

PREVALENCE OF THERAPEUTIC INERTIA AND ITS ASSOCIATED FACTORS AMONG PATIENTS ON BRONCHIAL ASTHMA MANAGEMENT IN A REFERRAL TEACHING HOSPITAL IN SOUTHWEST ETHIOPIA, 2023: A CROSS-SECTIONAL STUDY.

Getinet Assabie Lake^{1*}, Samuel Deok Jong Yoo², Gashahun Mekonnen Disasa³, Tenaye Abate Temesgen⁴

¹MD, Internal Medicine Resident, Jimma University Department of Internal Medicine.

²MD, pulmonologist, Professor of Internal Medicine, Jimma University Department of Internal Medicine.

³MD, Internist, Assistant Professor of Internal Medicine, Jimma University Department of Internal Medicine.

⁴MPH, BSc Nurse.

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ABSTRACT.

Background:

Therapeutic inertia may be one of the factors responsible for inadequate asthma control. However, the magnitude of therapeutic inertia in asthmatic patients has not yet been determined. In Ethiopia, a result showed that more than half of people with asthma had uncontrolled asthma.

Objectives: to assess the prevalence of therapeutic inertia and its determinant factors among patients on bronchial Asthma management.

Methodology:

An institution-based cross-sectional study was conducted on adult asthmatic patients attending the chronic follow-up department at Jimma University Medical College. A consecutive sampling with an interviewer-administered questionnaire and patient chart review was performed.

Results:

Therapeutic inertia was identified in 63 (47.7%) study subjects. The associated factors among patients on bronchial asthma management were poor adherence to medications prescribed by a doctor (p-value= 0.013; AOR 5.9; 95% CI 1.5-23.9), no regular follow-up (p-value=0.010; AOR 9.766; 95% CI 1.727-55.216), mild persistent chronic asthma (p-value <0.001; AOR 0.003; 95% CI 0.001-0.069) and poor provision of verbal explanation about asthma medication (p-value <0.001; AOR 0.113; 95% CI 0.049-0.261).

Conclusion:

The prevalence of therapeutic inertia among the study population was high. In the majority of cases with therapeutic inertia, asthma treatment necessitates treatment de-escalation and a step-up intervention. This is more likely to happen to patients with poor compliance and no regular follow-up. Mild persistent asthma and verbal explanations of medication dosage reduce the risk.

Recommendations:

The growing incidence of therapeutic inertia in asthma management calls for severity-based treatment plans, standard care, education on quitting smoking, appropriate medication counseling, and frequent follow-up visits. In 21% of patients with severe chronic asthma, uncontrolled cases may necessitate additional treatment alternatives.

Keywords: Therapeutic inertia, Bronchial asthma, Asthma, Prevalence, Jimma, Ethiopia.

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*Corresponding author: Getinet Assabie Lake**

Email: tenayeabate11@gmail.com

MD, Internal Medicine Resident, Jimma University Department of Internal Medicine.

INTRODUCTION.

Asthma is a heterogeneous disease often defined by persistent inflammation of the airways. It is characterized by a history of respiratory symptoms that change over time and in severity, as well as fluctuating expiratory airflow restrictions.¹ Asthma is a major chronic disease affecting approximately 334 million people worldwide.^{2,3,4,5}

Globally, the prevalence of asthma varies by region and typically ranges from 15% and 20% in industrialized

nations. It ranges from 2.7% to 6.9% throughout Africa, but it is said to reach 8.7% in Ethiopia. It is now a major public health concern.^{6,7,8} Asthma claims the lives of roughly 1150 people worldwide each day, the majority of which are avoidable.^{9,10}

The issue known as "therapeutic inertia," which is the failure to begin or increase therapy to avert adverse clinical outcomes, is becoming more widely acknowledged as a factor in the inappropriate management of chronic illnesses, including asthma.¹¹ Globally, achieving adequate asthma control

continues to be difficult even with the availability of various medications that are effective when taken regularly. Among the many causes contributing to this fall is therapeutic inertia, which might account for insufficient control depending on the severity levels of asthma. ^{12,13,14,15} It frequently occurs through intricate interactions between patients, healthcare providers, and practice systems. ^{16,17}

To achieve prolonged asthma control, an asthma standard of care includes not only pharmaceutical treatment but also efficient management of triggers and risk factors. ¹⁸ Disease burden may be minimized and quality of life improved through self-management strategies, including education sessions, written asthma action plans, symptom monitoring, breathing exercises, physical activity, and psychotherapeutic interventions. ¹⁹ There are many factors contributing to poor asthma control, including poor adherence to prescribed drugs, the under-prescribing of medications, and therapeutic inertia. However, the exact magnitude of therapeutic inertia in asthmatic patients has not yet been determined across the globe. Many patients with moderate-to-severe asthma are not prescribed appropriate therapies as indicated by current guidelines. ¹⁵, and is often driven by complex factors involving patients, providers, and practice systems.

Several studies have been conducted on uncontrolled asthma and its associated factors in Ethiopia. However, no study at Jimma University Medical Center (JUMC) has reported the prevalence of therapeutic inertia related to the management of asthmatic patients. This study aims to fill a knowledge gap assessing the prevalence of therapeutic inertia in adult asthmatic patient management, thereby providing recommendations based on the findings.

MATERIALS AND METHODS.

Study design

An institution-based, cross-sectional study design was used.

Study area.

The study was carried out at Jimma University Medical Center (JUMC), Jimma Town, south-west Ethiopia. The chest clinic is one of the hospital departments where patients with a variety of respiratory illnesses, including asthma, are treated. The hospital is the only referral teaching hospital in the area. The study was carried out from November 2022 to January 2023.

Study population.

The study population was asthmatic patients attending a follow-up at the chest clinic of JUMC, aged 18 years or older, who had been on follow-up for the last three consecutive months preceding the study.

Inclusion and Exclusion Criteria.

Inclusion criteria.

All adult asthmatic patients diagnosed based on history, the pattern of symptoms, and records, eighteen years of age and older, and patients under follow-up at the JUMC chest clinic for at least 3 months.

Exclusion criteria.

Patients whose medical records were lost or incomplete for important variables; critically ill patients; and asthmatic patients who were not willing to participate in the study.

Sample size determination.

According to recent data from the record of the chest follow-up clinic, about 274 asthmatic patients were supposed to attend the hospital. To date, the proportion of the asthma population with therapeutic inertia is unknown in Ethiopia. Thus, the sample size was obtained using a single population proportion and reduction formula. According to this formula, the estimated sample size was 384, to which a reduction formula was applied since the total asthmatic population attending the hospital was below 10,000 to obtain the minimum sample size required. Therefore, the following formula was used to obtain the final sample size of 160.

$$n = \frac{Z^2 P (1-P)}{d^2}$$

$$d^2$$

Whereas n = sample size

$$Z = 1.96$$

$$p = 0.5$$

$$d = 0.05 \text{ margin of error}$$

$$n = \frac{(1.962)^2 \times 0.5(0.5)}{(0.05)^2} = 384$$

Then, the reduction formula was applied to get the final sample size as follows:

$$N = \text{number of asthmatic patients attending JUMC} = 274$$

$$\text{Final sample size} = n / (1 + n/N)$$

$$= 384 / (1 + 384/274)$$

$$= 159.9 \sim 160$$

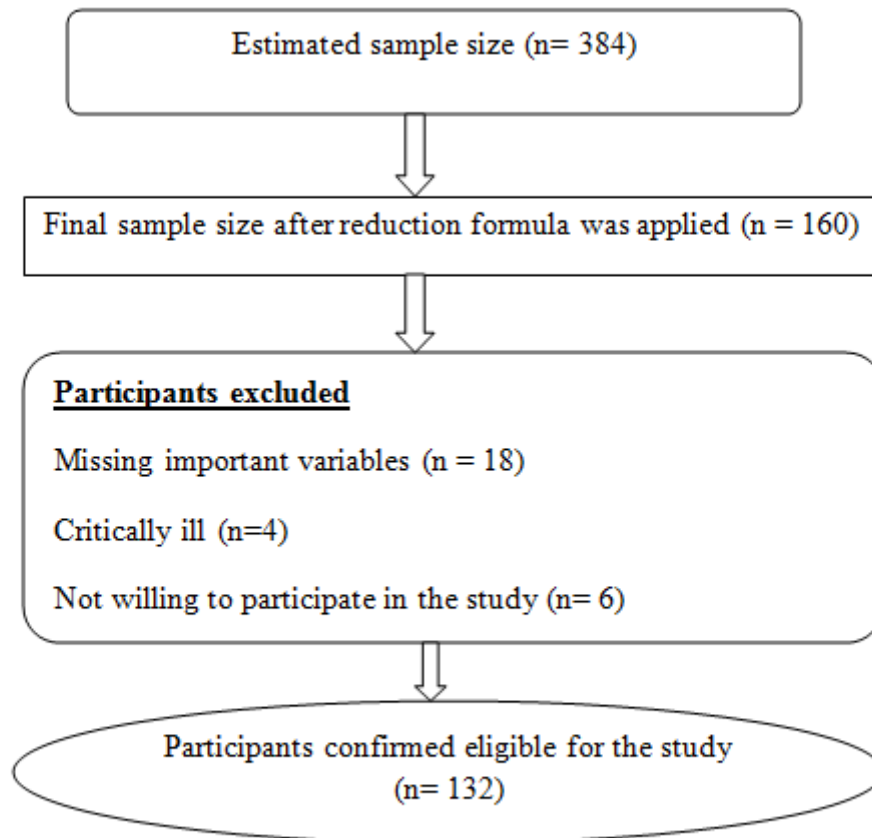


Figure 1 Flow diagram of participants included in the study

Sampling Procedure.

A consecutive sampling technique was used. All asthmatic patients on follow-up at the hospital clinic during the study period were interviewed, and their charts were also reviewed.

Data collection tools and methods.

Data was collected using a pre-tested, structured checklist prepared by reviewing the literature, which was filled by reviewing the patient charts and interviewing the patients and physicians who had been working at the chest clinic.

Data processing, analysis, and management.

The data was analyzed using Epi-Data and SPSS version 20.0. A descriptive analysis was performed, with Pearson's chi-squared tests for the nominal variable. Logistic regression was used to analyze therapeutic inertia and associated factors. Independent variables with $p \leq 0.25$ in bivariable analysis were included in the multivariable logistic regression model and variables with $p < 0.05$ were considered statistically significant. In this study, therapeutic inertia was considered when a patient

had uncontrolled or partially controlled asthma and treatment was not intensified; or controlled asthma was maintained for more than 3 months but treatment was not titrated down.

Ethical consideration.

Ethical approval was obtained from the Ethical Review Committee of the University of Jimma University Institute of Health before the commencement of the study with an ethical clearance number of JUIH/IRB/243/22. The outpatient director and hospital administration were consulted for official permits. The confidentiality and anonymity of the information obtained from medical records were maintained by not including participant names or phone numbers on the questionnaires.

RESULTS.

One hundred and thirty-two participants were recruited for the study and at each stage of the selection process patients who were not eligible were excluded (Fig 1). The study population had a median age of 47 years old, and the distribution of genders was about equal. When asked about their socioeconomic situation, the participating patients revealed that the majority of the study group (43.2%) was farmers (Table 1).

Table 1 Socio-demographic characteristics of study participants.

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| Characteristics | Frequency | Percentage |
|-------------------------------------|-----------|------------|
| Sex | | |
| Male | 67 | 50.8 |
| Female | 65 | 49.2 |
| Age | | |
| 18-39 | 47 | 35.6 |
| 40-59 | 60 | 45.5 |
| >60 | 25 | 18.9 |
| Residence | | |
| Urban | 58 | 43.9 |
| Rural | 74 | 56.1 |
| Occupational status | | |
| Farmer | 57 | 43.2 |
| self-employee | 28 | 21.2 |
| Government employee | 23 | 17.4 |
| unemployed | 17 | 12.8 |
| Others | 7 | 5.4 |
| Educational level | | |
| Higher education | 45 | 34.1 |
| No education | 43 | 32.6 |
| Primary | 25 | 18.9 |
| Secondary | 19 | 14.4 |
| Estimation of monthly income | | |
| Low income | 101 | 76.5 |
| Medium income | 26 | 19.7 |
| High income | 5 | 3.8 |
| Payment modality | | |
| Insurance | 62 | 47.0 |
| Out-of-pocket | 59 | 44.7 |
| Free | 11 | 8.3 |

The average duration of asthma illness was 13 years and about 24% of respondents said they smoked previously. When the status of those taking asthma medicines was evaluated, about 36% of people reported not taking them as prescribed. The majority of patients (75.4%) were in the mild persistent stage and 65.9% of asthmatic patients had uncontrolled asthma severity levels ([Table 2](#)).

Table 2. Clinical characteristics of the study participants

| Characteristics | Frequency | Percent |
|---|-----------|---------|
| Comorbidity | | |
| Yes | 60 | 45.5 |
| No | 72 | 54.5 |
| Smoking status | | |
| Current smoker | 8 | 6.1 |
| Previous smoker | 31 | 23.5 |
| Nonsmoker | 93 | 70.4 |
| Family history of asthma | | |
| Yes | 29 | 22 |
| No | 103 | 78 |
| Duration of asthma illness in a year, Median (Range) | 13 | 1-50 |
| Duration since follow-up started in year, Median (Range) | 8 | 0-45 |
| Current Follow-up visit gap in days, median(range) | 112 | 68-213 |
| Chronic bronchial asthma severity | | |
| Mild intermittent | 19 | 30.2 |
| Mild persistent | 57 | 75.4 |
| Moderate persistent | 31 | 23.5 |
| Severe persistent | 19 | 14.4 |
| Current Bronchial asthma GINA symptom control status of the patient | | |
| uncontrolled | 87 | 65.9 |
| Partly controlled | 25 | 18.9 |
| Well-controlled | 17 | 15.2 |
| Do you take asthma medication agreed upon by you and your care provider? | | |
| Yes | 52 | 82.5 |
| No | 11 | 17.5 |

Characteristics of respondents about therapeutic inertia status.

The mode of payment for bronchial asthma treatment had a strong association with therapeutic inertia (p-value= 0.042). There was no statistically significant association between the selected socio-demographic variables and the therapeutic inertia status of the respondents ([Table 3](#)).

Table 3. Association between socio-demographic variables and therapeutic inertia status of respondents.

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| Variables | Therapeutic Inertia (N=63) | No therapeutic Inertia (N=69) | Total (N=132) | p-Value |
|----------------------------|----------------------------|-------------------------------|---------------|--------------|
| Sex | | | | |
| Male | 30 (47.6) | 37 (53.6) | 67 (50.8) | 0.607 |
| Female | 33 (52.4) | 32 (46.4) | 65 (49.2) | |
| Age, Median (range) | 47 (18-85) | 45 (18-78) | 47 (18-85) | 0.347 |
| Residence | | | | |
| Urban | 27 (42.9) | 31 (44.9) | 58 (43.9) | 0.949 |
| Rural | 36 (57.1) | 38 (55.1) | 74 (56.1) | |
| Occupational status | | | | |
| Farmer | 27 (42.9) | 18 (26.1) | 57 (43.2) | 0.158 |
| Self-employee | 10 (15.9) | 12 (17.4) | 28 (21.2) | |
| Government employee | 11(17.5) | 30 (43.5) | 23 (17.4) | |
| Unemployed | 9 (14.3) | 8 (11.6) | 17 (12.9) | |
| Others | 6(9.6) | 1(1.4) | 7(5.4) | |
| | | | | |
| Educational level | | | | |
| No education | 20 (31.7) | 23 (33.3) | 43 (32.6) | 0.494 |
| Primary | 9 (14.3) | 8 (11.6) | 25 (18.9) | |
| Secondary | 11(17.5) | 16 (23) | 19 (14.4) | |
| Higher education | 23 (36.5) | 22 (31.9) | 45 (34.1) | |
| Monthly income | | | | |
| Low | 47 (74.6) | 54 (78.3) | 101 (76.5) | 0.338 |
| Medium | 12 (19.1) | 14 (20.3) | 26 (19.7) | |
| High | 4 (6.3) | 1(1.4) | 5 (3.8) | |
| Payment modality | | | | |
| Free | 6 (9.5) | 5 (7.2) | 11 (8.3) | 0.042 |
| Out-of-pocket | 21 (33.3) | 38 (55.1) | 59 (44.7) | |
| Insurance | 36 (57.1) | 27 (39.1) | 62 (47.0) | |

A relationship was observed (p-value = 0.026) between the length of asthmatic illness and treatment inertia. There was also a significant connection between smoking cigarettes currently and in the past (p-value = 0.001). Patients with a well-controlled current asthma (p-value < 0.001) and no regular follow-up (p-value = 0.025) had an impact on the patients' treatment inertia status. Analysis of the severity stage of bronchial asthma revealed that

mild persistent asthma was a significant factor influencing therapeutic inertia (p-value <0.001). (Table 4a). Regarding physician's care, the provision of verbal explanation about medication dose and timing was found to be highly significant for inertia to lessen (p-value < 0.001). Other factors did not play a significant role in therapeutic inertia (Table 4b).

Table 4 a). Association between clinical characteristics and therapeutic inertia status of respondents.

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| Variables | Therapeutic Inertia (N=63) | No therapeutic Inertia (N=69) | Total (N=132) | p-Value |
|--|----------------------------|-------------------------------|---------------|------------------|
| Comorbidity | | | | |
| Yes | 29 (46.0) | 31 (44.9) | 60 (45.5) | 1 |
| No | 34 (54.0) | 38 (55.1) | 72 (54.5) | |
| Smoking status | | | | |
| Current smoker | 5(7.9) | 3(4.3) | 8 (6.1) | 0.001 |
| Previous smoker | 23 (36.5) | 8(11.6) | 31 (23.5) | |
| Nonsmoker. | 35 (55.6) | 58(70.5) | 93 (70.4) | |
| Family history of asthma | | | | |
| Yes | 12(19.0) | 17(24.6) | 29(22.0) | 0.573 |
| No | 51(81.0) | 52 (75.4) | 103(78.0) | |
| Duration of asthma illness in a year, Median (Range) | | | | |
| | 10 (1-50) | 15 (1-40) | 13 (1-50) | 0.026 |
| Chronic bronchial asthma severity | | | | |
| Mild intermittent | 19 (30.4) | 6 (8.7) | 25 (18.9) | <0.001 |
| Mild persistent | 5 (7.9) | 52 (75.4) | 57 (43.2) | |
| Moderate persistent | 22 (34.9) | 9 (13.0) | 31 (23.5) | |
| Severe persistent | 17 (27.0) | 2 (2.9) | 19 (14.4) | |
| Current asthma GINA symptom control status of the patient | | | | |
| uncontrolled | 39 (61.9) | 48 (69.6) | 87 (65.9) | <0.001 |
| Partly controlled | 7 (11.1) | 18 (26.1) | 25 (18.9) | |
| Well-controlled | 17 (27.0) | 3 (4.3) | 17 (15.2) | |
| No regular follow up | | | | |
| Yes | 14 (22.2) | 5 (7.2) | 19 (14.4) | 0.025 |
| No | 49 (77.8) | 64 (92.8) | 113 (85.6) | |
| Counseled on asthma triggers | | | | |
| Yes | 14 (22.2) | 19 (27.5) | 33 (25) | 0.615 |
| No | 49 (77.5) | 50 (72.5) | 99 (75) | |

Table 4 b). Association between clinical characteristics and therapeutic inertia status of respondents.

| Variables | Therapeutic Inertia (N=63) | No therapeutic Inertia (N=69) | Total (N=132) | p- Value |
|---|-------------------------------|----------------------------------|------------------|--------------|
| No | 11 (17.5) | 36 (52.2) | 47 (35.6) | |
| Does the physician perform an assessment of lung function (e.g., spirometry, pulmonary function testing) | | | | |
| Yes | 4 (6.3) | 7 (10.1) | 11 (8.3) | 0.636 |
| No | 59 (93.7) | 62 (89.9) | 121 (91.7) | |
| Have you ever checked the inhaler technique at each visit? | | | | |
| Yes | 25 (39.7) | 23 (33.3) | 48 (36.4) | 0.564 |
| No | 38 (60.3) | 46 (66.7) | 84 (63.6) | |
| Type of Current treatment | | | | |
| Low-dose ICS whenever SABA used | 0 (0.0) | 1 (1.4) | 1 (0.8) | 0.011 |
| Low-dose ICS daily, with SABA as needed | 51 (88.9) | 57 (82.6) | 113 (85.6) | |
| Medium dose-ICS-daily-with-SABA as needed | 0 (0.0) | 7 (10.2) | 7 (5.3) | |
| Medium dose-ICS-LABA-daily and SABA as needed | 0 (0.0) | 2 (2.9) | 2 (1.5) | |
| Oral-glucocorticoids+ SABA as needed, n (%) | 2 (3.2) | 2 (2.9) | 4 (3.0) | |
| SABA as needed alone, n (%) | 5 (5.9) | 0 (0.0) | 5 (3.8) | |

Predictors of Therapeutic Inertia in the Multivariate Logistic Model.

In the multivariate logistic regression model, therapeutic inertia is six times more likely in patients who don't follow their doctor's prescription, (p-value= 0.013; AOR 5.9; 95% CI 1.5-23.9). Inertia was nearly ten times more likely to occur in patients with no routine follow-up (p-value=0.010; AOR 9.766; 95% CI 1.727-55.216).

Moreover, nonsmokers of cigarettes had a 97% lower probability of being therapeutically inert. Therapeutic inertia was 99.7% less likely to develop in patients with mild persistent chronic asthma (p-value <0.001; AOR 0.003; 95% CI 0.001-0.069). As indicated in Table 5, it was revealed that verbal explanation of medication regarding dosage, time, and administration techniques lowered therapeutic inertia by 88.7% (p-value <0.001; AOR 0.113; 95% CI 0.049-0.261).

Table 5. Predictors of therapeutic inertia on bronchial asthma management.

| Variables | β | p-value | AOR | 95% Confidence interval | |
|--|--------|------------------|-------|-------------------------|--------|
| | | | | Lower | Upper |
| Payment modality for treatment | -1.704 | 0.095 | 0.182 | 0.025 | 1.344 |
| Duration of Asthma illness | 0.056 | 0.257 | 1.057 | 0.96 | 1.164 |
| Cigarette nonsmoking status | -3.697 | 0.016 | 0.025 | 0.001 | 0.509 |
| Prior asthma symptom control status unknown | -0.758 | 0.16 | 0.469 | 0.163 | 1.349 |
| Current asthma symptom control status | -1.063 | 0.604 | 0.345 | 0.006 | 19.092 |
| Mild persistent Chronic asthma severity | -5.82 | <0.001 | 0.003 | 0.001 | 0.069 |
| Not Taking medication agreed upon by the patient and physician | 1.778 | 0.013 | 5.918 | 1.463 | 23.93 |
| Type of Current treatment | 20.484 | 0.997 | 1.271 | 0.001 | 1.997 |
| Physician's verbal explanation of treatment | -2.18 | <0.001 | 0.113 | 0.049 | 0.261 |
| No regular follow up | 2.279 | 0.01 | 9.766 | 1.727 | 55.216 |

Treatment inertia, which can happen at any point in the asthma symptom control status, is widely observed in clinical practice. The study found that 47.7% of the participants had therapeutic inertia; of these, over a third (31.8%) needed treatment intensification, while 15.9% needed medication de-escalation. The magnitude of therapeutic inertia was found to be high when compared to the magnitude in other chronic conditions²⁰. The difference might be due to the nature of the condition, where the management of asthma symptoms is used to determine the goal of treatment. This could increase the severity of the disease as more symptomatic complaints are raised and classified as uncontrolled asthma.

It was discovered that the patient's well-being and therapeutic inertia were related. This was refuted by similar studies conducted on other disease conditions²¹; this could be because smoking and the illness itself have a joint impact on the respiratory system. Given that smoke is a known trigger for bronchial asthma, even individuals who closely follow their treatment plan may frequently have exacerbations. This may lead the patient to assume that the medicine is no longer effective, even though it has become therapeutically inert.

Therapeutic inertia was more likely to occur in those who did not follow their doctor's prescription regimen. On the other hand, it seems that mild persistent chronic asthma and verbal explanation of medicine dosage and timing were linked to a decreased risk of therapeutic inertia. Nevertheless, it has been noted in other studies,^{4, 21, 22} those complex factors like the need to address inadequate inhaler adherence, diagnostic uncertainty, an abundance of medication options, managing comorbidities, patient preferences, and barriers in the healthcare system also contribute to therapeutic inertia.

Therapeutic inertia can be manifested at any point of chronic asthma severity. However, this research showed that patients with mild persistence had a lower likelihood of developing therapeutic inertia. This might be explained by the prescription pattern of the care provider. The majority (86%) of the patients were on low-dose ICS daily and SABA as needed which may have put them on the right course of treatment for the majority (43.2%) of the patients who had mild persistent asthma, but not for 14.4% of severe persistent having uncontrolled disease. This was incongruent with other studies^{22, 23, 24}, even with appropriate escalations in inhaled therapies, there is a significant portion of patients would still benefit from biologic initiation if their symptoms remained poorly controlled after receiving inhaled corticosteroids. Thus, preventing therapeutic inertia by simply increasing dosage may help manage asthma, but it is not a foolproof way to cure uncontrolled disease.

It was shown that 22.2% of patients without frequent follow-up had considerable inertia. Studies conducted in Gondar²⁵ and Jimma²⁶ also indicated that unplanned visits or lack of regular follow-up were linked to uncontrolled asthma, which may be caused by therapeutic inertia. This could be the result of healthcare professionals not having conversations with patients about the factors that could affect their diagnosis and course of therapy.

A decreased risk of developing therapeutic inertia was linked to patients who were taking medicine, as agreed upon by the patient and their healthcare provider. Therapeutic inertia is further explained by the relationship between the asthma patient and the clinician. It's possible that healthcare professionals don't fully convey to patients the significance of following treatment regimens and the seriousness of their diagnoses. Only 7.6% of research participants, meanwhile, received detailed written instructions. A higher percentage of patients (68.9%) received verbal explanations at each visit, including information on dosage, timing, and administration technique. This proved important in reducing the likelihood of developing therapeutic inertia, which decreases by almost half (48.2%) when compared.

GENERALIZABILITY.

The study can not be generalized to the larger population.

CONCLUSION.

The prevalence of therapeutic inertia among the study population was high in 47.7% of asthma treatments necessitates medication de-escalation and a step up in treatment intensity. This is more likely to happen to patients who don't follow up with their doctor as prescribed and don't have a regular follow-up. The risk is decreased by mild persistent asthma and verbal explanations of medicine dosage and timing.

LIMITATIONS.

The limitations were using small sample size, taking clinical parameters as the sole criteria for the recruitment of asthmatic cases, the presence of limited treatment options, and the absence of objective assessment during follow-up visits. Moreover, since it is a mono-center.

STRENGTHS.

This is a well-designed institution-based cross-sectional study design that aids in sorting the relationship between therapeutic inertia and all predictors investigated. Likewise, the nature of the study allowed us to collect complete information directly from the patients. Literature was scarce regarding therapeutic inertia in Ethiopia and globally as well. Thus, this research will fill the gap and serve as a foundation for further work to tackle asthma management barriers.

RECOMMENDATIONS.

The management of asthma has been impacted by the rising prevalence of therapeutic inertia. Considering treatment options based on the degree of asthma severity, standard care for patients with asthma, health education about quitting smoking, proper drug counseling based on a doctor's prescription, and encouragement to make regular follow-up appointments may all be crucial for the management and control of therapeutic inertia. Doctors ought to give verbal and written instructions on medication dosage to break the cycle of therapeutic inertia. Nonetheless, further treatment choices could be required because 21% of patients with severe chronic asthma have uncontrolled disease. Resources helpful in asthmatic patient monitoring ought to be accessible at chronic follow-up chest clinics,

CONFLICT OF INTEREST.

The author declares no conflict of interest.

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