Chapter 3

Evaluation of the Therapeutic Effect of Combined Conventional Asthma Drugs with Tianeptine in Treatment of Asthma — Double-Blind Controlled Trial Pilot Study

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Additional information is available at the end of the chapter

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1. Introduction

Asthma is a chronic inflammatory and immunologic common which associated with reversable obstruction of airflow. Arab countries are with 20% prevalence rate and ambient air pollution may contribute to rise in this rate with time. Environmental factors are known to play an important role in the elicitation of asthma in genetically predisposed individuals. Although there has also been an increase in the awareness among doctors to diagnose asthma, a combination of various other factors may also be involved in the increased prevalence of asthma. Further investigations are recommended to identify the etiologic factors contributing to the rising prevalence of this disorder in Arab countries [1].

Asthma is common with an increasing prevalence and mortality especially in low-income and minority populations. The National Heart, Lung, and Blood Institute (NHLBI) defined asthma as *"recurrent episodes of respiratory symptoms; variable airflow obstruction that is often reversible, either spontaneously or with treatment; presence of airway hyper reactivity; and, importantly, chronic airway inflammation in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T- lymphocytes, macrophages, neutrophils, and epithelial cells"*[2]

Asthma is an important worldwide health priority because of its high and increasing prevalence, high morbidity and mortality, and direct and indirect costs. Asthma is with a prevalence

of 12% of the population [3] with significant impact on quality of life and cost. [4]. The most important thing that relialized is asthma has been associated with significant comorbidities, especially depression [5-10]. Although stress triggered asthma symptoms, does not all of a sudden cause a person to develop the disease of asthma. [11,12]. The course of asthma appears to be influenced by mood and emotions and there is a high prevalence of depression or depressive symptoms in both children and adults with asthma.[11,12]

Recent studies indicated a positive association between stress and asthma exacerbation [13].

The chronicity of asthma course and episodic recurrences may lead to development of depression in asthmatic patients, specially in subjects with severe uncontrolled asthma [14]. Depression is associated with increased use of asthma-related urgent care services, emergency rooms, hospitals, and unscheduled appointments for asthma. as well as a variety of unfavorable asthma outcomes. Despite data on the frequency of depression in asthma and its adverse consequences, it is generally not recognized or treated.

Combination of conventional treatment drugs with antidepressants may amliorate asthma course and attack severity [15]. Both asthma and depression shared some biological linkage and antidepressant may be of therapeutic benefit through induction of bronchodilatation and reduction in cytokines production in asthmatic patients [16,17,18]. Immune and inflammatory responses in asthmatic patients may be modulated by antidepressants [18,19]. The ideal antidepressant to be used for treatment of asthma in combination with conventional drugs should have bronchodilator and anti-inflammatory activity and non-sedating such as tianeptine [20].

The present study was conducted to determine the therapeutic efficacy of Tianeptine in patients with asthma. Informed cosent taken from each subject included in the study and the study protocol was approved by the ethical committee.

Objectives: To determine the therapeutic efficacy of Tianeptine in patients with asthma.

2. Patients and methods

2.1. Study population

The study was performed on asthmatic patients. The subjects included in the study were recruited from the Habib Hospital outpatients Clinic in the Kingdom of Saudi Arabia. [Table 1]. The sample size in the study was 82 adult patients suffering from asthma for at least one year duration, and their age range was from 18 to 70 years, with a mean age of 35.8 years. The diagnosis and classification of asthma was performed by specialist physician and was established according to the National Heart Blood and Lung Institute / World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma [21]. The diseases severity classification was performed according to GIN criteria [22]. Patients were excluded if they were smokers, if they had malignancy, heart failure, history of venous

embolisms, coronary heart disease and liver or kidney diseases..Current substance or alcohol Abuse/dependence, MDD with psychotic features (delusions, hallucinations, disorganized thought processes) or schizophrenia or schizoaffective disorder or if they had mental retardation or other severe cognitive impairment or if they were on current antipsychotic or antidepressant therapy or psychotherapy. Initiation of other psychotropic medications or psychotherapy within past 2 weeks (e.g., anxiolytics, hypnotics) and if they were pregnant or nursing women.

Group	Used drugs	Total numbers of patient in the group	Number of patients completed the trial	Average of patients age/yr Mean [SD]	Number of male patients	Number of female patients
1	Conventional	22	18	35.88 [14.02]	9	9
2	Conventional+ Tianeptine	21	15	36.4 [13.33]	8	7
3	Singulair+ Tianeptine	19	15	35.53 [12.72]	8	7
4	Conventiona+ fexofenadine+ Tianeptine	20	17	35.7 [10.85]	8	9
P value		NS	NS	NS	NS	NS

Table 1. Study population

Inclusion criteria includes: Out patients; Bronchial asthma has been known at least for 1 year ; Absene of long-term remissions of asthma (lasting more than 3 months) ; Poorly controlled asthma, due to various reasons ; No changes in asthma medications. ; and Both male and female

2.2. Study design

This study is randomized controlled trial to evaluate the therapeutic activity of tianeptine for treatment of asthma. The patients were distributed randomly to the groups. Patients who were eligible for entry in the study were included and follow-up for 8 weeks. Each patient had three visits, the first when introduce him\her in the study then the second after a month and the third was after two months

2.3. Measurement of stress

Perceived Stress Scale (PSS)[23] was used to measure the perception of stress in our study population. The Perceived Stress Scale is the only empirically established index of general stress appraisal. "The PSS measures the degree to which situations in one's life is appraised as

stressful [24]. The PSS is not a diagnostic instrument, so there are no cut-offs. There are only comparisons between people in a given sample relationship between PSS scores and health behaviors and relationship among performance appraisal discomfort and belief, core self-evaluation and perceived stress.

There are three versions of the PSS: One with 4, one with 10, and one with 14 items. The 14-item version, which is the version that was adapted culturally to our study, as it had been used in previous studies and, at that time. Thus, the version we used has 14 items and is rated on a 5-point Liker type scale, ranging from 0 (*never*) to 4 (*very frequently*). Scores of items 4, 5, 6, 7, 9, 10, and 13 are reversed. Higher scores correspond to higher perceived stress. Internal consistency and factor structure data are mentioned in the introduction.[25]

2.4. Treatment schedule

The patients were distributed randomly into four groups each one include 25 patients. Selection of patients and distribution of them in the groups will be equally matched in gender, severity and presence of attack.

- **The first group** given conventional asthma treatment [SYMBICORT (budesonide and formoterol inhalation) or SEROTID (Salmeterol, fluticasone propionate).with or without salbutamol].
- **The second group** given conventional asthma treatment plus tianeptine12.5mg three times daily
- **The third group** given Singulair 10mg once daily (montelukast) plus tianeptine
- **The fourth group** is given conventional treatment with fexofenadine180 mg once daily plus tianeptine

2.5. Research methodolog

a. After making sure of the status of each individual from the patients have asthma and they are eligible for this study design and did not have any of the exceptions for the study will be admitted to one of the study groups. Informed written consent taken from all patients included in the study.

b. Baseline assessment conducted for each patient at the time of enrollment in the study,also recording the number of attacks suffered by the patient during the week and the number of times where he \she wake up because of shortness of breath and the number of times sprays ventolen during the week and the number of absences from school or work during the month due to asthma and assessing the severity of cough and the severity of breathing difficulty suffered by the patient that were divided to three degrees,simple, moderate and severe. Also study and record presence of wheezing or not. As spirometry remains an essential diagnostic tool in assessment of asthmatic patient But we will limit ourselves to study Peak Expiratory Flow Rate (PEFR) because it is a simple method of measuring airway obstruction the device is availa-

ble, accessible, and easy to use by the patient and it will detect moderate or severe disease. The simplicity of the method is its main advantage. It is measured using a standard Wright Peak Flow Meter or mini Wright Meter. The needle must always be reset to zero before PEF is measured. The measurement of peak expiratory flow rate (PEFR) three to four times allows the diagnosis and assessment of the severity of asthma. [26]. It will be studied for all patients, and the stress and anxiety status of patients will determined for all patients included in the study by using Perceived Stress Scale. Arabic version of the questions set prepared and used through the study.

c. Patients evaluation performed at interval of the study and at least to attend the chest clinic 3 times during the study period.

Visit 1: Screening visit:

The following actions were taken

- take the written consent of the patient on the study after explaining all matters relating thereto
- General medical history & physical examination.
- Study of stress and anxiety status by Complete Perceived Stress Scale
- Measure peak expiratory flow
- Complete asthma control questionnaire.

Visit 2: 4weeks after visit 1

The following actions were taken

- Baseline clinical measurements
- Complete asthma control questionnaire
- Measure peak expiratory flow

Visit 3: 4weeks after visit 2

Repeat all the actions taken in the visit 2

At each study visit the peak expiratory flow (PEF) will be performed, the best of three measurements will be recorded [27].

2.6. Asthma control questionnaire

International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimise asthma control (minimisation of symptoms, activity limitation, and bronchoconstriction and rescue β_2 -agonist use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The Asthma Control Questionnaire (ACQ) was developed to meet these criteria. It measures both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or

as a result of treatment [28]. We have developed a schedule for each patient where the following questions is registered for all visits to facilitate consideration of the patient's condition fully [29].

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?
2. During the past 4 weeks, how often have you had attacks of shortness of breath?
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, and shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?
5. Assessment of severity of cough, SOB.
6. Is there wheezing or no?
7. How would you rate your asthma control during the past 4 weeks?
8. Recording peak expiratory flow

2.7. Statistical analysis

SPSS package (version 17) was used for statistical analysis.

3. Results

Out of the total (82) patients with asthma included in the study, 79% (65 patients) of them continued until the end of the study and are eligiable for analysis. The subjects suitable for analysis are consisted of 33 men (52%) and 32 women (48%). The mean age was 35.8 years (Table 1).

3.1. Role of conventional asthma treatment in the first group

In this study 22 patients has been selected for the first group, 18 patients (81.8%) of them continued until the end of the study. Of the total, 9 patients were male and 9 were female and they were given conventional asthma treatment only [SYMBICORT (budesonide and formoterol inhalation) or SEROTID (Salmeterol, fluticasone propionate) with or without salbutamol]. Their results are shown in Table 3. The average age of patients was 35.8 year, average severity of symptoms was 2.78, medication score was 3.94 and PSS value was 22.94. There was significant clinical impact of ventolin, Symbicort and Seretide conventional in treatment of asthma. Then average of improvement after a month was 1.94 and increased to 2.11 after 2 months period (P= 0.001) from the base line and PEFR increased from 72.6% at the time of enrollement in the study to 83.6% at the end of the study (P=0.0001).

Variable		Mean	Std. Deviation	Std. Error Mean	95% Confidence interval
Age		35.89	14.02	3.31	28.92 – 42.86
Severity of asthma		2.78	1.26	0.30	2.15 – 3.41
Medication score		3.94	1.80	0.42	3.04 – 4.83
PSS Score		22.94	7.90	1.86	19.01 – 26.87
Rate of improvement	1 month	1.93	0.24	0.06	1.74-2.13
	2 month	2.11	0.47	0.11	1.83 – 2.39
	P value	0.001			
PEFR	Study onset	72.67	10.69	2.52	67.35 – 77.99
	End of the study	83.61	8.63	2.16	79.3 – 87.9
	P value	0.0001			

Table 2. Combined rates of all data for patients of Conventional treatment (group 1)

3.2. Role of conventional asthma treatment plus Tianeptine in the second group

These patients were given the same of traditional medicines which given to the first group, but was added Tianeptine to each patients in this group. The average patients age was 36.4 year, average severity of symptoms was 3.06, medication score was 3.9 and PSS value was 22.33. The treatment lead to improvement of 1.93 after a month and this increased to 2.4 after 2 months with significant difference (P= 0.001) from the baseline. In addition, PEFR increased from 77.4% at study enrollement to 89.13% at the end of the study (P= 0.0001).

Variable		Mean	Std. Deviation	Std. Error Mean	95% onfidence interval
Age		36.40	13.33	3.44	29.03 – 43.76
Severity of asthma		3.07	.96	.25	2.54 – 3.60
Medication score		4.73	1.44	.37	3.93 – 5.53
PSS score		22.33	7.79	2.01	18.03 – 26.63
Rate of improvement	1 month	1.93	.258	.067	1.74-2.13
	2 month	2.40	.63	.16	2.09-2.70
	P value	0.001			
PEFR	Study onset	77.40	7.88	2.03	73.05 – 81.75
	End of study	89.13	4.88	1.26	86.43 – 91.83
	P value	0.0001			

Table 3. Combined rates of all data for patients of Conventional treatment with Tianeptine [group 2]

3.3. Role of Tianeptine ± Singulair in asthmath in the third group

These patients were given Tianeptine12.5+Singulair10mg without addition or modification of traditional medicines. The average of patient's age was 35.53, average severity of symptoms was 2.46, medication score was 6, and average of PSS of this group was 23.06. The improvement after a month was 1.00 and increased to 2.13 after 2 months (P=0.001) from the baseline. Furthermore, average of Rate of peak expiratory flow at onset of study was 80.4% and increased to 88.4% at the end of the study (P=0.001).

Variable		Mean	SD	St. Error of mean	95% confidence interval
Age		35.53	12.72	3.28	28.50 – 42.56
Severity of asthma		2.47	0.92	0.24	1.96 – 2.98
Medication score		6.00	0.00	0.00	6.00 – 6.00
PSS score		23.07	5.88	1.52	19.82 – 26.32
Rate of improvement	1 month	1.00	0.38	0.10	0.81-1.19
	2 month	2.13	0.74	0.19	1.83-2.44
	P value	0.001			
PEFR	Study onset	80.40	5.55	1.43	77.33 – 83.47
	End of study	88.40	7.34	1.89	83.34 – 92.46
	P value	0.001			

Table 4. Combined rates of all data for patients of Singulair with Tianeptine [group3]:

3.4. Role of conventional medicines ± fexofenadine ± tianeptine in asthma in the fourth group

In this group, 17 patients continued until the end of the study, including 8 patients were male and 9 were female. The patients were given the same of traditional medicines given to the first group, but was added Tianeptine (12.5 mg) three time daily and fexofenadine (180 mg) once daily to each patients in this group. Average of patient's age of fourth group was 35.7, average of severity of symptoms was 3.17, medication score was 7, and average of PSS of this group was 26.67. The average of improvement after a month was 2.41and this increased to 2.58 after 2 month of treatment (P=0.0001). In addition, PEFR was increased to 88.41% at the end of the study (P=0.0001)

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Variable		Mean	Std. Deviation	Std. Error Mean	95% Confidence interval
Age		35.71	10.85	2.63	30.13 – 41.29
Severity of asthma		3.18	1.42	.35	2.45 – 3.91
Medication score		7.00	.00	.00	7.00 – 7.00
PSS score		26.65	4.65	1.13	24.26 – 29.04
Rate of improvement	1 month	2.41	.51	.12	2.23 - 2.59
	2 month	2.59	.51	.12	2.30-2.89
	P value	0.001			
PEFR	Study onset	73.29	7.99	1.94	69.18 – 77.40
	End of study	88.41	7.50	1.82	84.55 – 92.27
	P value	0.0001			

Table 5. Combinee rates of all data for patients of Conventional treatment with Fexofenadine + Tianeptine [group 4]:

3.5. Comparison between the rates of the key points for all groups

The averages of PSS for all groups were roughly convergent (P>0.05). All patients in the four groups have made improvement with lightly varying degrees in the first month, with the exception of the third group. However, the percentage of improvement in patients of this group in the first month was relatively low, but after two months the improvement became well. Furthermore, the average improvement after a month of treatment course was with highly significant differences between the groups (P=0.000). However, the average improvement after 2 month was with non significant differences between the groups (P=0.06). The same pattern of differences was achieved for PEFR, however, the changes in PEFR were significantly different between the groups. Although the severity of asthma was more in group 4, the increase change was more prominent in this group as compared to other 3 groups.Table 6.

Variable	Improvement		PEFR Percent		
	After 1 month	After 2 month	PEFR 1	PEFR 2	Change
Group 1	1.94	2.11	72.66	83.61	10.95
Group 2	1.93	2.40	77.40	89.13	11.73
Group 3	1.00	2.13	80.40	88.40	08.00
Group 4	2.41	2.58	73.20	88.41	15.21
P value ANOVA	0.000	0.067	0.034	>0.05	<0.05

Improvment1: Mean rate of overall improvement in the group after the first month

Improvment2: Mean rate of overall improvement in the group after the second month

PEFR1: Mean rate of peak expiratory flow of the group at the beginning of the study

PEFR2: Mean rate of peak expiratory flow of the group at the end of the study

Change: Mean the difference between the rate of peak expiratory flow between the beginning and end of the study

Table 6. Improvement comparison between the treatment groups

The proportion of decreasing of the mean percentage change of daily "as-needed" inhaled β-agonist using for patients of each group were 25.5%, 31.1%, 26.6% and 35.8% for groups1,2,3,and 4 respectively. The present study demonstrated non significant differences in proportion of decreasing between the 4 groups. However, all groups demonstrated significant differences in proportion of decreasing inhaled β-agonist use at the end of the study as compared to enrollement time. Table 7.

Variable	Number	Difference number of salbutamol using between onset and end study				P value
		Mean	SD	95% Confidence interval	Rate of decrease	
Group 1	18	2.56	2.57	1.27 - 3.83	25.5%	0.001
Group 2	15	3.13	1.58	2.86 - 4.61	31.1%	0.000
Group 3	15	2.67	1.05	2.09 - 3.25	26.6%	0.000
Group 4	17	3.59	1.94	2.59 - 4.58	35.8%	0.000
P value ANOVA		>0.05			>0.05	

Table 7. Proportion of decreasing of the mean percentage change of daily "as-needed" inhaled β-agonist using for patients of for treatment groups

In conclusion, the 4 treatment course were effective therapeutic approaches for asthma treatment, however, the combination of SYMBICORT (budesonide and formoterol inhalation) or SEROTID (Salmeterol, fluticasone propionate) plus Tianeptine (12.5 mg) three time daily and fexofenadine (180 mg) once daily was superior in treating severe asthma.

4. Discussion

Individuals with asthma have twice the risk of developing mood and anxiety disorders as individuals without asthma and these psychological factors are associated with worse outcomes and greater need for medical intervention. Similarly, asthma symptom onset and exacerbation often occur during times of increased psychological stress. Remission from depression, on the other hand, is associated with improvement in asthma symptoms and decreased usage of asthma medication. Yet research aimed at understanding the biological underpinnings of asthma has focused almost exclusively on the periphery. An extensive literature documents the relationship between emotion and asthma, but little work has explored the function of affective neural circuitry in asthma symptom expression.[30]

The present study indicated that in patients receiving Tianeptine plus conventional asthma treatment (group 2) demonstrate a hsigigher decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (31.1%) as compared to patients group receiving conven-

tional asthma treatment (group 1) only (25.5%). Also, there was a higher decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (35.8%) in the fourth group which given conventional treatment with fexofenadine plus tianeptine as compared to the other 3 groups of treatment. However, using ANOVA analysis, the differences in percentage change in daily "as –needed" between the four groups were not statistically significant. Furthermore, the percentage of change was highly significant for the four groups of treatment.

PEFR was improved significantly in the four groups, however, there was a significant differences in changes between the four ngroups of treatment. Furthermore, the PEFR change was more in group four (conventional + tianeptine + fexofenadine) and lowest in group 3 (singulair plus Tianeptine). The rate of improvement was highest in group 4 and lowest in group 3 after one month of treatment course and the there was a highly significant differences between the 4 groups in their rate of improvement. However, after 2 months of treatment there was no significant differences between the groups in their rate of improvement. This could be explasined on the basis that fexofenadine may exert antiinflammatory action that may influence the clinical improvement [31-38]

In this study the impact of Tianeptine was clear through the big improvement in patients who receice this medicine, as demonstrated in reduction of daily use and percent reduction of salbutamol, percent changes in PEFR and rate of improvement in group 2,3 and 4. However, the above parameters changes were lower in group of patients (group 3) receiving singulair with Tianeptine. This could be due to that singulair acts as antiinflammatory, it does prevent bronchoconstriction, but not relieve the present bronchoconstriction. In addition, it takes 3 -4 to reach high peak blood mean (Tmax)[39].

The therapeutic effect of Tianeptine in treatment of asthma may be contributed to its ability to suppress proinflammatory cytokines, interference with cholinergic and serotoninergic pathways, modulation of immune response and/or serotonin uptake by platelets and serotonergic axons at the central nervous system [40,41]. Serotonin induces bronchoconstriction via peripheral and central pathways resulting in increasing colinergic activity and histamine release[42]. These changes may explain why tianeptine has proven to be a powerful therapeutic tool in controlling asthma as this study indicated of better improvement in groups (groups 2,3,and 4) receiving tinaneptine. During asthma attack, catacholamines and free serotonin (f-5-HT), only f-5-HT levels correlated positively with pulmonary function clinical severity [43,44]. f-5-HT was taken up by pulmonary endocrine cells that were located at the parasympathetic terminals. Pulmonary endocrine cells located at the parasympathetic terminals taken up f-5-HT. Bronchial smooth muscle contracted due to effect of serotonin through potententiation of acetylcholine [39]. However, postsynaptic receptors (5-HT3 and 5-HT4) that located at the bronchial muscle mediated serotonin effects.

A reported studies [45,46] suggested that tinaneptine therapy reduce plasma f-5-HT, clinical rating and increase in pulmonary function. While, asthma attach triggered by drugs that increase f-5HT such as buspirone and serotonin-uptake inhibitors (like sertraline, paroxetine, etc).[47-50]. However, the side effects of buspirone and serotonin inhibitors may be controlled by atropine [51]. Dupon et al.[52] suggested that serotonin produced frequency- and concen-

tration-dependent facilitation of cholinergic contractions of human airways, which was mimicked by both 5-HT_3 and 5-HT_4 agonists, and subsequently 5-HT facilitates cholinergic contractions in the human airways. In addition, Tianeptine greatlly annulated pulmonary vasoconstriction and bronchoconstriction that induced by drugs through their ability to increase f-5HT serum levels [53-59]. Neuroepithelial autocrine serotonergic cells located at the bronchopulmonary system release 5-HT under the effect of acetylcholine stimulation, while, serotonin triggers acetylcholine release from the parasympathetic terminals [60].

Mood disordera are more common in individuals with atopy [13]. Through our study, we can say Tianeptine definitely seems to improve the asthma as it reduced the severity of symptoms and improved the daily functioning of a asthmatic patient and reduced absences from school or work, with increase PEFR, whether that it was added to traditional medicines (budesonide and formoterol inhalation or Salmeterol, fluticasone propionate)or Singulair or fexofenadine. But Group who took the traditional medicines for asthma with the addition of tianeptine and fexofenadine was better and their symptoms responded to treatment better than others. This finding may be due to synergistic antiinflamatory effects that induced by combination of Tianeptine and fexofenadine.

Tianeptine led to a clinical improvement of asthmatic symptoms in the second group, patients who were given the tianeptine in addition to traditional medicine has with better improvement as compared to the first group who took traditional medicines only. This suggests the positive effect of this drug for patients with asthma, of course not as a single medicine, but certainly as adjuvant drug to the essential approved medicines. The mechanism by which this positive impact was induced may be due to its significant anxiolytic properties for patients with asthma who worry more than others or due to positive association between free serotonin in plasma and severity of asthma in symptomatic patients. As tianeptine was the only agent known to both reduce free serotonin in plasma and enhance uptake in platelets,[45,46]. Previous studies have shown that antidepressants may be of therapeutic value in asthma [61,62] as there is increasing evidence that a biological linkage may exist between asthma and depression [61,63,64]. A defect in the function of the autonomic nervous system such as alpha-adrenergic and cholinergic hyperresponsiveness and beta-adrenergic hyporesponsiveness even distal from the airways has been demonstrated in asthmatic patients, as well as in depression [61,64]. Antidepressants may have a therapeutic role in asthma by supressing proinflammatory cytokines and preventing their brain effects [61,65]. They also interfere with cholinergic and serotoninergic pathways, both centrally and peripherally. Most antidepressants also induce adaptive changes in central monoaminergic neurotransmission, which itself might modulate immune reactivity [61,65]. Tianeptine is an antidepressant drug that has been recently used with success in the treatment of asthma. Tianeptine treats depression through the enhancement of serotonin reuptake from the synaptic cleft by serotoninergic terminals. It works by a mechanism that is just the pollar opposite of selective serotonin reuptake inhibition. It has been reported that this substance provoked a dramatic disappearance of clinical symptoms and improved the pulmonary function in asthmatic patients [61,66].

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Without the slightest doubt, the modern conventional medicine such as SYMBICORT (budesonide and formoterol inhalation) or SEROTID (Salmeterol, fluticasone propionate has provided great benefit for patients with asthma and It shall be the basis of good treatment for asthmatic patients in various degrees and severity. In the present study, these drugs had good results and improved symptoms of patient and their live quality. These treatment approach showed improvement in PEFR from 72.6% to 83.7%, with difference in the amount of 11% and significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use of about 25%. Some randomised controlled trial comparing stable dose Seretide with Symbicort, given as an adjustable maintenance dose, in 706 adults with persistent asthma [67]. Over one year, those taking Serotide experienced the equivalent of 24 more symptom-free days compared to those taking symbicort. The overall incidence of asthma exacerbations (a severe attack) was 47% lower in the Seretide group. Overall, the majority of exacerbations did not result in hospitalisation. Morning peak expiratory flow was significantly higher with Seretide and those taking Seretide experienced a significantly higher proportion of days free of rescue medication use [67].

In the present study, the two drugs had similar results in controling asthma and these results were better in group 4 (given conventional treatment with fexofenadine plus tianeptine). As table 6 shows the extent of improvement after 2 months of treatment comparison between the four groups, the improvement of patients in fourth group was significant. This finding support existence of the synergistic role of fexofenadine with tianeptine and conventional asthma treatment, where the improvement in PEFR was greater in fourth group patients who took the both of drugs together with conventional course. In addition to traditional medicine fexofenadine has been shown to have an impact on inflammatory mediators, other than histamine, such as decreasing the production of LTC_4, LTD_4, LTE_4, PGE_2, and $PGF_{2\alpha}$; and diminishing eosinophil adherence, chemotaxis, and opsonization of particles.[68] These effects may provide benefit to some of the inflammatory responses of an acute allergic reaction and provide a basis for future development of H1 antagonists with stronger anti-inflammatory effects.[68]

Repeated dosing with fexofenadine (180mg) and montelukast (10 mg) as add-on therapy improved AMP PC20 and other surrogate inflammatory markers along with asthma diary outcomes in ICS-treated atopic asthmatic patients. [69]. However, in our study the patients of third group [given Singulair (montelukast) plus Tianeptine] were less responsive and less improved compared with other groups especially in the first month. This may be due to the combination of Singulair (montelukast) plus tianeptine only without the addition of drugs such as SYMBICORT or SEROTID. However, results of imrovement in group thee at the end of second month was better compared with the same group in the first month. This confirms preventive influence of Singulair, Montelukast in a long term-controller medication which should not be substituted for short acting β-agonists. Furthermore, this finding suggest not to use Singulair alone and to be used in combination with other prophylactic agent.

Montelukast is a preventive agent, which should be used in addition to other drugs for the management of asthma. [39] Therefore, as it is well known and previously confirmed, monte-

lukast is effective as prophylactic drug and control of chronic asthmatic course for subjects aged ≥ 15 years, however, of no value as rescue treatment approach in acute attacks.[39]

The clinical benefit from adding Tianeptine to asthma therapy course may actually result in new indications for antidepressants. They could also help in understanding some common pathophysiological mechanisms existing between asthma and depression.[19]

The treatment for asthma and depression involves a coordinated approach that monitors both the symptoms of asthma and depression including using an asthma action plan. It is important to find the treatment that works best for each person. The most effective treatments are those that combine psychological and medical care, medical monitoring, individualised asthma education and adequate community support. It should be noted that while antidepressants seem to have no specific effect on asthma symptoms or medication, the National Asthma Council recommends that people should not take sedatives when having an acute attack of asthma as it may have an effect on breathing [70]

The natural course of asthma include a scenario of triggering phase followed by generation of symptom and inflammation phase to form a vicious cycle of subsequent phases [71]. Constitutional predisposition to the development of neurogenic generator component is necessary for asthma development. Although stress does not cause asthma, stress and asthma are definitely linked. Asthma causes stress, and stress makes it more difficult to control asthma. Even daily stress can make asthma symptoms worsen. The learning to change stress response to decrease asthma symptoms is important. Equally important is prioritizing patient daily schedule so he allow enough time to accomplish what the patient needs to do without feeling pressured or overwhelmed [71]

The study limitation is the small numbers of patients in each group. However, the power analysis calculated to determine the effect of sample size in each group. The power of analysis was 0.89 for reduction in PEFR for all groups, while that of rate improvement were 0.54 for group 2, 0.10 for group 3 and 0.72 for group 4. These findings indicated that sample size with influence on the finding of group 3 only. However, the power of analysis for the differences between the groups indicated a values of >0.97 for the 4 groups indicating non influence of sample sizes on the results.

In conclusion, the present study indicated the therapeutic activity of Tianeptine as add on drug in asthma control and treatment. The most effective combination course is that of fexofenadine, Tianeptine and conventional beta agonist such as symbicort or serotid. Until today, management of bronchial asthma was held in two main directions:Modification of factors inducing allergic reaction and interference on the certain stages of allergic reaction; and Interference with peripheral bronchial receptors. Both these directions do finally affect the trigger factors. Based on the present study findings, We suggest a 3rd direction in the management of bronchial asthma: application of antidepresion agents for the control of activity of generator neurogenic mechanisms of bronchial asthma. This new approach leads to the prevention of asthmatic attacks and opens up new perspectives for the management of this disease

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