CLINICAL STUDY ON THE USEFULNESS OF TIOTROPIUM IN POORLY CONTROLLED ASTHMA PATIENTS

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Submitted by
Reg. No: 261640604

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CERTIFICATE

This is to certify that the research work entitled **"CLINICAL STUDY ON THE USEFULNESS OF TIOTROPIUM IN POORLY CONTROLLED ASTHMA PATIENTS"** submitted by **Reg.No. 261640604** is a bonafide work carried out by the candidate at Pulmonology Department, Kovai Medical Center and Hospital, Coimbatore, under the guidance of Dr.**C.Sankar,** Head of the Department of pharmacy practice and submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY** during the academic year 2017-2018.

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PLACE: Coimbatore

DECLARATION CERTIFICATE

I do hereby declare that the dissertation work entitled **"CLINICAL STUDY ON THE USEFULNESS OF TIOTROPIUM IN POORLY CONTROLLED ASTHMA PATIENTS"** was carried out at Pulmonology Department, Kovai Medical Center and Hospital, Coimbatore and submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY,** was done under direct supervision and guidance of **Prof. Dr. C. SANKAR.,** during the academic year 2017-2018.

Reg. No: 261640604

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"CLINICAL STUDY ON THE USEFULNESS OF TIOTROPIUM IN POORLY CONTROLLED ASTHMA PATIENTS"** submitted by **Reg.No. 261640604,** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY** in **PHARMACY PRACTICE** is a bonafide work carried out by the candidate at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu and was evaluated by us during the university examination held on October 2018.

Examination Centre: Department of Pharmacy Practice, Coimbatore

Date:

Internal Examiner: **External Examiner:**

Convener of Examination:

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At the outset, I had sand and gravel in hand and dreamt of fine sculpture with perfectly cut cravings ,all smooth and polished.When I started working, sand and gravel did not suit.....I needed to strain,mix; I needed to mould remould....start again.Many a times I found myself surprised.....astonished and happy....depressed ...Jubilant....Now I feel happy to record my gratitude to those who shared the pain of molding and shaping.

The chain of my gratitude begins with our Prime-Mover –**God Almighty**, for his boundless blessings and his guiding spirit in successful completion of the study.

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ABBREVIATIONS

ATS/ERS	-	AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY
GINA	-	GLOBAL INITIATIVE FOR ASTHMA
WHO	-	WORLD HEALTH ORGANISATION
ACT	-	ASTHMA CONTROL TEST
ACQ	-	ASTHMA CONTROL QUESTIONNAIRE
NAEPP	-	NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM
ICU	-	INTENSIVE CARE UNIT
FEV_1	-	FORCED EXPIRATORY VOLUME
FVC	-	FORCED VITAL CAPACITY
LABA	-	LONG ACTING $ß_2$ ADRENERGIC AGONIST
ICS	-	INHALED CORTICOSTEROIDS
OCS	-	ORAL CORTICOSTEROIDS
PEF	-	PEAK EXPIRATORY FLOW
COPD	-	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
M_1, M_2, M_3	-	MUSCARINIC RECEPTORS RESPECTIVELY
LAMA	-	LONG ACTING MUSCARINIC RECEPTORS
Th-2	-	T-helper-2 LYMPHOCYTES
SM	-	SMOOTH MUSCLES

MUC5AC	-	MUCIN-5 SUBTYPE AC GENE
QoL	-	QUALITY OF LIFE
ANTI IgE	-	ANTI IMMUNOGLOBULIN E
DSC	-	DRUG SAFETY COMMUNICATION
SAQ	-	SEVERE ASTHMA QUESTIONNAIRE
GP-MDI	-	GLYCOPYRRONIUM METERED DOSE INHALER
eNO	-	EXHALED NITRIC OXIDE

ABSTRACT

Background: Asthma is the chronic disorder of airways in which many cells and cellular components are involved. Asthma requiring treatment with high-dose IC, plus a second controller and/or SC to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy is termed as Severe uncontrolled asthma.The prime objective of the study was to assess the usefulness of Tiotropium in poorly controlled asthma patients.

Methods: It is a retrospective and prospective observational study which was conducted in Kovai Medical Center and Hospital. A total of 70 patients with poorly controlled asthma were enrolled in this study. The assessment of asthma severity and control over the disease was measured by using Asthma Control Questionnaire (ACQ). The quality of life of the patients were assessed by using Mini Asthma Quality of Life Questionnaire (MiniAQLQ). Data were analysed by using descriptive and inferential statistics.

Results: Among the 70 patients 47 were males and 23 were females. Majority of the patients were in the age group above 40, mostly in 61-70 age group. Most of patients had poor control or exacerbation of asthma due to exposure towards the occupational allergens. 55 patients had exposure towards allergens as part of their occupation and lead to poor control over asthma. The prevalence of comorbid conditions was also analysed and it was found that 31 patients were GERD diagnosed and 21 were not diagnosed as GERD patients but they were symptomatic and had frequent heart burn sensation. Tiotropium was given as step-up therapy along with ICS.

Conclusion: In this study, patients showed significant improvement in the asthma control and quality of life, which was measured using ACQ and MiniAQLQ respectively. The FEV_1 value showed significant improvement within 3 month treatment. On statistical analysis significant changes were observed for before and after the initiation of Tiotropium. No serious adverse effects were reported, only a small number of patients reported adverse effects (dry mouth). Thus from the study it was concluded that Tiotropium as step-up therapy along with ICS had beneficial effect on poorly controlled asthma patients.

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1. INTRODUCTION

Asthma is the chronic disorder of airways in which many cells and cellular components are involved. The chronic inflammation is associated with airway hyper responsiveness which leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, specifically at night or early in the morning. These events are typically concomitant with extensive, but variable, airflow obstruction within the lung which is often reversible instinctively or else with treatment.[1]

In asthma airway inflammation is characterized by the bronchial wall infiltration which is done by eosinophil, activated mast cells, and T lymphocytes. Cytokines from the T helper 2 cells and leukotriene's show major role in facilitating airway inflammation, similarly goblet cell hyperplasia, mucus gland hypertrophy, and airway mucus accumulation are also seen. Other important characteristics of asthma are increased airway smooth muscle mass and reversible bronchoconstriction.

Airway inflammation, mucus accumulation, and bronchospasm account for the symptoms: [2]

1. shortness of breath
2. wheezing
3. cough
4. chest tightness

SEVERE ASTHMA:

"Asthma requiring treatment with high-dose IC, plus a second controller and/or SC to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy" is termed as Severe uncontrolled asthma.

ATS/ERS Consensus describes severe asthma as asthma which requires treatment at steps 4–5 of the Global Initiative for Asthma (GINA) clinical practice guidelines.

They are:

High-dose inhaled corticosteroids and a long-acting beta-antagonist, or a leukotriene modifier, or theophylline use in the previous year, or systemic corticosteroids for ≥50% of the

last year, thereby to prevent the disease from getting uncontrolled, or the disease which remains uncontrolled despite all this treatment.[3]

EPIDEMIOLOGY:

An estimated 300 million people are affected by asthma worldwide. The asthma global prevalence varies from 1-18% population of different countries. WHO estimated that due to asthma 15 million disability adjusted life years are lost annually, which symbolises 1% of the global disease burden. Annual deaths from asthma has been valued as 250,000 and mortality does not correlate with variations in prevalence within and the populations. It is estimated that 400 million people worldwide will be affected by 2025. Even though from the perspective of both patient and the society the budget to control appears high, but the budget of not treating asthma appropriately is even more higher.[1]

SEVERE ASTHMA EPIDEMIOLOGY:

It fluctuates in the prevalence between one country and the another (18% in Western Europe, 19% in the United States and 32% in Central Europe) 3 and about 50% of these patients are expected to have poor control over the disease.3 In 2011 at Spain, the severe uncontrolled asthma prevalence, as per the medical criteria, is reported as 3.9% of all asthma cases. Furthermore, much higher use of resources are done by this small proportion of people which will be more than other asthmatic patients. Uncontrolled asthma is defined as at least any one of the following:

1. There is poor control over the symptoms which are measured using questionnaires such as ACT and ACQ, there by which enables us to evaluate disease control .a score of more than1.5 and 19 for ACT are being considered as the criteria for poor control as per the clinical practice guidelines of GINA/National Asthma Education and Prevention Program (NAEPP).
2. Frequent severe exacerbations: Requiring bursts of systemic corticosteroids for 3 or more days each in the previous year, because of 2 or more exacerbations.
3. Exacerbations which requires at least 1 hospitalization, which includes ICU admission or need for non-invasive mechanical ventilation in the previous year.

4. Airflow limitation: The FEV1 if remains <80% of predicted value even after using of a suitable bronchodilator and the FEV_1/FVC ratio below the lower limit of normal (best FEV_1 is >80%).

Inadequate control over asthma is a serious problem present, in spite of all advances in our understanding about the inflammatory basis of asthma and the disease management guidelines. Patients who are with inadequately controlled asthma have limited therapeutic options and they remain at high risk of serious mortality and morbidity.[3]

OBJECTIVE OF ASTHMA MANAGEMENT:

To minimize symptoms, prevent acute exacerbations and avoid adverse medication effects is the ultimate aim of asthma management.[2]

CLASSIFICATION OF ASTHMA SEVERITY:

	Current treatment step			
	Step 1 No controller	**Step 2** <500 µg BDP	**Step 3** 200–1,000 µg BDP + LABA	**Step 4** >1,000 BDP µg + LABA ± other
Clinical features				
Step 1 Symptoms <1 x week Nocturnal symptoms ≤2 x month Lung function normal between episodes	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Step 2 Symptoms >1 x week Nocturnal symptoms <1 x month Lung function normal between episodes	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Step 3 Symptoms daily Nocturnal symptoms ≥1 x week FEV, 60–80% predicted	Moderate persistent	Severe persistent	Severe persistent	Severe persistent
Step 4 Symptoms daily Frequent nocturnal symptoms FEV, <60% predicted	Severe persistent	Severe persistent	Severe persistent	Severe persistent

Figure 1: GINA guidelines for classification of asthma severity.[5]

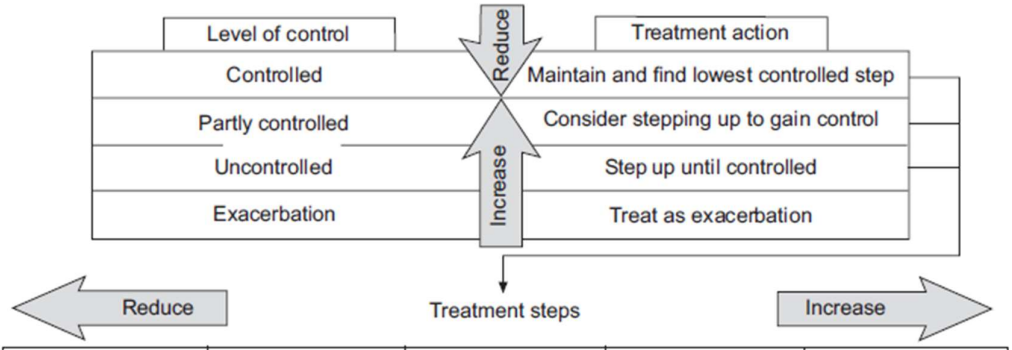
When previous guidelines described the ideal asthma control, the global initiative of asthma (GINA) guidelines provided a working scheme there by to formalise the classification of asthma control.

Asthma is categorized as follows:

1. "Controlled": patient will be having symptoms and the use of rescue medications will be twice per week or even less than that , night waking will be absent , activity limitation or airway obstruction or an exacerbation will not be there;
2. "Partly controlled": the symptoms or rescue medications use will be present for more than twice per week ,night waking ,activity limitation or airway obstruction or an exacerbation will be present in any week;

   "Uncontrolled": the presence of any three or more of this individual characteristics with in any week.

   Asthma treatment, should be stepped up if the asthma is partly controlled.[7]



Step 1	Step 2	Step 3	Step 4	Step 5
	Asthma education Environmental control			
As-needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose ICS	Low-dose ICS plus long-acting β_2-agonists	Medium- or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier#	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

Figure 2: shows the pictorial representation for the management of different categories of asthma With varying control over the disease.[1]

ADVERSE EFFECTS OF STEPPING UP STEROIDS DOSE, IN UNCONTROLLED SEVERE PERSISTENT ASTHMA PATIENTS:

Cases of asthmatic Patients developing acute adrenal crisis after initiating high-dose inhaled fluticasone propionate therapy were reported. Acute adrenal crisis in each case were confirmed by investigations:

- acute phase cortisol levels measurements,
- glucagon stimulation test
- short and long Synacthen stimulation tests[7]

Oral corticosteroids has been enormously used for over 50 years and has a major role in treatment of asthma, inflammatory joint disorders, and other gastrointestinal tract and central nervous system affecting diseases. Though effective in all such medical conditions, osteoporosis is the most serious adverse effect faced during this therapy. Many studies has reported the decline in bone mineral density during oral corticosteroid therapy. Bone loss occurs more rapidly in trabecular bone and it relative to dose of the therapy.

The risk of fracture are greater for a given degree of bone loss with oral corticosteroid treatment when compared with that of postmenopausal osteoporosis.

Epidemiological studies have evaluated the relation of fracture risk with oral corticosteroids therapy and found out that an increase of about 50% and 100% risk is there in oral corticosteroid using patients.[8]

Other adverse effects due to long-term exposure towards OCSs are:

1. Arterial hypertension,
2. Diabetes and metabolic syndrome
3. Dyslipidaemia
4. Obesity
5. Cataracts and glaucoma

6. Gastrointestinal bleeds/ulcers

7. Tuberculosis

8. Depression

9. Herpes

10. Sepsis

Even the asthma treatment guidelines recommend that those patients who are taking long-term systemic OCSs have to receive preventive therapy for osteoporosis.[9]

TIOTROPIUM

History of anticholinergic therapy perhaps was initiated in ancient Greece and India, it was when the wheezing patients were noted to have improvement with the inhalation of different belladonna plants which contains anticholinergic alkaloids. In the 1800s, atropa belladonna, hycoscyamus Niger and datura stramonium leaves and roots were introduced into the western medicine there by for the relief of respiratory symptoms like wheezing. By 1920s, adrenergic agonists become popular as the medication of emphysema and asthma. Likewise, smoking anticholinergic alkaloid cigarettes which contained stramonium belladonna and not tobacco were also very popular for the relieve from the distress of bronchial asthmatic paroxysm. In the 1970s, short acting anticholinergic called as ipratropium bromide was developed by nadel. In 2006 Tiotropium bromide was approved for use in the patients with COPD.[10]

CHOLINERGIC ACTIVITY: ROLE IN THE PATHOPHYSIOLOGY OF ASTHMA:

Cholinergic parasympathetic nerves deliver a dominant innervation to lungs. Acetylcholine release from these nerves controls the airway tone, cholinergic activity and vasodilation. It is predominant preceder of the contraction of bronchial smooth muscle. Asthma patients have an increased release of acetylcholine from cholinergic nerve endings which leads to bronchoconstriction. The local airway inflammatory mediators with the same mechanism, are driving an increase in cholinergic tone.

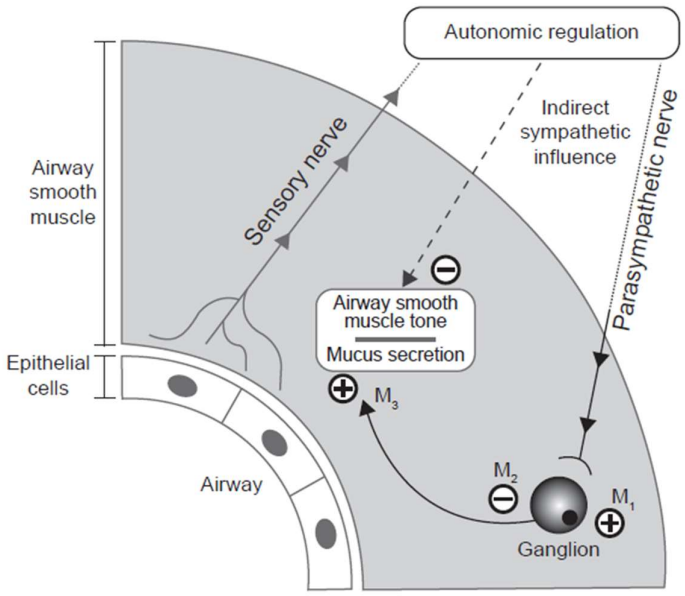


Figure 3: shows the role of cholinergic activity in the pathophysiology of asthma. Autonomic regulation of the airway smooth muscle tone. M_1, M_2 , M_3 represent muscarinic receptors 1, 2, 3. + and – symbols represent signals increasing and decreasing airway smooth muscle tone.[11]

LAMAs may be beneficial for the control of asthma, other evidences which suggest that are:

1) Non-neuronal anti Inflammatory actions are there for the cholinergic antagonists

2) Abnormal muscarinic (M) receptor expression are present for asthmatic patients

3) Airway hyper responsiveness are contributed by an increased cholinergic and smooth muscle tone.

MECHANISM OF ACTION OF TIOTROPIUM:

Tiotropium have been officially declared for the use in COPD for over 10 years, and the mechanism of action of the as a bronchodilator has been studied extensively in COPD. The release of acetylcholine from parasympathetic nerves controls airway smooth muscle contraction, airway tone, and vasodilation and mucus secretion through the interactions with the M- receptors on the airway glands, pulmonary vasculature and the smooth muscle, in the lungs. M1 and M3 anticholinergic receptors blockade decrease the smooth muscle tone and

leads to bronchodilator, but M2 receptor inhibition has the opposite effect. Tiotropium dissociates more slowly from the M1 and M3 receptors, thereby making it to be a more potent bronchodilator. Tiotropium have a long lasting effect and a strength of clinical data in COPD that support its 24-hour profile, which was shown by the single dose studies. In *invitro* and in vivo studies using experimental models for the anti-inflammatory effects of anticholinergics have been done. combination therapy with anticholinergics and corticosteroids combination therapy was found to have additive protective effects on the airway inflammation and then this effect was investigated in guinea pig models.it was found that combined treatment with Tiotropium inhibits chronic allergen – induced airway inflammation and the followed remodelling.

Since acetylcholine is having a key role in pathophysiology of asthma, a clear validation is there for the development of anticholinergic bronchodilators as a therapy in asthma.[11]

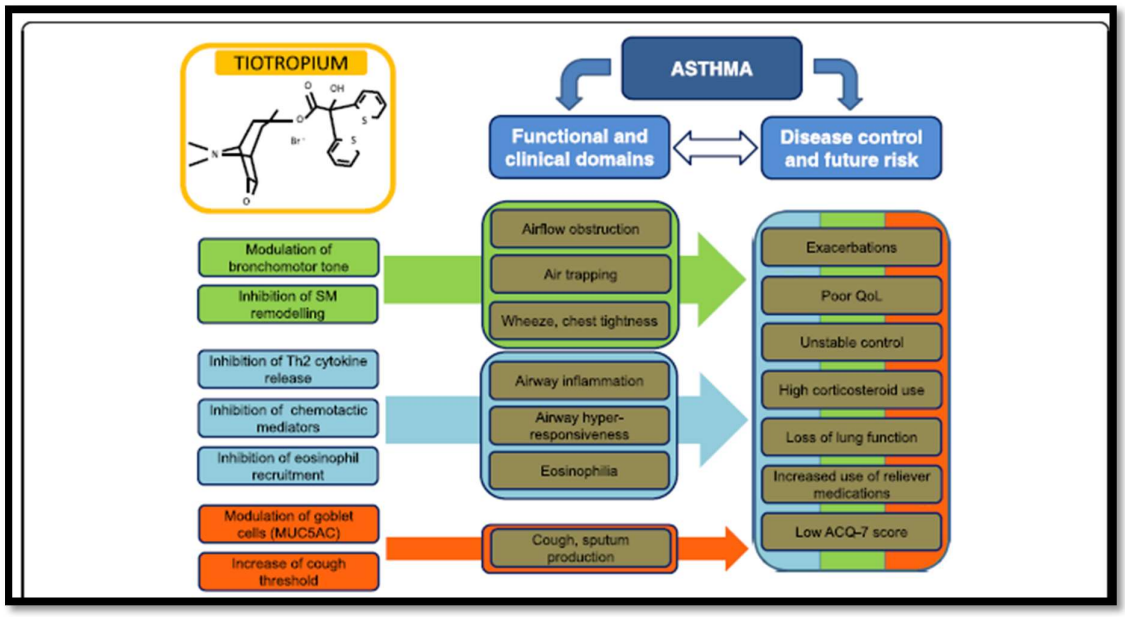


Figure 4: Shows the possible role of tiotropium bromide in the management of asthma. The colour code refers to the functional and clinical characteristics, that tiotropium should be able to modify according to its pharmacological properties. If the effect on functional and clinical asthma domains is effected prevalently by specific tiotropium properties, the effect on asthma control and future risk might be modulated by the concomitant action of different characteristics taken together. Th2, T helper-2 lymphocytes; SM, smooth muscle cells; MUC5AC, mucin-5 subtype AC gene; QoL, Quality of Life; ACQ-7, Asthma Control Questionnaire.[12]

Combination of inhaled corticosteroids (ICs) along with Long-acting ß$_2$-adrenergic agonists (LABAs) plays a significant role in the management of asthma.

But the role of long-acting anticholinergic bronchodilators (Eg, Tiotropium bromide) have not been fully investigated till date and therefore they are not included in the asthma management guidelines.

It is contradictory to the fact that Tiotropium have been the first drug of choice long acting bronchodilator for patients with chronic obstructive pulmonary disease (COPD).

Limited use of anticholinergics in asthmatic patients are because of:

1. The slower onset of action

2. Inferior bronchodilator responses was obtained in studies comparing short-acting anticholinergic (ipratropium bromide) with short-acting ß$_2$ -adrenergic agonists.

Studies on the efficacy of Tiotropium as maintenance therapy in asthmatic patients was limited.

PURPOSE:

1. Significant proportion of the asthmatic patients fail to achieve control over the symptoms with the present treatment options including LABA even with high dose of ICSs.

2. There are also concerns about the safety of regular use of LABAs in patients with asthma.[13]

The final step recommended in the Global Initiative for Asthma (GINA) guidelines was the addition of another treatment, like theophylline's, anti-IgE, antileukotrienes, and immunosuppressant's (Eg, systemic corticosteroids or cyclosporine). Despite of all this many patients fail to attain control and they stay both symptomatic and obstructed.

An effective alternative approach for this condition is to include a second bronchodilator which has a difference in the mechanism of action. Thus, it signifies the

relevance of the use Tiotropium bromide the anticholinergic, which was shown to be effective in COPD patients.

Recently Peters *et al* proved the beneficial effect of Tiotropium in asthmatic patients that by the addition of Tiotropium into low dose ICSs showed superior improvements in the morning and evening PEF, prebronchodilator FEV1, asthma control days and symptoms with that of doubling the dose of ICSs.[14]

Tiotropium has been approved in Europe since 2014 as an add-on maintenance treatment in therapy for adults with asthma treated with ICS/LABA and had a history of severe exacerbations.

In USA by 2015 Tiotropium was approved as once daily long-term, o maintenance treatment in patients of ≥12 years of age with asthma (this indication was extended in 2017 to include patients ≥6 years of age with asthma).[15]

Tiotropium have not been examined in a randomized controlled trial in patients with severe uncontrolled asthma. The aim of this study is to evaluate and validate the safety and efficacy of

Tiotropium added in asthmatic patients whose symptoms are poorly controlled with at least high-dose ICS plus LABA treatment (GINA step 4-5).[14]

Based on these observations, we have chosen to work on the topic **"Clinical Study on the Usefulness of Tiotropium in Poorly Controlled Asthma Patients".** Thereby to provide a pathway for the better management of poorly controlled asthma patients. Research are enclosed in this thesis.

2. LITERATURE REVIEW

- **Jacqueline *et al*., (2018)** conducted a study to describe the effect of FDA issued 2 main drug safety communications (DSCs) on medication dispensing of Tiotropium. The drug safety communication was issued in March 2008 on the cardiovascular safety of Tiotropium, which was a warning of a potential increased stroke risk and January 2010 which was an information which stated an absence of a significant increased stroke risk or cardiovascular events based on findings from a large trial. It was finally concluded that cardiovascular safety concerns may have affected the initiation of Tiotropium as indicated by the decrease in Tiotropium dispensing which was immediately shown after the issuing of the initial drug safety communications (DSCs).[16]
- **Michael *et al*., (2018)** documented a final quantitative validating data for the Severe Asthma Questionnaire (SAQ). SAQ were designed to detect the impact of both asthma symptoms and treatment on quality of life. Finally SAQ was developed using the recommended qualitative and quantitative procedures for the scale development and thereby it can be used to gain an insight into the patient perceptions of how severe asthma and its treatment affects their lives.[17]
- **Edward *et al*.,(2018)** conducted a study to investigate the safety and efficacy of glycopyrronium administered by metered dose inhaler formulated using co-suspension delivery technology and was compared with salmeterol dry powder inhaler in those patients with intermittent or mild-to-moderate persistent asthma.it was concluded from the study that glycopyrronium metered dose inhaler (GP MDI) can be a major treatment option as a maintenance therapy for asthma.[15]
- **Chien *et al*., (2018)** conducted a retrospective study at a single medical centre and they used the asthma control test (ACT) to assess the effectiveness of Tiotropium as add-on therapy in uncontrolled asthma patients. The effect of Tiotropium was indicated by an increase in the ACT score from the baseline score 3 or greater than that after 3 months add-on therapy with Tiotropium. From the study it was concluded that use of Tiotropium as an add-on therapy in patients with uncontrolled asthma is effective.[39]

- **Patrick *et al*., (2017)** conducted a retrospective cohort study on asthmatic patients of 18years and older to determine the relationship between oral corticosteroids (OCS) and the incidence of adverse effects. It was concluded from the results that OCS prescription may result in a cumulative burden on current and future health status irrespective of the dose and duration of treatment. Therefore to improve the patient outcomes OCS- sparing strategies are extremely important.[9]
- **Akbar *et al*., (2017)** conducted a study to determine the frequency of prescriptions for the short term use of oral corticosteroids and thereby to analyse the development of adverse effects such as sepsis, venous thromboembolism, fractures. From the study it was found out that one in five adults in a commercially insured plan were given prescriptions for the short term use of oral corticosteroids in a three year period ,along with an increased risk for the development of adverse events.[22]
- **Josefin *et al*., (2017)** conducted a study to investigate temporal variation in the Health-Related Quality of Life (HRQL) and the factors influencing the low HRQL, in asthmatic patients. The study was concluded with the findings that high educational level and knowledge on self-management paved the way towards higher HRQL, while overweight ,exacerbations, obesity, heart disease, self-rated moderate/severe disease, rhinitis and depression/anxiety were factors that lead to lower HRQL.[36]
- **Kim *et al*., (2016)** conducted a study to analyse the relation between asthma exacerbations and occupational exposures this study included all the presently working adults (n = 1356), who reported asthma in population based- cohorts. Finally, from the study it was concluded that jobs handling with low molecular weight agents, exposure to organic dust, smoke or dust, any gas, cold, damp conditions, physically strenuous work were associated with inducing asthmatic exacerbation. Reducing such occupational exposure can help to reduce the exacerbation of asthma.[40]
- **Pierluigi *et al*., (2015)** conducted a study to examine the safety and efficacy of once daily Tiotropium respimat and it was compared with placebo respimat as anadd on therapy to low- to medium – dose ICS for adults with symptomatic asthma. Once- daily dosing of Tiotropium improved the lung function after 12

week treatment when compared with placebo. Finally Tiotropium respimat was found to be a efficacious bronchodilator when used as an add on therapy for adult patients with not fully controlled ,mild to moderate asthma.[18]

- **Carolina *et al*.,(2015)** this study was done to attempt classification of various manifestations of severe uncontrolled asthma ,a proposal for stepwise diagnostic procedure and phenotype-targeted treatment, since new data's made on asthma need to be reviewed, analysed and incorporated into the guidelines according to the level of evidence and recommendation.[3]
- **Wang *et al*., (2015)** this study was done to evaluate the best second-line treatments for patients having uncontrolled moderate asthma. After the add on therapy for 4 and 12 weeks, the average daily diurnal peak expiratory flow (PEF) variability, the concentration of exhaled nitric oxide (eNO) and asthma control test (ACT) scores were measured. Patients were divided into 3 groups, which was given different add on treatments. The groups were Tiotropium bromide group, monteleukast sodium group and double dose inhaled corticosteroid (ICS) group. Finally it was concluded that Tiotropium in combination with ICS plus LABA showed the similar effects with double-dose ICS plus LABA, without any adverse effects , this was estimated to be a best option for optimal control of asthma.[19]
- **Jeannette *et al*., (2014)** conducted a study to examine the use of Nijmegen Clinical Screening Instrument (NCSI) in comparison with the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) in severe asthmatic patients. Severe areas it will provide a comprehension on the patient requirements since it determines the burden of disease. The Nijmegen Clinical Screening Instrument (NCSI) was developed recently for use in clinical practice for COPD patients and thereby it gives a detailed picture of the patient's physiological functioning, symptoms, functional impairments and quality of life. From the study it was understood that NCSI, ACQ and AQLQ measures the highly relevant aspects of health status of the severe asthmatic patients. But NCSI was found to measure more aspects of health status which were not covered by the ACQ and AQLQ.[20]
- **Eric *et al*., (2014)** performed a systematic network meta-analysis to analyse the magnitude of AQLQ and ACQ responses obtained with frequently used

asthma drugs and elements influencing these end points. It was concluded from the analysis that in addition to reporting the changes in mean of the instruments, other measurement criteria's should also be considered, along with analyser responder.[21]

- **Kai *et al*., (2014)** conducted a study to assess the safety and efficacy of three different doses of Tiotropium respimat, as an add on therapy with ICS in patients with moderate persistent asthma. From the study it was observed that Tiotropium-Respimat once daily dose improved the lung function, it was effective and safe as an add-on therapy for moderate persistent asthmatic patients. And among the three doses studied (5,2.5,1.25µg) greater improvement was observed in 5µg Tiotropium Respimat group.[41]
- **Francois *et al*., (2013)** conducted a study with an objective to assess the agreement between five specific questionnaires. From the study it was concluded there existed only a moderate agreement between the most commonly used five asthma control questionnaires. The GINA score has shown the lowest percentage of controlled and then the highest percentage of uncontrolled asthma, which depicted that all these scores do not evaluate the same symptoms.[24]
- **Spears *et al*., (2013)** conducted an exploratory study to examine whether smoking in asthma is associated with elevated levels of corticosteroid resistant sputum cytokines. In the study blood and sputum cytokine concentrations in never, ex and current smokers with asthma were analysed before and after oral corticosteroids. It was concluded from the study that cigarette smoking in asthma lead to corticosteroid insensitivity increase in multiple airway cytokines, while distinct airway cytokines were present in current smokers and never smokers with asthma. Several plasma cytokines were lower in smokers with asthma compared to never smokers with asthma.[42]
- **Huib *et al*.,(2012)** conducted a to study the safety and efficacy of Tiotropium in patients who have frequent exacerbations and persistent airflow obstruction even after the treatment with inhaled glucocorticoids and long acting beta agonists (LABAs). From the study it was concluded that the addition Tiotropium significantly increased the time to the first severe exacerbation and

provided an effective bronchodialation, in patients with poorly controlled asthma even after the usage of inhaled corticosteroids and LABAs.[25]

- **Bateman *et al*., (2011)** conducted a study to compare the safety and efficacy of long acting anticholinergic Tiotropium with salmeterol and placebo which were added to an ICS in B16-Arg/Arg patients with asthma which were not controlled by ICSs therapy alone. From the study it was concluded that long term anticholinergic drug, Tiotropium was noninferior to salmeterol and superior to placebo in moderate asthmatic patients with B16-Arg/Arg genotype which were not under control by ICSs therapy alone. Thus the study has shown the evidence for that Tiotropium can be used as an effective alternative for patients uncontrolled severe asthma under the ICSs and LABAs.[13]
- **Bernd *et al*., (2011)** conducted a study to compare the efficacy and safety of 2 different doses of Tiotropium doses administered through respimat inhaler with placebo as a step up therapy in patients with severe uncontrolled asthma, even after the treatment with a high dose inhaled corticosteroid and a long acting $ß_{2\text{-agonist}}$. At the end of the study it was concluded that the addition of once daily Tiotropium in severe uncontrolled asthmatic patients along with a high dose inhaled corticosteroid plus long acting $ß_2$ adrenergic agonist improved lung function remarkably.[14]
- **Stephen *et al*., (2010)** conducted a study to evaluate the effectiveness of addition of Tiotropium bromide as a step-up therapy for patients with severe uncontrolled asthma in low dose inhaled glucocorticoids. Currently available treatment options available for severe uncontrolled asthma on low dose inhaled glucocorticoid are addition of leukotriene modifier, the addition of LABAs, or increasing the dose of inhaled glucocorticoid. As per the guidelines of National Asthma Education and Prevention Program encourages the last two steps. But recently FDA has questioned the safety of administering LABA and suggested strategies for minimising there use. Therefor an urge for and effective alternative arise. Finally from the study it was concluded that the use of Tiotropium as a step-up therapy showed superior effect with that of doubling the dose of inhaled corticosteroids and it equivalent to the addition of LABAs in patients with inadequately controlled asthma.[26]

- **Carla *et al*., 2009** conducted a retrospective study to assess prevalence of comorbidities in severe asthma patients. From the study it was concluded that rhinitis and gastro oesophageal reflux disease were the most commonly observed comorbidity. So the severe asthmatic patients should be analysed for the comorbid diseases as cause for the worsened respiratory symptoms and uncontrolled asthma.[43]
- **Bateman *et al*., (2008)** has published a comprehensive workshop report "A Global Strategy for Asthma Management and Prevention" and in that it recommends a change in approach towards asthma management with asthma control rather than asthma severity should be the focus of treatment decisions. It emphasizes the importance of self-guided management, patient care givers partnership in controlling asthma and also the importance of setting goals for the treatment.[1]
- **Helena *et al*., (2008)** conducted a retrospective cross-sectional study by using the health databases in a Canadian province with about 1 million population. In this study the 6 quality-of-care among the asthmatic individuals were assessed. The result obtained from the study was in 18% there was poor symptom control, about 37% of people with poor control were not dispensed with ICS, while 40% received potentially inadequate doses. Hospital admission because of asthma was higher in the age group 6-9 years and females aged 20-44 years. Males and adult in the age group 20-44 years had worst asthma quality care for the examined 4 indicators. It was concluded from the study that suboptimal asthma management can be improved through the increased use of ICS and preventer medications and consensus guidelines recommended a decline on the dependence short acting ß- agonist medications.[37]
- **Mary *et al*., (2008)** conducted a study to evaluate the effects of smoke free law on the emergency department visit rate for asthma. The study showed decrease in emergency department visit rate associated with asthma, because of the smoke free law.[44]
- **Tom *et al*., (2007)** conducted a study to evaluate the effects of the reducing the inhaled steroid dose plus salmeterol, or salmeterol and Tiotropium. It was concluded that there is a role for Tiotropium in controlling severe asthmatic

patients ,they may enable reduction in the dose of inhaled corticosteroids and there causing a decline the adverse effects.[23]

- **Mortimer *et al*., (2006)** performed a case control study using computerised general practice data from The Health Improvement Network, thereby to quantify the relation between adrenal insufficiency and inhaled and oral corticosteroid exposure. From the study it was concluded that the people prescribed with oral or inhaled corticosteroid are at a dose related increased risk for adrenal insufficiency and it also suggested that increased risk for people prescribed with inhaled corticosteroids were because of oral corticosteroid exposure. At the same time it was suggested that inhaled corticosteroid may have effect if they are taken in high doses.[27]
- **Elizabeth *et al*., (2005)** conducted a study with an aim to analyse three shortened versions of ACQs measurement properties and to determine whether the usage of shortened versions will cause any alteration in the results of the clinical trial. From the study it was concluded that this three shortened versions of ACQ can be used for large clinical trials without causing any loss in validity and change in the interpretation.[28]
- **Nicole *et al*., (2005)** conducted a study with objective to evaluate the relation between occupational exposures and severity of asthma. The methodology of the study was to perform an epidemiological study on the genetics and environment of asthma combined with a case control study with a family study of relatives of the asthmatic patients. Finally from the results it was suggested that a strong deleterious role of occupational asthmogens in severe asthmatic patients. And therefore it was concluded that the clinicians should consider occupational exposure in patients with moderate to severe asthma.[29]
- **Eric *et al*., (2004)** conducted a one year prospective trial, Gaining Optimal Asthma control, thereby to compare the efficacy of two recommended controller therapies. That is an increasing dose of fluticasone propionate alone or in combination with long acting $ß_2$ agonist salmeterol to achieve asthma control as defined in the Global Initiative for Asthma/National Institutes of Health guidelines. This study was very significant since till date no studies have done to evaluate the benefits of aiming for achieving a complete, comprehensive and sustained clinical control over asthma in a controlled study

that allows to perform dose escalation which is essential to achieve this. From the study it was concluded that guideline defined asthma control could be achieved in patients with uncontrolled asthma with a combination of salmeterol/fluticasone propionate.[30]

- **Stephen *et al.*, (2003)** conducted a study to investigate the relation between the sensitization and exposure towards the indoor allergens such as dust, mite, cat, and dog in home. Their relation on pulmonary function, exhaled nitric oxide (eNO) and the airway reactivity were studied. The study showed that asthmatic patients when exposed to allergens in home to which they were sensitized will be having a more severe form of the disease.[45]
- **Todd *et al*., (2002)** conducted a survey on adrenal crisis in relation with intake of inhaled corticosteroids and find out the frequency of the side effect in United Kingdom. In this study the questionnaires was sent to all consultant paediatrician and endocrinologists registered with an enquiry that whether they have come across any asthmatic patients with acute adrenal crisis due to the use ICSs. From the study it was found out that the frequency of acute adrenal crisis was greater than what was expected as the majority of the patients were treated with ICSs doses as per the British Guidelines on Asthma Management. And it was found out that fluticasone despite being the least prescribed and most recently introduced ICSs was responsible for 94% of acute adrenal crisis , therefore it was suggested that until adrenal function has been assessed patients receiving high dose ICS should not have this therapy and should be suddenly stopped as this could lead to acute adrenal crisis.[31]
- **Walsh *et al*., (2001)** conducted a study to find out the adverse effects of oral corticosteroids in relation to dose in patients with lung disease. They conducted a two part cross sectional study in which they matched the adverse effects in patients taking oral corticosteroids and control subjects, then associated the adverse effect to corticosteroid dose in the patient group. From the study it was concluded that we should encourage policies to prevent the adverse effects and help rational prescribing of these valuable and most widely used drugs, because the adverse effects were strongly related to the oral cumulative dose of prednisolone taken.[32]

- **Juniper *et al*., (2001)** conducted a study to find out that whether the exclusion of forced expiratory volume in 1 sec (FEV_1) and $ß_2$ –agonist queries from the seven item asthma control questionnaire will cause a variation in the measurement properties and validity of asthma. Finally, it was found that such study results will be only helpful to apply ACQ in clinical trials and epidemiological surveys. They cannot be used for interpretation in the estimation of asthma control in the individual patients, because international guidelines on the management of asthma control in individual patients recognises all three factors (symptoms, airway calibre and rescue $ß_2$ – agonist) are important in the identification and estimation of asthma control since the patients will be showing a wide variation in the in adequacy of asthma control. In large studies we are excluding the measurement of FEV_1 and $ß_2$ – agonist use from the asthma control assessment are that in a large group studies the patient effect of heterogeneity is lost. Thus, it was concluded that asthma symptoms alone can be used to estimate the asthma control in large studies, thereby it will help the investigators to improve the efficiency of data collection and also for those who do not have access to estimate the airway calibre or inhaled $ß_2$ agonist use.[33]
- **Van *et al*., (2000)** conducted a study with an objective to evaluate the fracture risk of patients exposed to oral corticosteroids in a representative general medical practice. The study data's were collected from General Practice Research Database (GPRD) which consist of the computerised medical records of the general practioners (GP). In the conclusion it results indicated an increased risk of fractures during oral corticosteroid treatment with an increased effect on the hip and vertebral body than that on the fore arm. This fracture risks increased shortly after the initiation of oral corticosteroid treatment which was reversed to the baseline after the discontinuation of oral corticosteroids.[8]
- **O'Byrne *et al*., (1999)** conducted a study with an aim to develop and validate Asthma Control Questionnaire (ACQ). From the study it was observed that asthmatic patients who had stable clinic visit, reliability of the ACQ was high. The questionnaire were quite responsive for asthma control. Thus it was concluded that Asthma Control Questionnaire has a strong evaluative and

discriminative properties and therefore it can be used with confidence to measure asthma control.[34]

- **Brian *et al*., (1999)** conducted a study with an objective to appraise the data on systemic adverse of the inhaled corticosteroids. The conclusion obtained from the results was that all inhaled corticosteroids exhibit dose related systemic adverse effects, even if it is lesser when compared to the dose of oral corticosteroids. The meta-analysis has shown that fluticasone propionate exhibits greater dose-related systemic bioactivity when compared other available inhaled corticosteroids at doses specifically above 0.8 mg/d. however we can minimise the long term systemic burden by introducing the lowest possible maintenance dose that is relative to the optimal asthmatic control and quality of life.[35]
- **Juniper *et al*., (1999)** conducted a 9 week observational study of 40 adults with symptomatic asthma for the development and validation of the MiniAQLQ. From the study it was concluded the Mini Asthma Quality of Life Questionnaire showed good measurement properties but were not as strong as that of Original Asthma Quality of Life Questionnaire. So the selection of questionnaire for analysing quality of life depend on the type of study.[38]
- **Susan *et al*., (1999)** conducted a prospective study to examine the prevalence of GERD in asthma patients without reflux symptoms. The study suggested that GERD is present in asthma patients even in the absence of oesophageal symptoms.[46]

3. AIM & OBJECTIVES

AIM:

- To study the usefulness of Tiotropium in poorly controlled asthma patients.

OBJECTIVES:

- To study the beneficial effect of Tiotropium in poorly controlled asthma patients.
- To assess the adverse drug effects of Tiotropium.
- To assess the effect of Tiotropium in Pulmonary Function Test.
- To assess the asthma control and severity in poorly controlled asthma patients using Asthma Control Questionnaire (ACQ) and the beneficial effect of Tiotropium on it.
- To assess the quality of life of poorly controlled asthma patients and the beneficial effect of Tiotropium in the quality of life using Mini Asthma Quality of Life Questionnaire (MiniAQLQ).

4. METHODOLOGY

STUDY DESIGN:

Retrospective and Prospective Observational Study

STUDY SITE:

Kovai Medical Centre and Hospital KMCH; Avinashi Road, Coimbatore – 14

STUDY DURATION: 6 month (February – July)

STUDY POPULATION:

A total of 70 patients were included in this study.

STUDY CRITERIA:

Inclusion Criteria: Any poorly controlled asthmatic patients aged 18 years and above receiving and had received TIOTROPIUM will be included in the study.

Exclusion Criteria: Pregnant women,chronic obstructive pulmonary disorder (COPD)patients, Heart Failure patients will be excluded from the study.

STUDY TOOLS / SOURCE DOCUMENTS:

Data collection: A specially designed data collection form will be utilized to collect patient's demographic details ,past and present medical conditions ,diagnosis,laboratory data and prescribed medications and all other details required for the study.

ASTHMA CONTROL QUESTIONNAIRE (ACQ): To assess the patients control over asthma and to determine severity of asthma,this questionnaire was used. It is a validated questionnaire and it has scoring system. The responses are given on a 7-point scale and the overall score is the mean of the responses (0 = totally controlled, 6

= severely uncontrolled). If a patient has an overall score of above 1.50, his asthma is poorly controlled and requires medical attention.

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (MiniAQLQ): To assess the quality of life of patients. This is a miniature version of a 32-item Asthma Quality of Life Questionnaire(AQLQ). The miniature version also had good measurement properties and was validated. This questionnaire comprises of questions from five different domains. That is symptoms, environment, emotions and activities. It is having 7 point scaling in which a value '1' signifies worst possible quality of life and a value '7' signifies a normal quality of life. Individuals with low MiniAQLQ values have poor quality of life and their asthma will be poorly controlled, they will require medical attention.

STUDY PROTOCOL:

SELECTION OF PATIENT

Patient who has been diagnosed with uncontrolled severe persistent asthma with the following criteria:

Uncontrolled severe persistent asthma, under the use medications (ICS/OCS plus LABA).

Patient having an FEV_1 less than or equal to 60% of predicted in the Pulmonary Function Test (PFT).

Patients who meet with the inclusion criteria are selected.

FIRST VISIT:

In the first visit the patients pulmonary function report is being analysed and their FEV_1 is observed and if there was a severe exacerbation an emergency medications to regulate the symptoms are given for 5-7 days. The patients where asked questions related to their asthma severity and control (ACQ) and also related to their quality of life (MiniAQLQ) and scorings were given correspondingly. After that the patient is prescribed with Tiotropium as a step-up therapy with ICS. LABA is also prescribed as a rescue medication that is to be taken in any case of emergency. The therapy will be given for period of 3 months.

FOLLOW UP:

Review of the patient is done 3 months after the initiation of drug (Tiotropium). In between the patient's condition is being enquired by contacting the patient in phone. The patient is subjected for a PFT and the percentage of FEV_1 is noted. The patients where asked questions related to their asthma severity and control (ACQ) and also related to their quality of life (MiniAQLQ) and scorings were given correspondingly.

STATISTICAL ANALYSIS:

Demographic details, comorbidities, lung function values, adverse effect, FEV_1, ACQ and MiniAQLQ were analyzed by using percentage of the frequency. The student't' test was used to analyze the difference in scores at review after 3 months. A p Value of <0.05 shows significance.

5. TABLES AND GRAPHS

Table 1: Shows the distribution of the gender among the study group (n = 70).

GENDER	FREQUENCY	PERCENTAGE
Male	47	67.1
Female	23	32.9

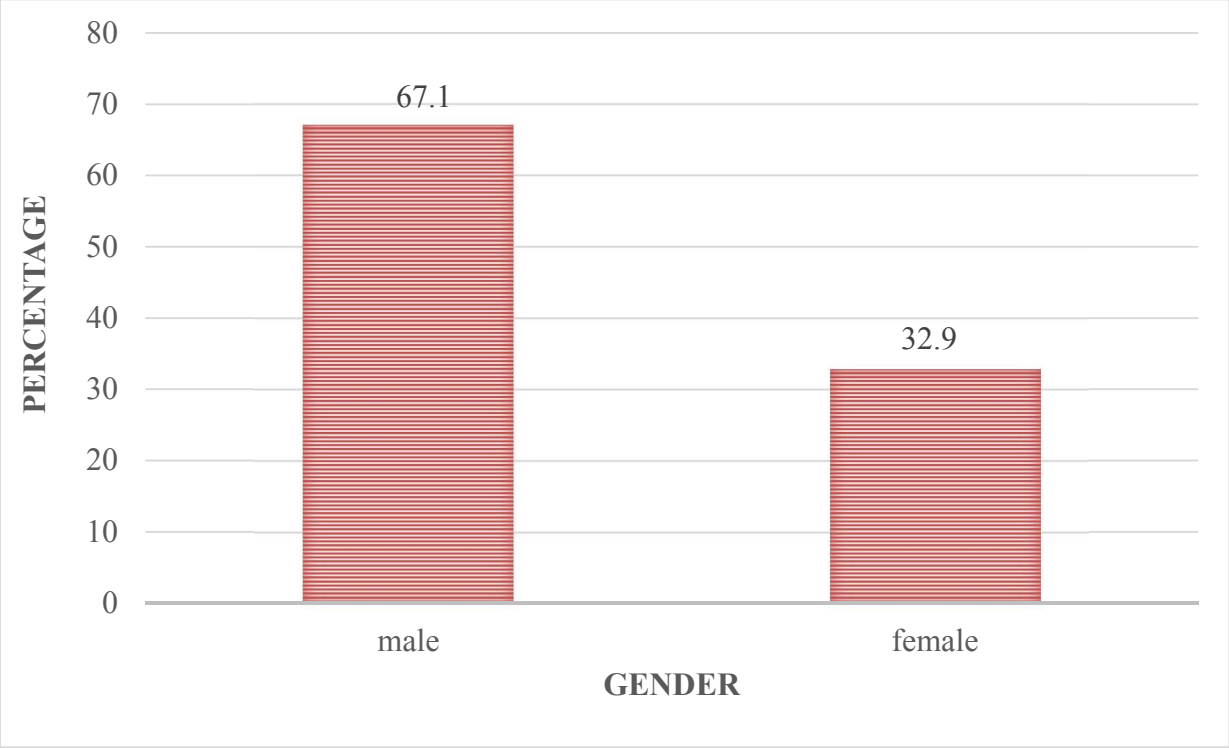


Figure 5: Shows the graphical representation of the distribution of gender among the study population (n = 70).

Table 2: Shows the age distribution in the study population (n = 70)

AGE	FREQUENCY	PERCENTAGE
11-20	1	1.4
21-30	2	2.9
31-40	5	7.1
41-50	12	17.1
51-60	12	17.1
61-70	20	28.6
71-80	16	22.9
81-90	2	2.9

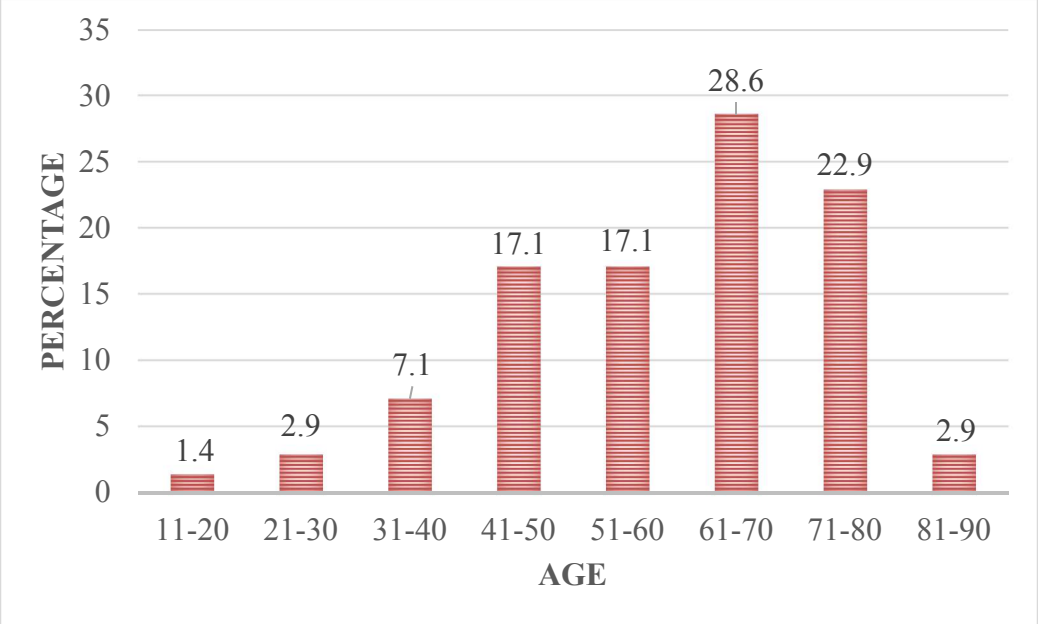


Figure 6: Shows the graphical representation of distribution of age among the study population (n = 70).

Table 3: Shows the occupation of study population (n = 70)

OCCUPATION	FREQUENCY	PERCENTAGE
cotton mills ,textiles, industry, automobile workshop	42	60.0
agriculture, farmer	13	18.6
others	15	21.4

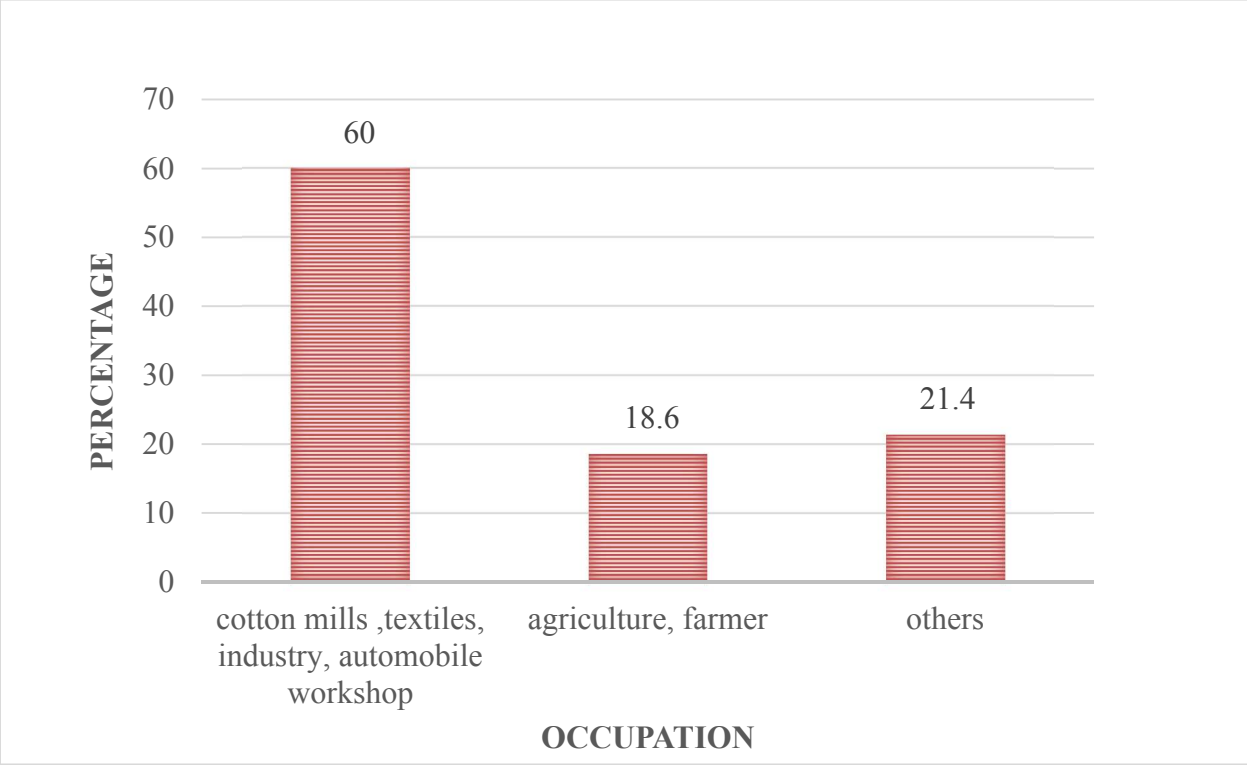


Figure 7: Shows the graphical representation of occupation of the study population and their frequency (n = 70)

Table 4: Shows the smoking status of the study population (n = 70)

SMOKING STATUS	FREQUENCY	PERCENTAGE
past	13	18.6
never	57	81.4

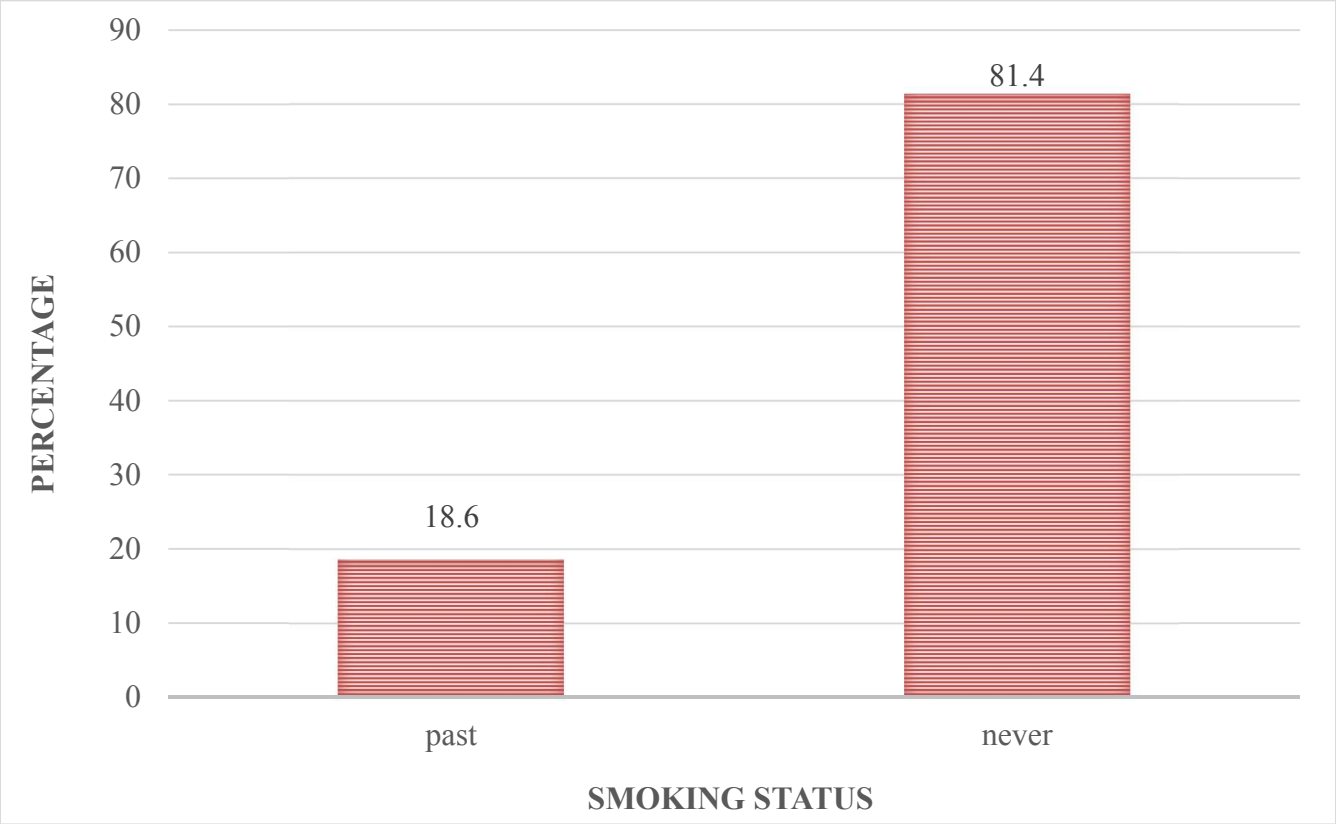


Figure 8: Shows the smoking status of the study population (n = 70)

Table 5: Shows the frequency of comorbidities present in the study population (n = 70)

COMORBIDITY	FREQUENCY	PERCENTAGE
NIL	18	25.7
heart burn	21	30.0
GERD	31	44.3

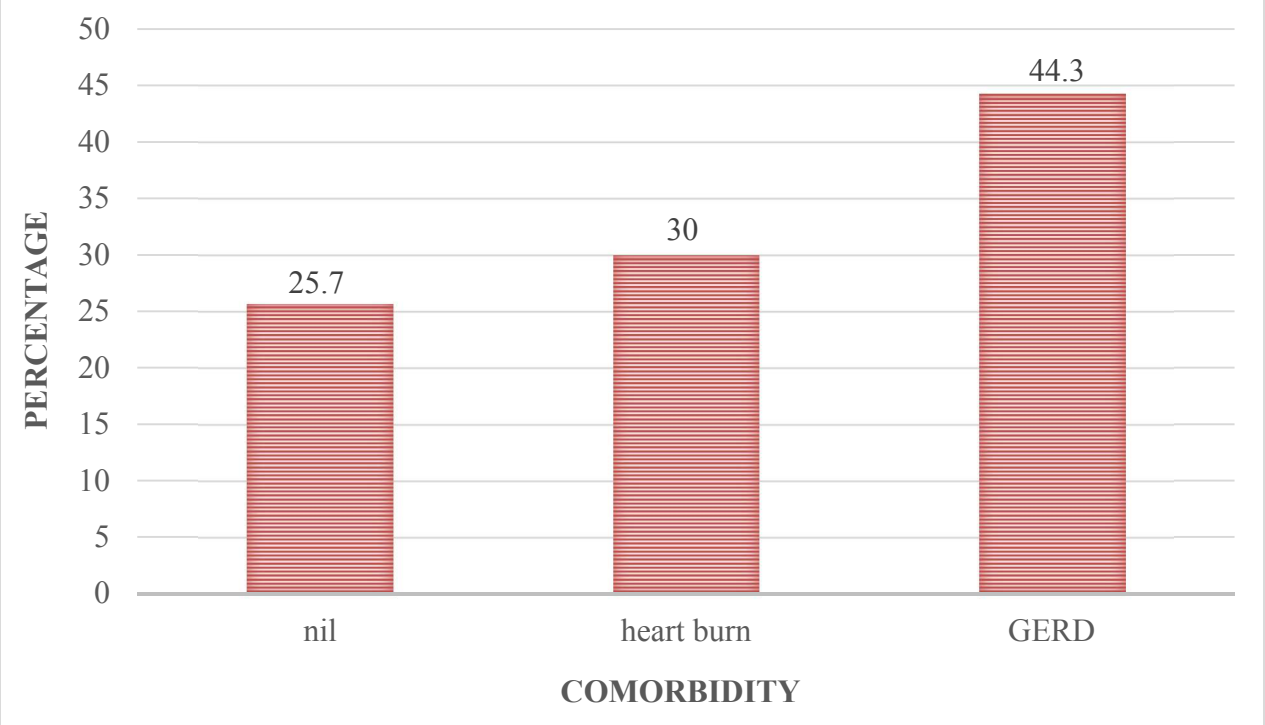


Figure 9: Shows the graphical representation of the frequency of comorbid conditions present in the study population (n = 70)

Table 6: Shows the range of FEV_1 for the study population before the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
69%-60% (4)	3	4.3
59%-50% (5)	52	74.3
<50% predicted (6)	15	21.4

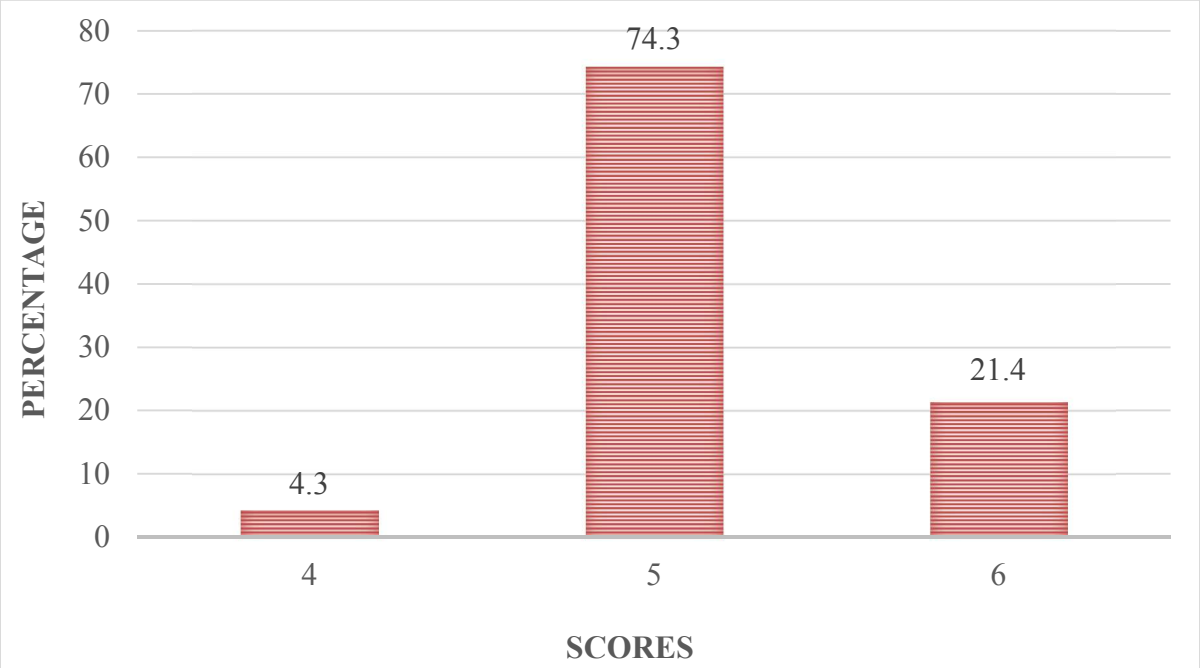


Figure 10: Shows the graphical representation of the FEV_1 of the study population before the initiation of Tiotropium (n= 70)

Table 7: Shows the range of FEV_1 for the study population after the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
79-70% (3)	5	7.1
69-60% (4)	53	75.7
59-50% (5)	8	11.4
<50% PREDICTED (6)	4	5.7

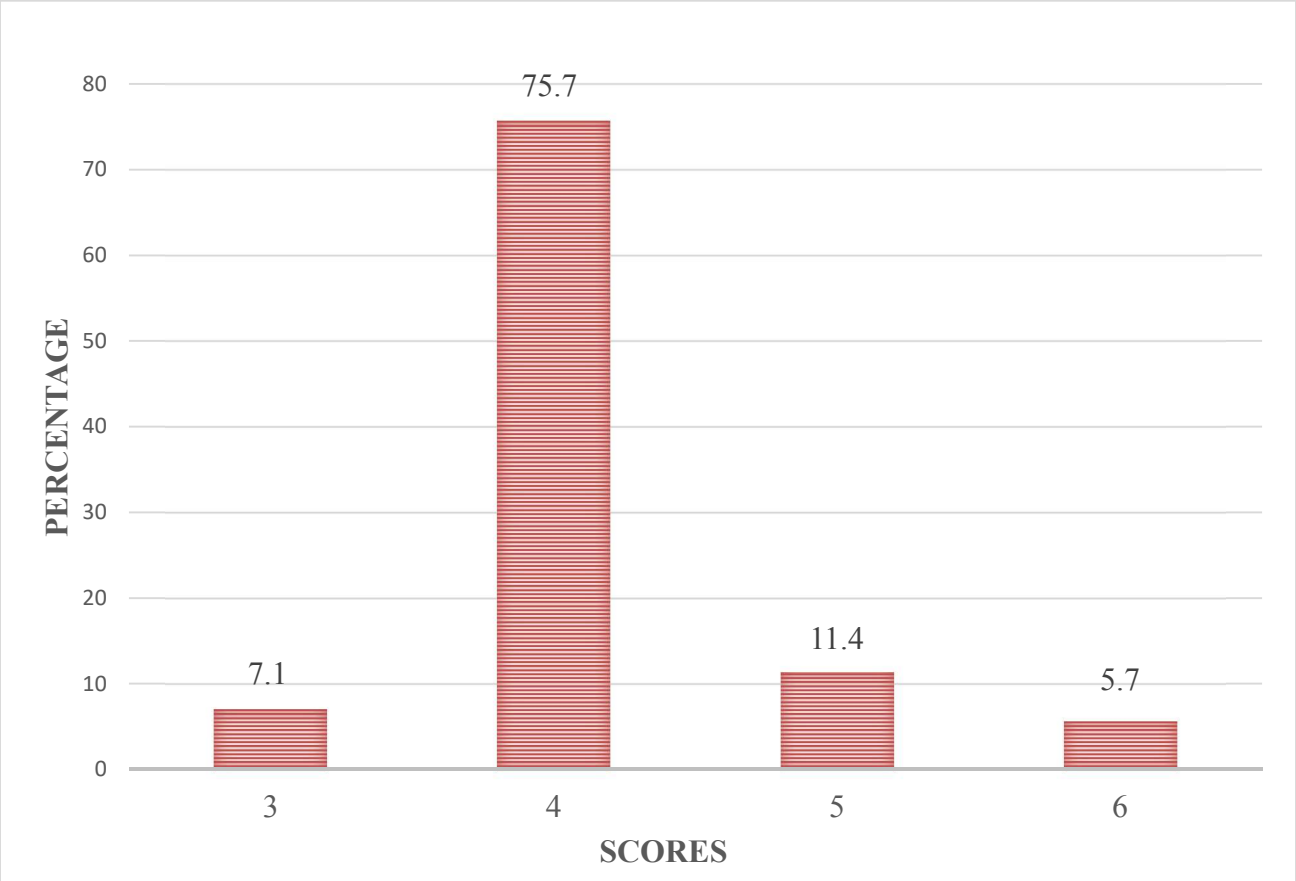


Figure 11: Shows the graphical representation of the FEV_1 of the study population after the initiation of Tiotropium (n= 70)

Table 8: Shows the ACQ mean range among the study population before the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
MODERATELY UNCONTROLLED (3)	2	2.8
DIFFICULT (4)	22	31.4
VERY DIFFICULT (5)	33	47.2
SEVERELY UNCONTROLLED (6)	13	18.6

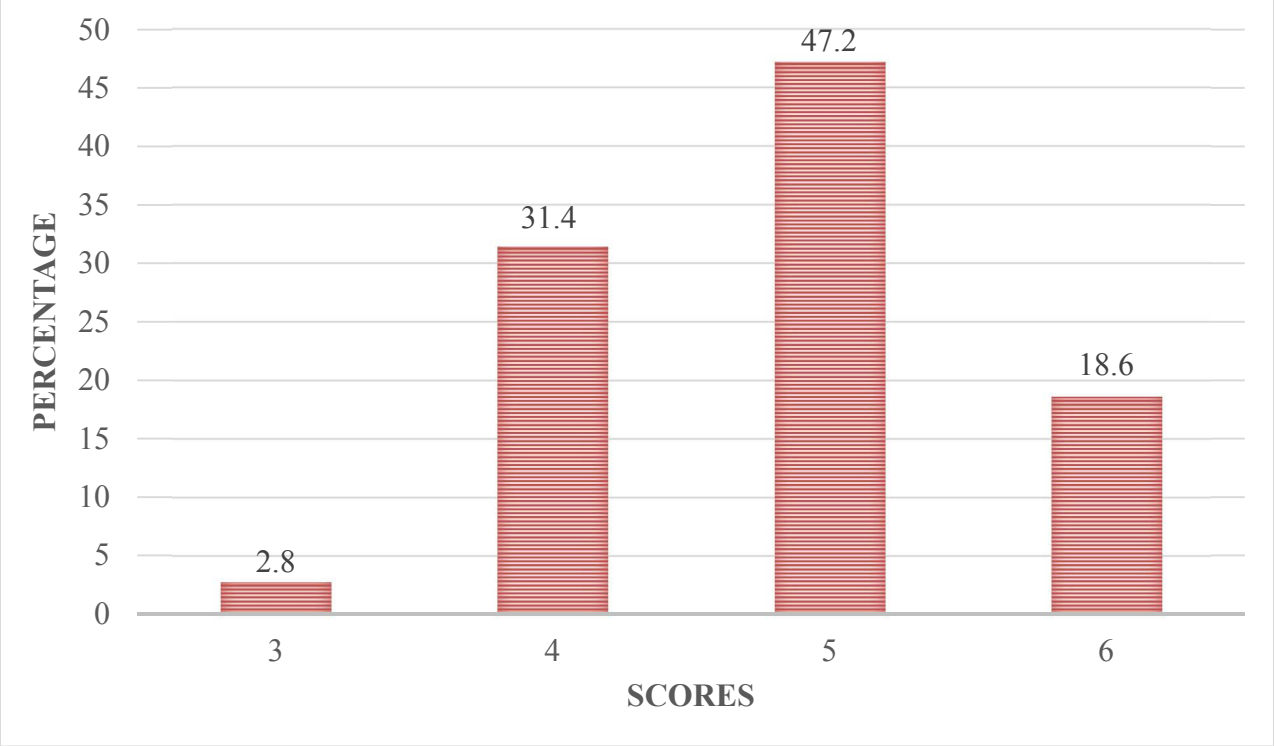


Figure 12: Shows the graphical representation of the ACQ mean among the study population before the initiation of Tiotropium (n= 70).

Table 9: Shows the ACQ mean range among the study population after the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
Very slightly uncontrolled (1)	10	14.3
Slightly uncontrolled (2)	27	38.5
Moderately uncontrolled (3)	28	40
Difficult (4)	4	5.7
Very difficult (5)	1	1.4

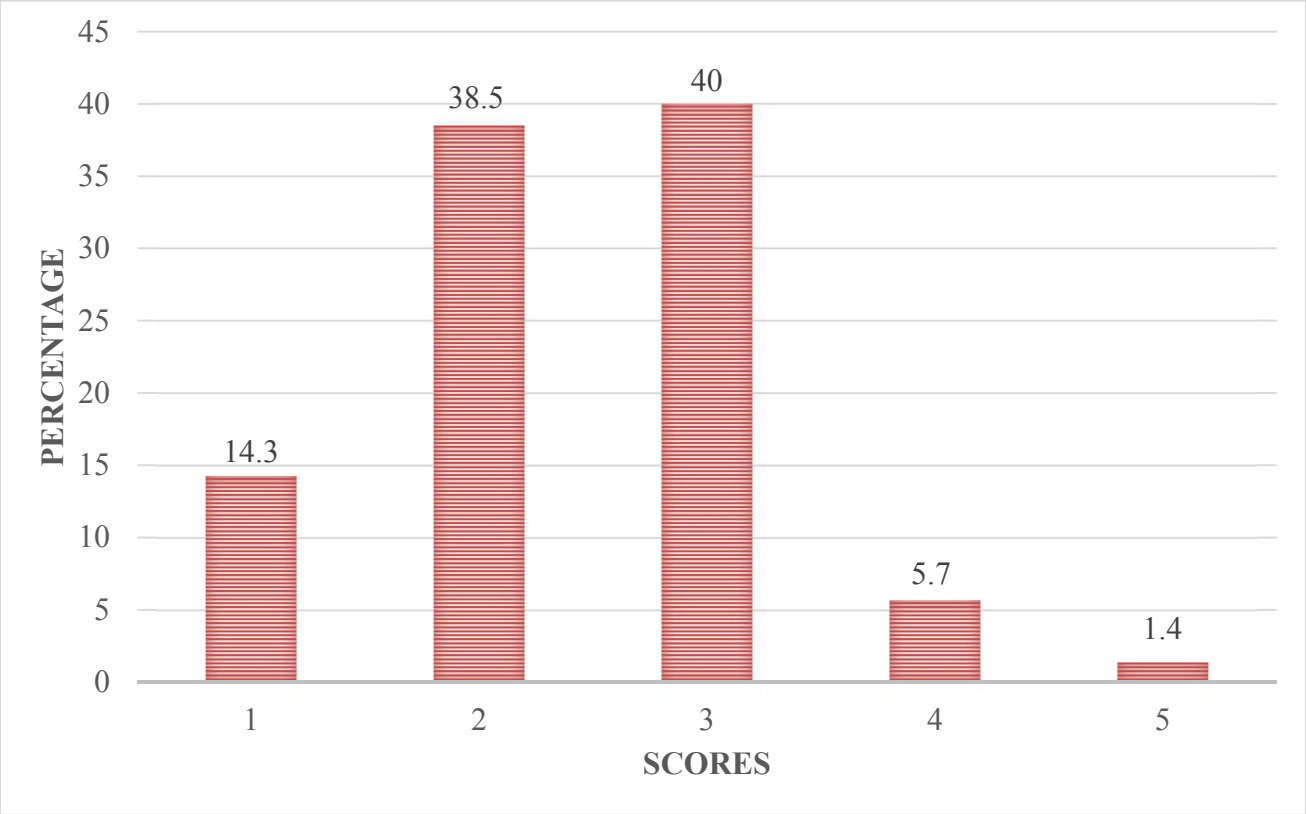


Figure 13: Shows the graphical representation of the ACQ mean among the study population after the initiation of Tiotropium (n= 70)

Table 10: Shows the distribution of mean value, standard deviation, standard error mean and p value for the ACQ: Before & After

GROUP	BEFORE & AFTER	MEAN	STD.DEVIATION	STD.ERROR MEAN	p VALUE
Pair 1	WOKEN UP BY ASTHMA	3.043	1.148	.137	.000
Pair 2	ASTHMA SYMPTOMS	2.971	1.351	.161	.000
Pair 3	ACTIVITY LIMITATION	2.486	1.100	.131	.000
Pair 4	SHORTNESS OF BREATH	2.643	1.036	.124	.000
Pair 5	WHEEZE	2.571	1.124	.134	.000
Pair 6	SHORT ACTING BRONCHODILATOR	1.843	.973	.116	.000
Pair 7	FEV_1	1.014	.525	.063	.000

Table 11: shows the AQLQ mean value among the study population before the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
Very very difficult (1)	5	7.1
Very difficult (2)	30	42.8
Difficult (3)	27	38.5
Moderately difficult (4)	8	11.4

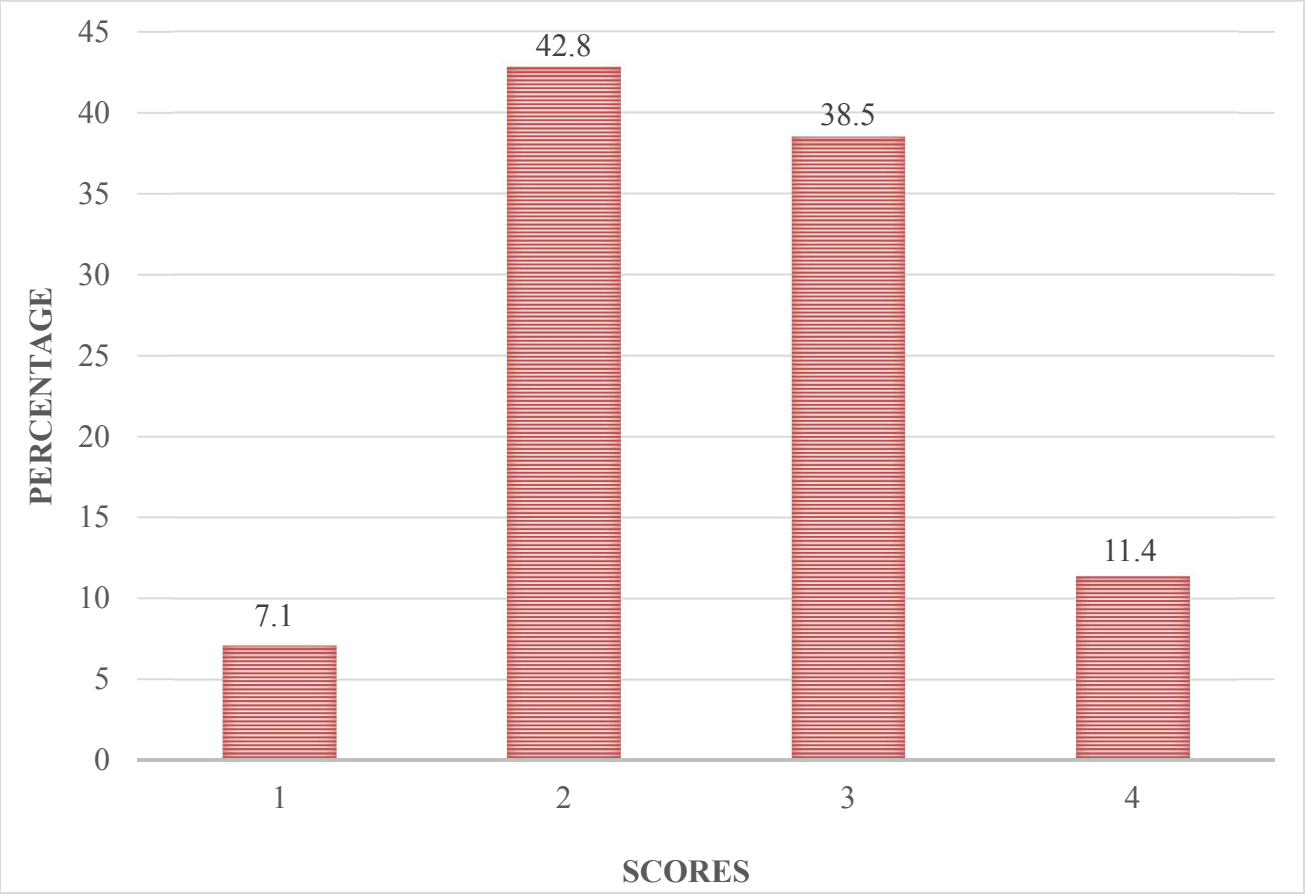


Figure 14: Shows the graphical representation of the AQLQ mean among the study population before the initiation of Tiotropium (n= 70)

Table 12: shows the AQLQ mean value among the study population after the initiation of Tiotropium, scores are depicted in the bracket (n= 70)

SCORES	FREQUENCY	PERCENTAGE
Difficult (3)	3	4.2
Moderately difficult (4)	16	22.9
Slightly difficult (5)	32	45.7
Very slightly difficult(6)	18	25.7
No problem(7)	1	1.4

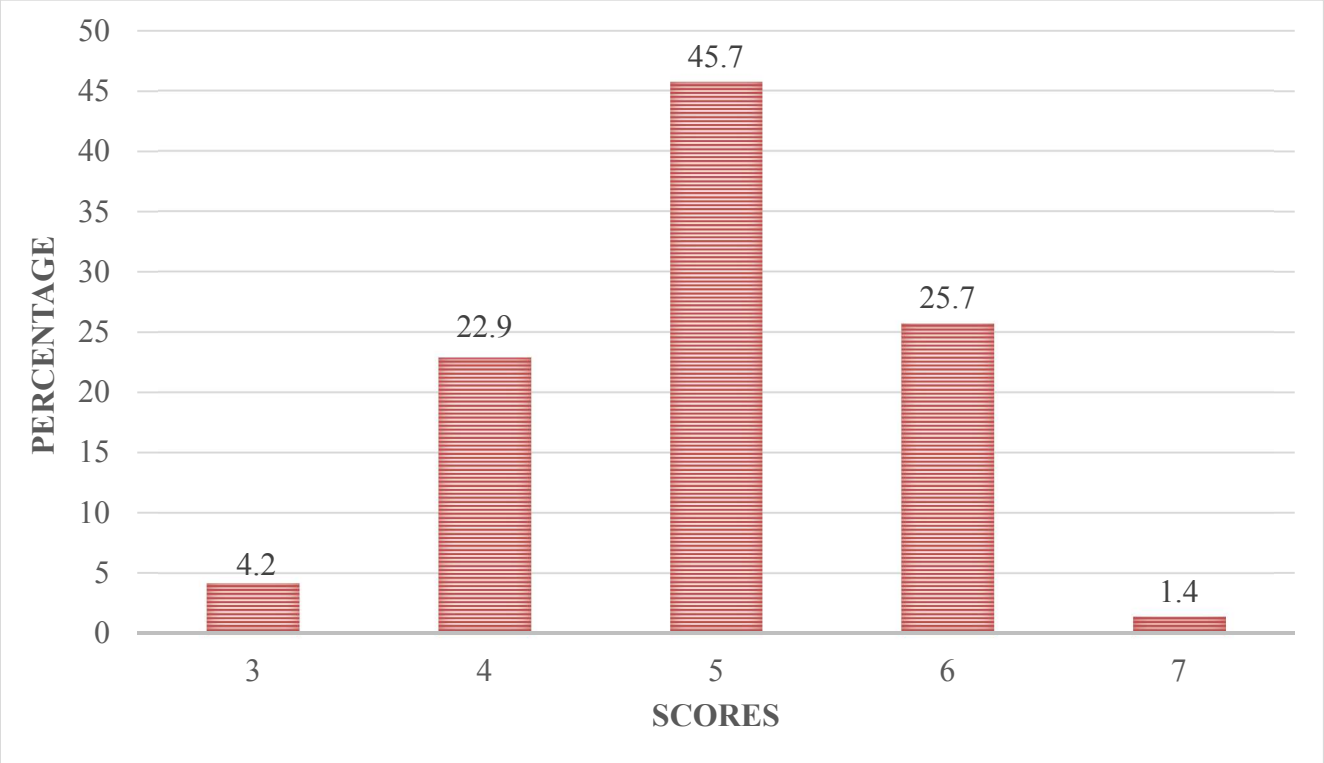


Figure15: Shows the graphical representation of the AQLQ mean among the study population after the initiation of Tiotropium (n= 70)

Table 13: Shows the distribution of mean value, standard deviation, standard error mean and p value in AQLQ: Before & After

Domains	Group	Before & After	MEAN	Std. Deviation	Std. Error Mean	p Value
SYMPTOMS	PAIR -1	SHORT OF BREATH	2.500	1.052	.125	.000
	PAIR -4	COUGHING	2.914	1.239	.147	.000
	PAIR -6	CHEST TIGHTNESS	2.957	.885	.105	.000
	PAIR -8	GOOD NIGHT SLEEP	3.100	.943	.112	.000
	PAIR -10	WHEEZE	2.729	1.041	.124	.000
ENVIRONMENTAL	PAIR -2	DUST	2.329	1.204	.143	.000
	PAIR -7	CIGARETTE SMOKE	2.314	1.178	.140	.000
	PAIR -11	AIR POLLUTION	2.614	1.125	.134	.000
EMOTIONAL	PAIR -3	FRUSTRATED	2.471	1.065	.126	.000
	PAIR -5	ASTHMA MEDICATION	2.200	1.440	.171	.000
	PAIR -9	CONCERNED	2.671	1.306	.155	.000
ACTIVITY LIMITATION	PAIR -12	STRENOUS ACTIVITIES	1.186	.946	.112	.000
	PAIR -13	MODERATE ACTIVITIES	2.229	.848	.101	.000
	PAIR -14	SOCIAL ACTIVITIES	2.514	1.156	.137	.000
	PAIR -15	WORK-RELATED ACTIVITIES	2.557	.966	.115	.000

Table 14: Shows the distribution of mean value, standard deviation, standard error mean and p value in ACQ and AQLQ: Before & After

Pairs	Before & After	Mean	Std. Deviation	Std Error Mean	p Value
Pair 1	TOTAL MEAN ACQ	2.414	.876	.105	.000
Pair 2	TOTAL MEAN AQLQ	2.386	.839	.100	.000

Table 15: Shows the frequency of adverse effect occurred in the study population (n = 70)

Adverse effect	Frequency	Percentage
yes	5	7.1
no	65	92.9

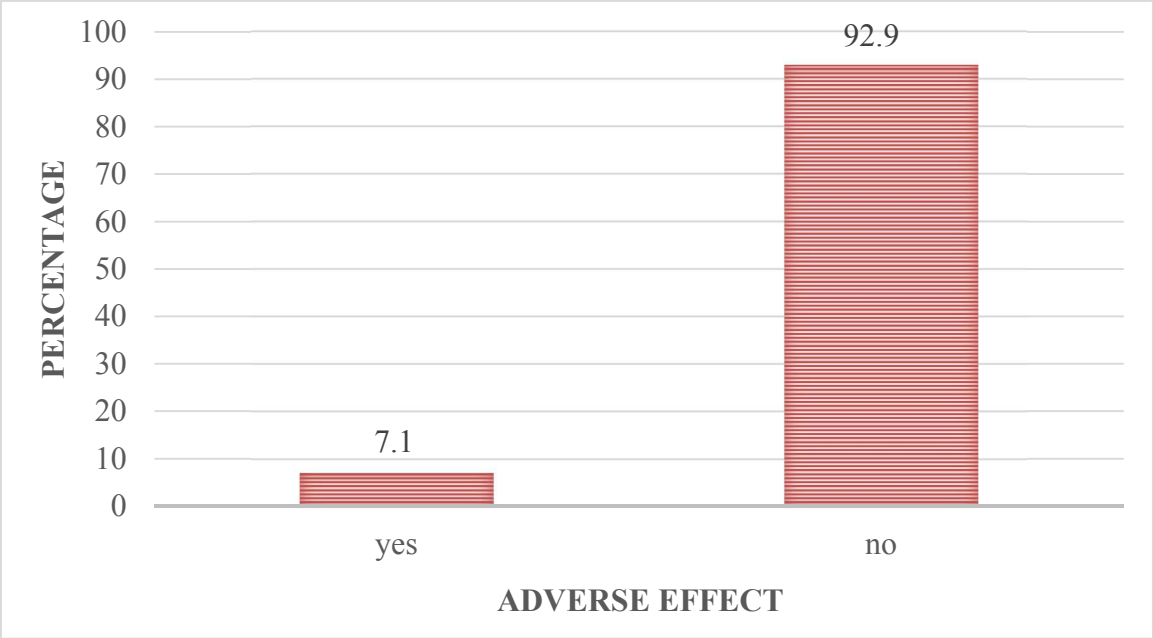


Figure 16: Shows the graphical representation of the frequency of adverse effect occurrence in the study population (n = 70)

6. RESULTS

A total of 70 patients with poorly controlled asthma were analyzed for the study. Among them 47 (67.1%) were males and 23 (32.9%) were females. This is depicted in table 1 and figure 5.

The total number of patients (n=70) were categorized into different age groups. Lowest age being 18 and highest age group is 81-90. The patients falling in each category of age group is depicted in the table 3 and figure 6 and from the results obtained through the study it was analyzed that patients in the age group 61-70 were affected more and was diagnosed as poorly controlled asthmatic patients, that is 20 (28.6%) of the total patients. This was followed by the age group 71-80, which contributed about 16 (22.9%) of the total number of patients. Individuals less than 40 years of age was least diagnosed as poorly controlled asthmatic patients. Elderly people were found to be more affected by uncontrolled asthma and was diagnosed as poorly controlled asthmatic patient.

The effect of occupation on the individual's disease status was assessed during the study, it is depicted in table 3 and figure 7 and it was found that the majority of patients who had poorly controlled asthma was having a continuous exposure towards allergens. They contributed about 42 (60.0%) out of 70 patients. Followed by farmers who were exposed to mites and pollens 13 (18.6%) out of 70 patients, both of this category were exposed towards their occupational allergens and they were advised to change their occupation if possible and if not to use mask and other preventive measure and there by avoid the exposure towards the allergens to maximum possible. Other professionals contributed 15 (21.4%) out of 70.

Smoking always had a negative effect over the respiratory system. Chain smokers mostly developed chronic obstructive pulmonary disorder (COPD). Sometimes it can also have an effect on asthmatic patients and can be the reason for their poor adherence. Therefore it was also analyzed during the study, it is depicted in table 4 and figure 8 and from the observations it was found that the majority of the diagnosed poorly controlled asthma patient were not because of smoking. Majority of patients were not having a habit of smoking. A total of 57 (81.4%) patients were nonsmoker's only. 12 (18.6%) patients had a past history of smoking and it was expected to be the reason for their poor adherence and poor control over asthma.

Since all patients were diagnosed for asthma long before and were under asthma medication. The comorbidity present in patients were also assessed during the study, it is depicted in table 5 and figure 9 and it was found that 31 out of 70 (44.3%) patients had gastro oesophageal reflux disorder (GERD) and 21(30.0%) out of the 70 had heart burn, which is a symptom of GERD but they were not having confirmed diagnosis of GERD. Only 18(25.7%) was found to be absent from any of the comorbities. The presence of comorbidity affected the quality of life and they were supposed to take medications for the respective comorbidities.

Forced expiratory volume (FEV_1) is an important marker in categorizing asthma based on severity, the patients whose FEV_1 was 60% or less than that, in spite of drugs intake (ICS/OCS+ LABA) was considered as having poorly controlled asthma as per the guidelines. The patients with poorly controlled asthma was selected for the study based on this criteria and from the study it was analyzed that 52 (74.3%) patients had an FEV_1 ranging between 59%-50%. And 15 patients had FEV_1 falling less than 50% while 3 of them falls in the category 60-69% (4.3%) during the first visit. It is depicted in table 6 and figure 10.

In the second review it was observed that after the administration of Tiotropium bromide as a step-up therapy along with corticosteroids ,53 (75.7%) patients showed improvement in their pulmonary function test (PFT) and 53 (75.7%) patients improved and fallen in range of 69-60%, followed by 8(11.4%) fallen in the range of 59-50%,followed by 5(7.1%) has been in the category of 79-70% while 4 patients was in the category of >50% of predicted FEV_1 values. It is depicted in the table 7 and figure 11.
Thus it showed significant improvement in the FEV_1 value from first visit to the second visit which was after 3 months.

On assessing the Asthma Control Questionnaire (ACQ) mean during the first visit it was found that 33 (47.2%) out of 70 have very difficult severely uncontrolled asthma, followed by 22 (31.4%) had difficultly uncontrolled asthma, 13(18.6%) out of 70 patients had severely uncontrolled asthma. Table 8 and figure 12 shows this.

It was compared with the review which was 3 months after the initiation of Tiotropium bromide along with corticosteroids as a step-up therapy. And in the review it was observed that only a single (1.4%) patient was with very difficult uncontrolled asthma, while 28 (40%)

patients came in the category of moderately uncontrolled asthma and 27 (38.5%) came in the category of slightly uncontrolled asthma while 10 (14.3%) out of 70 has improved towards very slightly uncontrolled asthma. The number of patients with difficultly uncontrolled severe asthma was reduced to 4 (5.7%). Table 9 and figure 13 shows this.

There found to be significant improvement over the asthma severity and control over asthma in patients.

Asthma quality life was also assessed for all the patients. while assessing the Asthma Quality of Life Questionnaire (AQLQ) total mean of patient before starting Tiotropium bromide it was observed that 30 (42.8%) out of 70 had a very poor quality of life, followed by 27 (38.5%) had difficultly poor quality of life.8(11.4%) had moderately difficult quality of life and 5 (7.1%) had worst possible quality of life. This is depicted in the table 11 and figure 14.

When it was compared with the AQLQ total mean in the review which was 3 months after initiation of Tiotropium bromide, 32(45.7%) improved towards slightly difficult quality of life, followed by 18(25.7%) improved towards very slightly difficult quality of life, followed by 16(22.9%) has improved towards moderately difficult quality of life, the number of individuals in the difficultly poor quality of life has reduced to 3 (4.2%). Single patient has shown improvement and he was not having any problem with his quality of life. It is depicted in table 12 and figure 15.

The AQLQ analysis also showed significant improvement in patients when compared the pre and post data's. This showed the usefulness of Tiotropium in patients with poorly controlled asthma as a step-up therapy was also analyzed during the study.

It is depicted in table 15 and figure 16. It is observed that only 5(7.1%) out of 70 patients developed dry mouth and the remaining 65 (92.9%) did not report any adverse effect or difficulty due to the intake of Tiotropium bromide.

8. DISCUSSION

In this study we present the data that shows the usefulness of Tiotropium bromide in poorly controlled asthma by showing its positive effect on spirometry performed. This study also provides evidence for the improvement in the asthma control by using the Asthma Control Questionnaire (ACQ) and the improvement in the quality of life of patient using the Asthma Quality of Life Questionnaire (AQLQ). The occurrence of any adverse effect due to the initiation of Tiotropium bromide in patients is also monitored.

Out of 70 poorly controlled asthmatic patient included in the study, 47 (67.1%) were males and 23 (32.9%) were females.

Stephen P. Peters[26] in his study which is analyzing the efficiency of Tiotropium bromide as a step- up therapy for adults with uncontrolled asthma, 32.9% were males and 67.1% were females. Elizabeth F. Juniper[28] conducted a study and in their study 45.1% was males and 54.89% was females who were affected by severe persistent asthma. Huib A. M. Kerstjens[14] conducted a study to analyze whether Tiotropium improves ling function in patients with severe uncontrolled asthma and in the study it says that 54.2% were females and 45.8% males were affected with severe uncontrolled asthma. In this epidemiology, since there were more men going for work in textiles and all, and so they were having more poorly controlled asthma and exacerbations. Therefore in this study more number of patients were males.

In this study more number of patients with poorly controlled asthma was observed in age group 40-80.Stephen P. Peters[26] in his study the mean age was found to be 42.2 ± 12.3.Elizabeth F. Juniper[28] conducted a study and in their study the mean age was found to be 44.7.Eric D. Bateman[13] conducted a study and in that the mean age was found to be 53.5 ± 12.6. Huib A. M. Kerstjens[14] conducted a study and in that the mean age was found to be 54.8 ± 11.7. Pierluigi Paggiaro[18] conducted a study and in that the mean age was found to be 42.9 ± 13.0. Ke Wang*l*[19] conducted a study and the mean age was 36.4 ± 5.93.

In this study 78.6% of patients were having poorly controlled asthma because of their exposure towards occupational asthmogens (60.0% were exposed to the cotton dust, textiles and other industrial allergens, while 18.6% were exposed to allergens from farms and agriculture). Nicole Le Moual[29] conducted a study on asthma severity and exposure to

occupational asthmogens and in their study they found that 61.2% of people were suffering from uncontrolled severe persistent asthma because of continuous exposure towards occupational asthmogens. Studies conducted on occupational asthma and the asthmogens[45, 47], says that trigger factors to severe asthma include occupational agents.

In this study the smoking status of the patients were analyzed and it was found that 81.4% of patients were not having a habit of smoking, while 18.6% patients were having a past history of smoking. And from our study we observed that a habit of smoking can lead to poor control over asthma and poor compliance towards the medication and it can also cause worsening of the asthma status of the patient. But in this study not the majority of patients were having poorly controlled severe persistent asthma because of the smoking status, there reasons are different. But for 18.6% of people who had a past history of smoking, it paved the way towards poor control over asthma even under medications. Eric D. Bateman[13] conducted a study, in this 69.5% patients never smoked, 30.5% were ex-smokers. No one was having a habit of smoking at present. In this study they mention that smoking is having a negative impact in attaining appropriate asthma control. In order to attain an optimum asthma control smoking should be stopped. Dejan Radovanovic[12] conducted a study in this it is specified that cigarette smoke is one among the factors that can induce airway inflammation and there by chronic airway inflammation can lead to airway remodelling also. Huib A. M. Kerstjens[14] conducted a study, in this 68.2% of patients with poorly controlled asthma never smoked while 31.8% patients were ex-smokers. Pierluigi Paggiaro[18] conducted a study and in this 78.7% individuals never smoked while 21.3% individuals were ex-smokers. This study shows that Tiotropium improved the mean lung function parameter responses from baseline to week 12 for both non-smokers, ex-smokers.

In this study the patients without comorbidity was only 18 (25.7%) while the majority was having comorbidity 52 (74.3%). In which 31 (44.3%) patients were having Gastro Oesophageal Reflux Disorder (GERD), while 21 (30.0%) patients were having heart burn, which shows patients symptomatic for GERD. Susan. M . Harding[46] conducted a study and in the study it says that 62% of asthma patients were having GERD as a comorbidity. The relationship between the worsening of the disease in severe asthmatic patients due to GERD has been explained in this study convincingly. Francois Vermeulen[24] conducted a study and in this study it says that 34.0% patients with uncontrolled asthma were having GERD as a

comorbid condition. Carla Bisaccioni[43] conducted a study and evaluated the frequency of comorbidities. And in this study it states that patients with GERD symptoms were reported about 70.6% (173), though patients confirmed with the GERD diagnosis was 58 (33.6%) patients.

In my study severe uncontrolled asthma patients were selected based on their FEV_1 value as the major criteria, which was mentioned in the GINA guidelines to identify the severe uncontrolled asthma. As per the guidelines the patients who have an FEV_1 value less than or equal to 60% of predicted, while already under medications as per in the guidelines are considered as patients with uncontrolled severe persistent asthma patients. In my study all such patients were selected that is patients who had an FEV_1 equal to or less than 60% of predicted. Majority of patients that is 74.3% (52) were falling under the range of 59-50%, this range is given a score 5 in the asthma control questionnaire which out of 6 and it indicates a very difficultly uncontrolled persistent asthma. 21.4% (15) patients were in the category of FEV_1 less than 50% predicted which was given a score of 6 as per the asthma control questionnaire scoring scale and it indicated severely uncontrolled persistent asthma for such patients. 4.3% (3) of patients had a 60% of predicted FEV_1, and this was given a score of 4 as per the asthma control questionnaire which indicated difficultly uncontrolled persistent asthma.

After the initiation of Tiotropium bromide (18µg) as once daily dose taken in the afternoon for 12 weeks, spirometry was performed and the FEV_1 was analyzed. All the patients had improvement in their control over asthma and the severity of the disease, majority had a significant improvement while a few had only a slight improvement. But there was difference in all the patients' disease status after the initiation of the therapy. Majority of patient in the post examination 75.7% (53) had fallen in the category of 69-60% which was given a score 4 as per the asthma control questionnaire which indicated difficultly uncontrolled asthma. This showed a significant improvement in the FEV_1 value from pre towards the post on initiation of Tiotropium bromide. 11.4% (8) were in the category 59-50% which was given a score 5 as per the asthma control questionnaire scoring which indicated a very difficultly uncontrolled persistent asthma. 7.1% (5) patients were having a FEV_1 in the range of 79-70% which was given a score 3 as per the asthma control questionnaire scoring which indicated moderately uncontrolled persistent asthma. 5.7% (4) had a FEV_1 less than 50% of predicted which was given a score of 6 as per the asthma control questionnaire which indicated severely uncontrolled

asthma patients. The post analysis of patients showed improvement after a 12 week therapy of Tiotropium bromide, individuals were having response towards the drug.

Huib A. M. Kerstjens[14] conducted a study in this, it states that the addition of once daily dose of Tiotropium as a maintenance therapy along with ICS and LABA in patients with severe uncontrolled asthma significantly improves lung function. Tiotropium was superior when compared with all other spirometric assessments. Pierluigi Paggiaro[18] conducted a study in this, it states that Tiotropium is an efficacious bronchodialator when added to low to medium dose ICS**.** Ke Wang[19] conducted a study,in this study Tiotropium bromide a dose of 18µg was administered to one of the groups as a once daily dose ,for a period of 12 weeks and was found from the study that Tiotropium in combination with ICS plus LABA was efficient to provide an optimum control over asthma equivalent to that of doubling the dose of ICS plus LABA without causing any adverse effects. So it was found to be the best second line treatment for patients with uncontrolled moderate asthma patients. Stephen P. Peters[26] in his study in this it was found that Tiotropium when added to an ICS it improved the lung function (FEV_1) in patients with inadequately controlled asthma. And the effect produced by Tiotropium was superior when compared with doubling the dose of ICS and was equivalent to the effect of LABA.

In my study to identify well and not well controlled asthma and to determine the severity of asthma the asthma control questionnaire (ACQ) is being used. The asthma control questionnaire (ACQ) consist of 7 questions. This questionnaire is short one, which comprises of questions related to symptoms which is considered to be the most important in assessing the asthma sufficiency of asthma control. Questions related to the use of short acting $ß_2$ agonist as a rescue medication. Question on the pulmonary function test of the patient. And ACQ has scoring system in 7- point scale, 0 is indicative of totally controlled while 6 is indicative of severely uncontrolled.

In my study majority of patients were having poor control over asthma and they were suffering because of the disease in the first visit. That is majority of patients was found to have very difficultly uncontrolled asthma, they were having a score 5 as per the ACQ, 47.2% (33) patients were in this category. 31.4% (22) patients were having a score 4 which indicated difficultly uncontrolled asthma as per the ACQ. 18.6% (13) were having a score 6 through

ACQ which indicated a severely uncontrolled persistent asthma. 2.8% (2) were having a score 3 through ACQ which indicated moderately uncontrolled asthma.

After the initiation of Tiotropium bromide (18µg) as once daily dose for a duration of 12 weeks and then the patients were assessed using the ACQ and given scoring. 40% (28) of patients were given a score 3 which indicated moderately uncontrolled asthma. 38.5% (27) were given a score 2 through ACQ which indicated slightly uncontrolled asthma. 14.3% (10) were given a score 1 through ACQ which indicated very slightly uncontrolled asthma. 5.7% (4) were given a score 4 through ACQ which indicated difficultly uncontrolled asthma. 1.4% (1) was given a score 5 through ACQ which indicated very difficultly uncontrolled asthma. None of the patients has fallen in the category of severely uncontrolled asthma after the initiation of therapy, there was improvement in the total mean score of ACQ for each patient, which indicated an improvement in their symptoms, use of rescue medication and the lung function. This also showed that patients were having a good response towards the drug.

Stephen P. Peters[26] in his study which is analyzing the efficiency of Tiotropium bromide as a step- up therapy for adults with uncontrolled asthma, in this study it is showed that the addition of Tiotropium to an ICS showed improvement in the ACQ score of patient which had significance (p value <0.001). This study also stated that the Tiotropium as step-up therapy with ICS had a superior outcome than doubling the dose of ICS. Ke Wang[19] conducted a study to evaluate the best second line treatment for uncontrolled moderate asthma patients maintenance therapy whose asthma is not fully controlled, mild to moderate asthma. In this study Tiotropium bromide a dose of 18µg was administered to one of the groups as a once daily dose,for a period of 12 weeks and was found from the study that Tiotropium in combination with ICS plus LABA showed significant improvements in symptom control, FEV_1,reduce the risk of acute exacerbation and thereby has shown a significant improvement in the ACQ score after the initiation of drug. Pierluigi Paggiaro[18] conducted a study to analyze the effect of Tiotropium in asthmatic patients despite the use of low to medium dose of inhaled corticosteroids and in the study it stated that there was an improvement in the ACQ score from baseline towards a period after 12 weeks treatment with the drug. That is from uncontrolled to partially uncontrolled with a dose of 5µg and 2.5µg of Tiotropium. This study provided that Tiotropium lead to an improved lung function and control in asthma and states that it is an effective bronchodialator. Jean Bousquet[48] conducted a study to determine a cut- point on the

ACQ there by to differentiate between well controlled and not well controlled asthma, using ACQ. In the study it is said that if a patient have an ACQ score of 1.50 or greater, there is an 88% chance that his or her asthma is not well controlled. A change in ACQ score by 0.5 shall be considered clinically important.

MiniAQLQ was being used in my study and there the quality of life of patient with severe uncontrolled asthma were measured and their difference in the quality of life after the initiation of therapy was analyzed and assessed. The original AQLQ was a 32-item questionnaire which consisted of four domains: symptoms (12 items), activity limitation (11 item), emotional function (5 item) and environmental stimuli (4 items), since it was a pretty difficult to assess all this in large surveys their arised the need for the development of a shorter version of this but which was called as MiniAQLQ, which would construct measure the same construct and meet the same specification as that of the original AQLQ. MiniAQLQ also consisted of the four domains: symptoms (5 items), activity limitation (4 items), emotional function (3 items) and environmental stimuli (3 items). MiniAQLQ had 7 point scoring scale, in which 1- indicated worst possible quality of life and 7- indicated a normal quality of life (no problem). During the initial visit majority 42.8% (30) of the patients had score 2 as per the AQLQ which was indicative of a very difficult quality of life. 38.5% (27) patients had a score of 3 as per the AQLQ which indicated a difficult quality of life. 11.4% (8) had a score 4 as per the AQLQ which indicated moderately difficult quality of life. 7.1% (5) had a score 1 as per the AQLQ which indicated a worst possible quality of life.

After the initiation of Tiotropium bromide 18µg as once daily dose for a period of 12 week the AQLQ was measured and in that the majority of patients 45.7% (32) had a score 5 which indicated slightly difficult quality of life as per AQLQ. 25.7% (18) had a score 6 as per AQLQ which indicated very slightly difficult quality of life. 22.9% (16) had a score 4 as per the AQLQ which indicated moderately difficult quality of life. 4.2% (3) had a score 3 as per the AQLQ which indicated difficult quality of life. 1.4% (1) patient had a score 7 as per the AQLQ which indicated normal quality of life (no problem). There showed an improvement in the quality of life of patient within a 12 weeks duration. None of the patients were in the category of worst possible and very difficult quality of life (1 and 2 respectively). The quality of life of patients showed improvement with the initiation of therapy.

Stephen P. Peters[26] in his study which is *analyzing* the efficiency of Tiotropium bromide as a step- up therapy for adults with uncontrolled asthma, in this study it is showed that the addition of Tiotropium to an ICS showed improvement in the MiniAQLQ of the patients and showed significance (p value = 0.01). Stacy J. Chin[49] conducted a commentary on 5 clinical trials in adults on the effect of Tiotropium for the treatment of asthma. In this study it states administration of Tiotropium lead to improvement in the quality of life. Huib A. M. Kerstjens[14] conducted a study to analyze whether Tiotropium improves lung function in patients with severe uncontrolled asthma. In this study it is stated that the MiniAQLQ scores over the entire treatment period of 0.1 points for both the active treatments when compared with placebo. There is no significant improvement in the quality of life. The dose of Tiotropium was 5 and 10µg respectively for a period of 8 weeks.

On statistical analysis of the asthma control questionnaire (ACQ) for all the 7 asthma control questions pre and post, significance was observed (p=.000) with respect to a standard deviation ± mean. Pair 1 (woken up by asthma) had 1.148 ± 3.043, p value = .000, Pair 2 (asthma symptoms) had 1.351 ± 2.971, p value = .000, Pair 3 (activity limitation) had 1.100 ± 2.486, p value = .000. Pair 4 (shortness of breath) had 1.036 ± 2.643, p value = .000. Pair 5 (wheeze) had 1.124 ± 2.571, p value = .000. Pair 6 (short acting bronchodilator) had .973 ± 1.843, p value = .000. Pair 7 (FEV_1) had .525 ± 1.014, p value =.000

On the statistical analysis of the Mini asthma quality of life questionnaire (MiniAQLQ) when compared the pre and the post quality of life significance was obtained with respect to standard deviation ± mean for the 15 questions which consisted of four domains.

Domain -1(symptoms): pair 1(short of breath) had 1.052 ± 2.500, p value .000. Pair 4 (coughing) had 1.239 ± 2.914, p value = .000. Pair 6 (chest tightness) had .885 ± 2.957 .p value = .000. Pair 8 (good night sleep), had .943 ± 3.100, p value = .000. Pair 10 (wheeze) 1.041 ± 2.729, p value = .000.

Domain -2 (environmental): Pair 2 (dust) had 1.204 ± 2.329, p value = .000. Pair 7 (cigarette smoke) had 1.178 ± 2.314, p value =.000. Pair 11(air pollution) had 1.125 ± 2.614, p value = .000.

Domain – 3(emotional): Pair 3 (frustrated) had 1.065 ± 2.471, p value = .000. Pair -5 (asthma medication) had 1.440 ± 2.200, p value = .000. Pair – 9 (concerned) 1.306 ± 2.671,p value = .000.

Domain – 4 (activity limitation): Pair – 12 (strenuous activities) had .946 ± 1.186, p value = .000. Pair – 13 (moderate activities) had .848 ± 2.229, p value = .000. Pair – 14 (social activities) had 1.156 ± 2.514, p value = .000. Pair-15 (work related activities) had .966 ± 2.557, p value = .000.

On statistical analysis of the total mean of ACQ and AQLQ: we obtained a result that is total mean ACQ (pre & post) .876 ± 2.414 (standard deviation ± mean), p value = .000. Total mean AQLQ (pre & post) .839 ± 2.386 (standard deviation ± mean), p value = .000. Both for ACQ and AQLQ total mean (pre & post) significance was observed.

In this study drug induced adverse effects were assessed and only dry mouth was reported, and even it was with a very minimum number of patients. That is 7.1% (5) patients reported dry mouth while 92.9 % (65) didn't report any adverse effects. This indicated that Tiotropium was not having any serious adverse effects on the patients, and it is safe for use. Michael Engel[25] conducted a study in this study it is stated that dry mouth was reported in less than 2% of all patients and was reported more frequently in Tiotropium group than in the placebo group. It was a known adverse event of Tiotropium (anticholinergic). Huib A. M. Kerstjens[14] conducted a study in this study it states that 6.8% (7) with Tiotropium reported dry mouth, in patients with 10µg of Tiotropium. While in Tiotropium 5µg dose was given, only 1.9% (2) reported dry mouth.

Studies conducted on safety of Tiotropium[18,50] , says that adverse events leading to discontinuation of the therapy was infrequently reported and it stated that Tiotropium was safe and well tolerated.

6. CONCLUSION

In this retrospective and prospective study, the patients were having very poor asthma control (uncontrolled severe persistent asthma) and correspondingly their quality of life was also very poor at the baseline. The patients were already on ICS and stepping up the therapy can cause adverse effects. So Tiotropium was found as an efficacious step – up therapy for poorly controlled asthma patients. After the initiation of Tiotropium bromide as a step up therapy along with ICS there found improvement in the patient control over asthma and also their quality of life. The initiation of Tiotropium improved the lung function of patients and the drug was safe to be taken and well tolerated. Only a very small percentage reported adverse effect,that too was not serious. Though some studies have been done on this, but the use of Tiotropium has not yet been done in the daily life. Therefore more large studies should be done to give more authenticity towards this small study regarding the usefulness of Tiotropium in severe persistent uncontrolled asthma patients, who are already under ICS and LABA.

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DATA COLLECTION FORM

IP/OP. No.: DATE:

NAME: AGE: SEX:

WEIGHT: HEIGHT: BMI: ADDRESS:

OCCUPATION:

DIET: VEG/ NON-VEG

SOCIAL HABITS – ALCOHOL - present / past / never

SMOKING/ TOBACCO - present / past / never

PAST MEDICAL & MEDICATION HISTORY:

COMORBIDITIES:

PRESENT COMPLAINTS:

Have you been treated before for the same complaints:

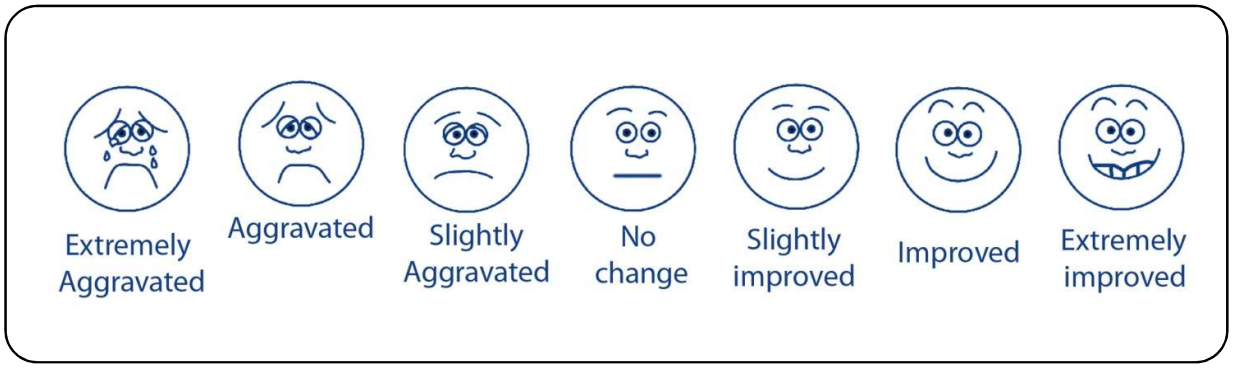
Symptom Severity Scale:

Sl. No	SYMPTOMS	YES/ NO	DURATION	SEVERITY SCALE (DAY 1)		
				MILD	MODERATE	SEVERE
1	Night time awakening					
2	Short acting $ß_2$ adrenergic agonist used for symptom control					
3	Interference with normal activity: • Breathlessness • Talks in • Alertness					
4	Lung function (spirometry)					
5	Requirement of oral steroid in past 1 year					
6	No:of exacerbation in past 1 year					
7	Heart burn					
8	Previous medication					

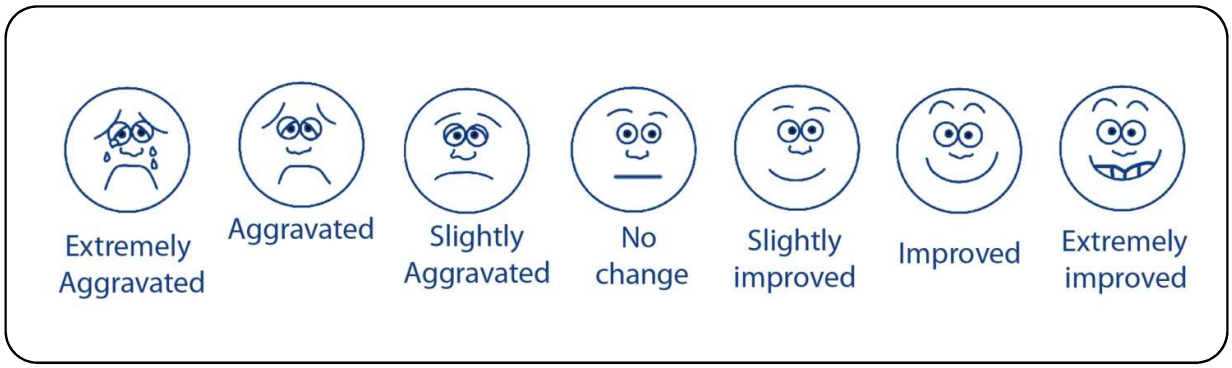
Sl. No	SYMPTOMS	YES/NO	DURATION	SEVERITY SCALE		
				MILD	MODERATE	SEVERE
1	Night time awakening					
2	Short acting $ß_2$ adrenergic agonist used for symptom control					
3	Interference with normal activity: • Breathlessness • Talks in • Alertness					
4	Lung function (spirometry)					
5	Requirement of oral steroid in past 1 year					
6	No:of exacerbation in past 1 year					
7	Heart burn					
8	Previous medication					

OVERALL TREATMENT EFFICACY (OTE) SCALE:

ON FIRST DAY:



AFTER



You indicated that you are taking medication for your (identify health concern, such as "high blood pressure"). Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your [health concern] medication. Interviewers may self identify regarding difficulties they may experience concerning medication-taking behavior.

(Please circle the correct number)

	No=0	Yes=1
1. Do you sometimes forget to take your [health concern] pills?		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your [health concern] medicine?		
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?		
5. Did you take your [health concern] medicine yesterday?		
6. When you feel like your [health concern] is under control, do you sometimes stop taking your medicine?		
7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?		

8. How often do you have difficulty remembering to take all your medications? **(Please circle the correct number)**

   Never/Rarely.....**0**

   Once in a while.....**1**

   Sometimes.....**2**

   Usually.....**3**

   All the time.....**4**

Source: Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive Validity of a Medication Adherence Measure for Hypertension Control. *Journal of Clinical Hypertension* 2008; 10(5):348-354.

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Fig. 1. MAQ (Medication Adherence Questionnaire)