7.17. Prevalence of respiratory symptoms of compliant patients with asthma and its severity assessed with the ACT questionnaire at each visit in the group of asthmatic patients

The assessment of respiratory function using spirometry is shown in Fig. 7.18. This had a very good evolution in compliant patients, with its normalization in most patients (7%). Very few patients experienced mild obstructive ventilatory dysfunction (0.3%). The clinical examination of the patients, shown in Fig. 7.18., was normal at most control visits, but there were people who presented sibilant or bronchial rales (12.9%).

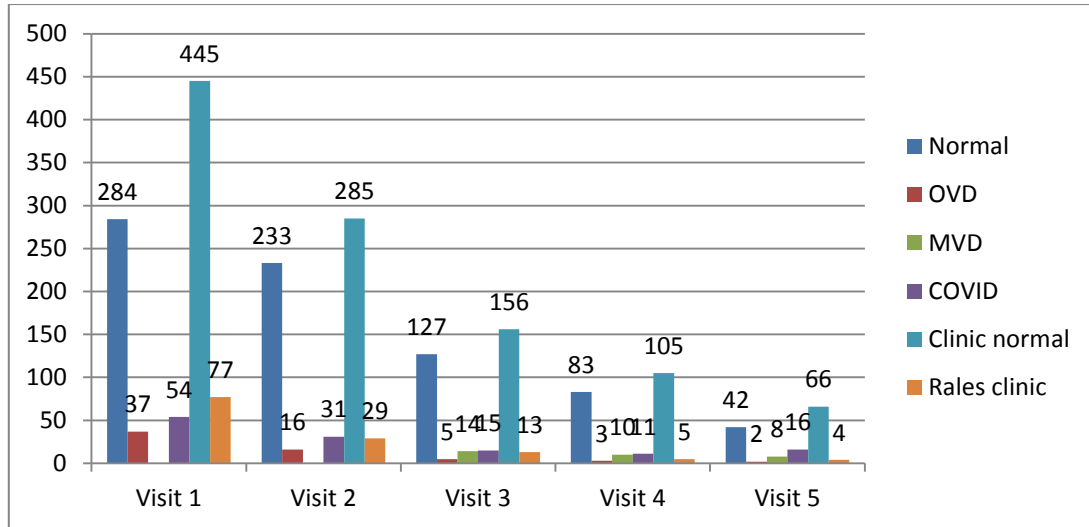


Fig 7.18. Prevalence of the evolution of spirometry and clinical examination at each visit in the group of compliant patients with asthma

Symptoms associated with anxiety present with a low global score of 62.8%, a medium score of 12.4% and a high score of 12.4% at the first visit. The somatic dimension data shows the following: low score 70.9%, average score 15.9% and high score 0.8% at the first visit, then at visit 5 we have 10.7% low score and 1% high score medium. The analysis of the behavioral dimension indicates a low score of 75.7%, an average score of 11.2% and a high score of 0.6%, and at visit 5 we have a low score of 11.4% and an average score of 0.3%. The data on the cognitive dimension show at the first visit a low score of 72.1%, an average score of 14.2% and an increased score of 1.3%, and at the 5th visit we have a low score of 10% and an average score of 1.6%. (Fig. 7.19.)

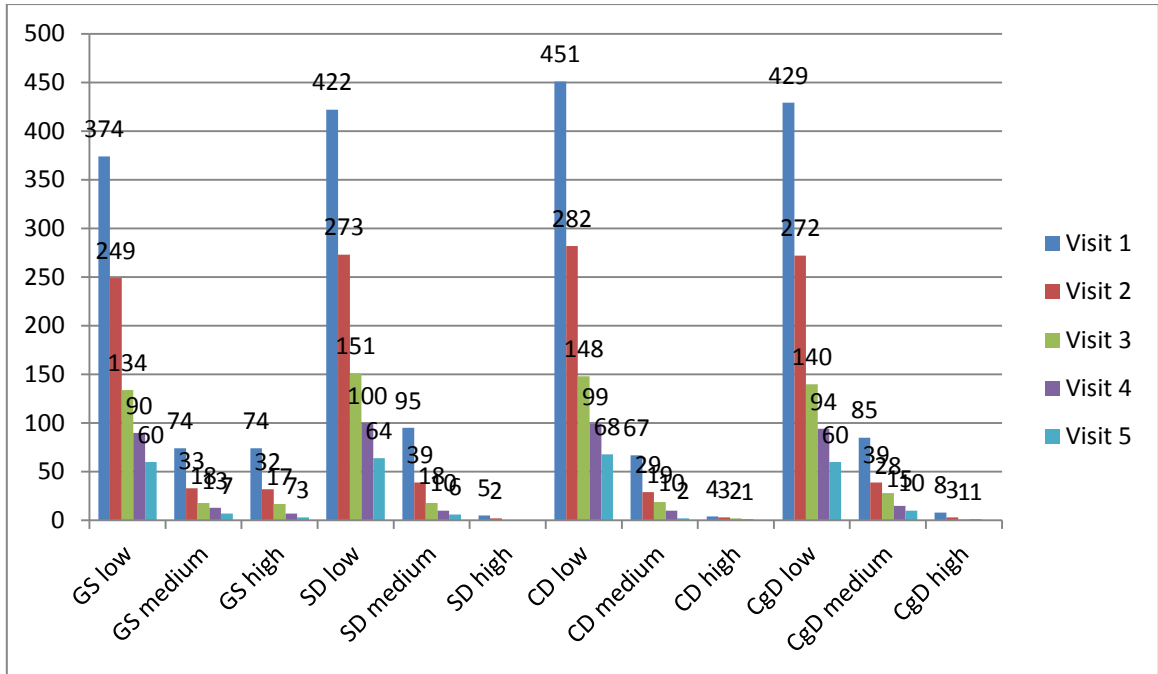


Fig. 7.19. Evaluation of the global score, the somatic, behavioral and cognitive dimensions of anxiety at each visit in the group of compliant asthmatics

## 7. Conclusions and personal contributions

The present study, a multicenter, multiinstitutional, case-control study, with a prospective component, is part of a broad beneficial cooperation between the city of Târgu Jiu (Allergology Outpatient Clinic, Pneumology Clinic, "Tudor Vladimirescu" Pneumophthysiology Hospital) and Timișoara Allergology Clinic. This cooperation aimed at addressing patients with asthma, COPD and asthma-COPD, being a collaborative model for assessing and improving remote treatment compliance of patients with chronic respiratory diseases, a real challenge for medicine everywhere. Correction of noncompliance factors is the "gold standard" for treatment use.

The multiparametric analysis of the experience gathered over a period of 6 years (2015-2020) led to the formation of the following conclusions:

1. From the point of view of the planned visits, carried out by patients with chronic respiratory diseases, the percentage of non-compliers was high; 12.2% are fully compliant and present 5 visits, 46% are partially compliant and present 2-4 visits, and 41.6% are noncompliant and do not present any visit after the one initially performed. Long-term compliant patients can benefit from an improvement in symptoms (90.4% have at least partially controlled ACT) and pulmonary function (57.53% normal values of functional spirometry parameters); they present a low score on the dimensions of anxiety (84.93%).

2. 1.4% administer "treatment as needed" and present sibilant rales - indicating low compliance in these people.

3. Based on the results obtained from the inhalation technique evaluation we can consider that 8% of the patients had a faulty technique at visit 2. This non-compliance factor is improved during the visits (1.1% at visit 4), following that at visit 5 all patients present a correct technique.

4. In the case of evaluating compliance from the perspective of checking the doses used, it was identified that 36.8% have unused doses at visit 2 and 10.3% at visit 4, and a total compliance with the correct use of all doses in those who presented 5 visits.

5. 3 categories of non-compliance factors were highlighted: doctor, patient and regime factors. The group of fully compliant patients with 5 visits was able to overcome all noncompliance factors. The advanced measures of explanations from specialists and complex



monitoring led to the correction of non-compliance factors related to the medical team and patients (the factor related to antipathy to drugs was corrected by 10.6%, by 7.8% the factor related to the chronic nature of the disease, with 6.3% the self-interruption was corrected, with 6.9%, the inhalation technique was corrected, with 4.8% the forgetfulness factor was corrected, the fear of adverse effects with 2.6% and the factor concerning the state of good with 6%).

6. Exacerbations are absent in the group of compliant patients with 5 visits.

7. A higher proportion of the reduced level of anxiety was identified in the case of the female sex, from the urban environment and in those aged up to 19 years. Patients aged over 60 show an increase in the weight of the high level of anxiety. In the case of those without other conditions, a greater share of the reduced level of anxiety was identified compared to those with several conditions.

7. Totally controlled ACT is associated with a low score on anxiety dimensions. Anxiety is 1.4 times more common in people with severe asthma compared to non-severe asthma.

8. A high CAT score correlates with a moderate to high global anxiety score.

The long-term evaluation of patients provides more accurate data on their clinical and paraclinical evolution, but also on how to maintain compliance with the prescribed treatment. Early correction of noncompliance factors is important for achieving symptom control, establishing treatment, and increasing quality of life. The disadvantage of the full assessment and correction of non-compliance factors is explained by the fact that it is very time-consuming.

Studies in large numbers of people with COPD and asthma-COPD are needed to determine the level of compliance in them. Not all identified noncompliance factors could be corrected, and it remains to be determined by future studies how these factors can be corrected. Despite the non-compliance, the medical staff does not make much effort or have enough time to understand the factors that interact with the patient's behavior. Even though efforts have been made to identify noncompliance factors and correct them where possible, it can be inferred that noncompliant patients may also present a problem related to the regimen or their own behavior.

In order to ensure long-term benefits, it is important that future studies on ways to improve compliance, deeper involvement of doctors in explaining the technique of using the

device and more active promotion of correction of non-compliance factors among patients are continued. with asthma, COPD and asthma-COPD from Romania. Correcting non-compliance factors is made easier by introducing validated and standardized questionnaires. Discussion in the medical systems of the results obtained and the introduction of assistance programs for people with financial difficulties. The implementation of new services within those settled by the state (e.g. "Services attributed to the care of patients with chronic respiratory diseases" or "Technical inhalation advice"), would motivate the medical staff in detecting and correcting non-compliance factors.

In the conditions of austerity in our country, the non-compliance factors in patients with asthma, COPD and asthma-COPD syndrome remain a desideratum, the possibilities of resolution being limited only in case of aggravation of symptoms. Healthcare professionals should be aware of compliance issues and take the opportunity to educate patients each time they contact the healthcare system.

Limitations of the study consisted of the small number of patients with COPD and asthma-COPD. The sample of patients with COPD is low because a small number of people present to the allergology specialty, however their addressability to the pneumology specialty is high. The large number of patients with asthma is due to the fact that I work as an allergist and the addressability of asthmatics is high in this specialty. The context of the COVID-19 pandemic reduced the number of patient presentations, and between March and December 2020, spirometry could not be performed due to SARS COV 2 virus infection.

This work is original through the complex way of evaluating patients with asthma, COPD and asthma-COPD in Romania, over a long period of time in order to identify non-compliance factors. The experience regarding remote compliance to treatment of patients with asthma, COPD and asthma-COPD is a unique experience in the country, obtaining comparable results to other studies carried out up to this point, our results indicate that compliance is multifactorial and low.

#### **Personal contributions.**

Compliance regarding regular patient visits revealed low compliance (12.2%). (CHAP. 8, paragraph 1). The prompt intervention of doctors using tools (planned visits, good doctor-patient relationship, feedback at each visit, highlighting the triggering factors, explaining the inhalation technique and the treatment scheme, explaining the importance of administering the

treatment and highlighting the adverse effects) to motivate the importance of administration treatment led to a favorable outcome. (CHAP. 8, paragraph1 ). Factors such as drug aversion, chronic nature of the disease, self-discontinuation, inhalation technique, forgetfulness, fear of adverse effects and well-being could be overcome due to the continuous involvement of both doctors and patients, thus the patient could overcome the fears that have arisen (CHAP. 8, paragraph1 ). The technique of using the device improved by 16% and the regular use of medication doses by 54% (CHAP. 8, paragraph1 ). And with regard to the need to administer treatment "as needed", there is a total improvement in compliance in people over 19 years old (CHAP. 8, paragraph2 )..

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