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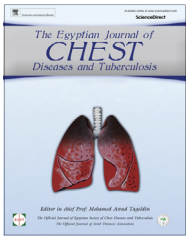

ORIGINAL ARTICLE

Effect of treatment of depression and anxiety on physiological state of severe COPD patients

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KEYWORDS

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Abstract *Background:* Anxiety and depression are mental health problems that result in reduced health-related quality of life (HRQL), and increased mortality. Patients with COPD have a higher risk of anxiety and depression compared to healthy individuals. Recent studies reported a significant relationship between the presence of anxiety and depression and the functional status of COPD patients.

Objectives: To study the effect of treatment of anxiety and depression on the physiological status in COPD patients.

Materials and methods: The study included 50 severe COPD patients with depression and/or anxiety as evaluated and scored by Montgomery and Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating (HAM-A) Scale. They were classified into 2 groups: group I included 25 patients who received antidepressant/anxiolytic therapy in addition to COPD treatment and group II included 25 patients who received COPD treatment only. Modified Borg scale dyspnea score, spirometry (vital capacity, forced vital capacity, forced expiratory volume in first second and forced expiratory flow through 25–75% of expiration), arterial blood, MADRS and HAM-A scale were assessed in all patients at the start of the study and after 3 months.

Results: Patients with severe COPD who were treated for depression and/or anxiety showed a significant improvement in MADRS, HAM-A and dyspnea scales, spirometeric parameters and oxygenation. MADRS and HAM-A scale showed a significant negative correlation to FEV1.

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Conclusion: Treatment of depression and anxiety in COPD patients is recommended as it is associated with a significant improvement in pulmonary physiological status and HRQL. Further studies on larger scales are recommended.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and mortality. Disability, functional limitations and decreased health related quality of life (HRQL) in patients with COPD are correlated with objective physiologic measures of disease severity [1–3]. However, a large proportion of the variance in functional status and HRQL associated with COPD are not explained by measures of pulmonary physiology. Several studies reported a significant relationship between functional status of COPD patients and the presence of anxiety and/or depression [1–11]. These psychological factors may play an important role in determining the impact of COPD on patient's functional state. For example, anxiety in patients with COPD has been associated with decreased HRQL, more severe dyspnea, greater disability, and impaired functional status [4,5] even after improvement in lung function abnormalities [6,7]. Moreover, depression and anxiety have been found to be related to the disease characteristics of COPD, including chest symptoms [8], forced vital capacity [9], and dyspnea [10,11]. Co-morbid depression and/or anxiety also increase the economic burden of the disease where COPD patients with depression and/or anxiety were found to have a higher rate of exacerbation, hospitalization and relapse after discharge compared with COPD patients without depression and/or anxiety [8]. Another study suggested that depression has a possible causal effect on COPD exacerbations and hospitalizations [12]. Furthermore, recent data indicate that mortality risk is three times greater in COPD patients who had depressive symptoms in one series [13]. In this work, we evaluate the effect of treatment of anxiety and depression on the physiological status in severe COPD patients.

Patients and methods

This prospective study was carried out on 50 patients with severe COPD. All patients had been admitted for flare up of COPD in El-Minia University Hospital and were fully evaluated for our study after becoming stable. They were selected after the diagnosis of depression and/or anxiety. COPD diagnosis and disease severity classification were done according to the Global Initiative of Chronic obstructive Lung Disease (GOLD 2009) [14].

All patients were subjected to the following: (1) Full history and examination. (2) Assessment of dyspnea score using modified Borg scale [15], arterial blood gas (ABG) analysis, spirometry with measuring vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory flow through 25–75% of expiration ($FEF_{25-75\%}$) after improvement in COPD exacerbation before discharge and after 3 months. Spirometry was done according to the American Thoracic Society standards [16] and spirometric values used in this report were calculated using normal reference values derived from Crapo and colleagues [17].

Depression was assessed by Montgomery and Asberg Depression Rating Scale (MADRS) [18]. It is composed of 10 main items graded from 0 to 6. Cut-off scores have been assessed as follows: 0–6 indicates the absence of depression (or recovery in the setting of a clinical trial); 7–19: mild depression; 20–34: moderate depression; and 35 and above: severe depression. Anxiety was assessed by Hamilton Anxiety (HAM-A) [19]. It is composed of 14 items graded from 0 (not present) to 4 (disabling). The total score ranges from 0 to 56. A total score of 18 or more means anxiety, 18–24: mild anxiety, 25–29: moderate anxiety, 30 and above: severe anxiety. Depression and anxiety were assessed after improvement in COPD exacerbation before discharge and after 3 months.

Patients were divided into 2 groups: group I included 25 patients of stage III and IV COPD associated with anxiety and/or depression and received antidepressant/anxiolytic therapy for 3 months in addition to COPD treatment. Group II included 25 age and sex matched patients of stage III and IV COPD associated with anxiety and/or depression and received COPD treatment only. They did not receive antidepressant/anxiolytic therapy. Baseline MADRS and HAM-A scores were matched in both groups. A selective serotonin reuptake inhibitor (SSRI); fluoxetine in a fixed dose of 20 mg/d was given to all patients of group I because of the known safety of this group of antidepressants for COPD patients and its considerable anxiolytic effect. All patients were assessed at the start of the study and then monthly for 3 months. Patients with one of the following items were excluded: (1) Depression or anxiety under treatment. (2) Depression or anxiety caused by neuropsychiatric or other disorders. (3) COPD with other comorbidities that may cause depression.

Statistics

Descriptive statistics were computed for each of the variables analyzed. Results were presented as mean ± SD. In order to compare the different groups; the dependent- and independent-samples *t*-test between two groups was used. Chi-squared test was used for comparison between categorical variables. Pearson correlation test was used for detecting the relation of MADRS and HAM-A scores to PFTs. Multivariate analyses were performed to identify association between MADRS and HAM-A scores as well as spirometric parameters and the following patient characteristics: age, smoking index, body mass index and dyspnea scale. All statistical analyses were performed using SPSS version 14.0 statistical software (SPSS Inc., Chicago, IL, USA). A probability value of $p < 0.05$ was used to determine statistical significance.

Table 1 Prevalence of anxiety and depression in COPD patients.

Studied patients (Stage III and IV COPD patients)	Number	Percentage
Patients had both anxiety and depression	13	26
Patients had depression alone	32	64
Patients had anxiety alone	5	10
Total	50	100

Results

The present study included 50 patients with severe COPD selected after diagnosis of depression and/or anxiety. They included 33 males (17 in group I and 16 in group II) and 17 females (9 in group I and 8 in group II) with the mean age of 63.52 ± 2.43. All patients were classified as stage III and IV COPD at the start of the study. Prevalence of anxiety and depression in the studied patients is shown in Table 1 where 32 patients had depression alone, 5 patients had anxiety alone and 13 patients had both anxiety and depression. Baseline MADRS and HAM-A scores in both groups were comparable at the start of the study where there was an insignificant difference between them in both groups (Table 2). Effect of treatment with antidepressant/anxiolytic therapy on MADRS and HAM-A scores in group I is shown in Table 3 where there was a significant reduction in both scores after 3 months of regular therapy reflecting a significant improvement in HRQL. In group II there were no significant changes in MADRS after 3 months of COPD treatment and HAM-A score significantly increased reflecting worsening of anxiety in this group at the end of the study (Table 4). Dyspnea scale, oxygenation and spirometric parameters were significantly improved in group I patients who had received antidepressant/anxiolytic therapy but not in the non-treated group II patients (Tables 5 and 6). There was a significant negative correlation between means of MADRS and HAM-A scores and COPD severity assessed by FEV1 (r: −0.61, p 0.001 for MADRS and r: −0.74, p 0.001 for HAM-A scores).

Discussion

Anxiety and depression are common mental health problems that result in reduced HRQL, and increased mortality [5–7]. Patients with COPD have a higher risk of comorbid diseases such as anxiety and depression compared to healthy

Table 5 Dyspnea scale, spirometry and ABG at the start of study and after 3 months in patients of group I.

Test variable	At the start	3 months later	p Value
Dyspnea scale	4.36 ± 0.99	3.68 ± 1.09	0.001
VC (L/s)	2.32 ± 0.66	2.39 ± 0.60	0.05
FVC (L/s)	2.08 ± 0.54	2.18 ± 0.55	0.01
FEV1 (L/s)	1.10 ± 0.49	1.20 ± 0.44	0.01
$FEF_{25–75\%}$	0.63 ± 0.39	0.71 ± 0.38	0.01
pH	7.37 ± 0.02	7.39 ± 0.03	0.5
$PaCO_2$ (mm Hg)	54 ± 8	48 ± 6	0.4
PaO_2 (mm Hg)	65 ± 7	79 ± 6	0.05
SaO_2 (%)	91 ± 2	96 ± 2	0.03

VC: vital capacity, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, $FEF_{25–75\%}$: forced expiratory flow through 25–75% of expiration, PaO_2: partial arterial oxygen pressure, SaO_2: arterial oxygen saturation.

Table 2 MADRS and HAM-A in group I and II at the start of the study.

Scale	Score at the start of the study in group I	Score at the start of the study in group II	p Value
MADRS (mean ± SD)	27.54 ± 3.34	26.29 ± 3.82	0.65
HAM-A (mean ± SD)	24.45 ± 3.34	23.9 ± 4.23	0.08

MADRS: Montgomery and Asberg Depression Rating Scale; HAM-A: Anxiety was assessed by Hamilton Anxiety Rating Scale.

Table 3 Effect of antidepressant/anxiolytic therapy on MADRS and HAM-A scores in group I at the start of the study and after 3 months.

Patient group I	At the start of the study	After 3 months	p Value
MADRS (mean ± SD)	27.54 ± 3.34	9.54 ± 2.34	0.001
HAM-A (mean ± SD)	24.45 ± 3.34	20.56 ± 2.34	0.01

MADRS: Montgomery and Asberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale.

Table 4 MADRS and HAM-A scores in group II at the start of the study and after 3 months.

Patient group II	At the start of the study	After 3 months	p Value
MADRS (mean ± SD)	26.29 ± 3.82	25.98 ± 2.56	0.65
HAM-A (mean ± SD)	23.9 ± 4.23	28.35 ± 2.76	0.01

MADRS: Montgomery and Asberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale.

Table 6 Dyspnea scale, spirometry and ABG at the start of study and after 3 months in patients of group II.

Test variable	At the start	3 months later	*p* Value
Dyspnea scale	4.50 ± 1.01	5.17 ± 0.99	0.001
VC (L/s)	2.10 ± 0.51	2.9 ± 0.42	0.5
FVC (L/s)	1.86 ± 0.44	1.83 ± 0.41	0.5
FEV1 (L/s)	1.06 ± 0.38	1.04 ± 0.29	0.8
$FEF_{25–75\%}$	0.61 ± 0.31	0.58 ± 0.24	0.2
pH	7.36 ± 0.03	7.37 ± 0.02	0.1
$PaCO_2$ (mm Hg)	54 ± 4	56 ± 4	0.8
PaO_2 (mm Hg)	68 ± 4	67 ± 3	0.7
SaO_2 (%)	94 ± 2	93 ± 2	0.8

VC: vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow through 25–75% of expiration; PaO_2: partial arterial oxygen pressure; SaO_2: arterial oxygen saturation.

individuals [7–10]. The incidence of anxiety and depression increased with increased severity of COPD [20]. Recent studies reported a significant relationship between functional status of COPD patients and the presence of depression [5–8]. Indeed co-morbid psychological outcomes such as depression and anxiety have been associated with increased functional disability and poorer predicted outcomes [21].

Although dyspnea may be partially attributed to the psychological process, the depressed PFTs highlighted the negative effect of depression and anxiety on the pathophysiological process in COPD. This attracted our concern to study the effect of treatment of depression and anxiety on pulmonary physiological parameters in COPD patients.

The current study included 50 stage III and IV COPD patients with depression and/or anxiety: 25 patients received antidepressant/anxiolytic therapy in addition to COPD treatment (group I) and 25 age and sex matched patients were given COPD treatment only (group II). In group I patients who had received antidepressant therapy, there was a significant improvement in both anxiety and depression after 3 months of treatment as reflected by a significant reduction in MADRS ($p < 0.001$) and HAM-A scores ($p < 0.01$) at the end of the study. In group II patients who had not received antidepressant therapy, MADRS score was reduced after 3 months though this reduction was not statistically significant. HAM-A score on the contrary showed significant elevation after 3 months reflecting clinical deterioration of anxiety in non-treated patients. This elevation in HAM-A score in group II at the end of the study may be attributed to the poor response to treatment which makes the patient more anxious in addition to the physiological deterioration in patient's functional status with time.

In this study, we used spirometric, ABG values and modified Borg scale dyspnea score as the physiological parameters to estimate improvement in COPD status. Dyspnea scale is a subjective method to detect improvement whereas spirometric and ABG values are an objective method. Although improvement in dyspnea score is an important marker of improved quality of life, it may be affected by various medical and psychological aspects not related to pulmonary functions. However, spirometric, ABG values which are objective parameters are superior in detection of "physiological" improvement in lung function and health status of COPD patients.

In our study pulmonary physiological parameters, as measured by modified Borg scale dyspnea score, spirometric and ABG values were assessed before and after treatment. Dyspnea scale showed a significant improvement in group I compared to deterioration in group II after 3 months of therapy. There was a significant improvement in spirometric parameters in group I patients after 3 months of the antidepressant therapy. Also ABG values showed a significant improvement in PaO_2 and SaO_2 in group I patients after 3 months of treatment. However there was worsening of most of these parameters in group II patients who had not received antidepressant therapy. In addition, MADRS and HAM-A scores showed a significant negative correlation with FEV1 where lower scores of MADRS and HAM which indicate improvement in depression and anxiety were associated with higher FEV1 levels reflecting improvement in COPD state. A significant improvement in PFTs along with dyspnea scale in group I indicates that improvement in pulmonary physiological functions comes hand in hand with improvement in depression and anxiety. These results highlight the obvious relation of depression and anxiety in the pathogenesis of worsening and improvement in COPD status. This was in agreement with some results which proved that better detection and treatment of depression in patients with COPD may result in improved clinical outcomes and health resource utilization [22]. It should be mentioned that variations of PFTs and modified Borg dyspnea scale were avoided by assessment of these tools in all patients in all situations in the basal conditions (after correction of any reversible causes that could alter any of these tools). In addition, treatment guidelines of COPD were submitted to all patients by monthly clinical assessment. Thus improvement in these PFTs and dyspnea scales could be attributed to treatment of depression and anxiety rather than to any other contributing factors.

Limited studies were done on the assessment of safety and efficacy of different antidepressants in COPD patients and used different tools for scoring of depression and anxiety though only dyspnea scales and/or six or twelve minute walking distance (6MWD, 12MWD) were used for the assessment of physiological response to treatment. Our results come in accordance with the results of Borson and colleagues [23] who found that treatment of depression resulted in a significant improvement in depression and anxiety scores as well as improved pulmonary function measures (12MWD and dyspnea score). Lacasse and colleagues [24] also found that treatment of depression and anxiety resulted in a clinically significant improvement in both depression and anxiety scores and quality of life. On the other hand, other studies had found no significant difference between patients treated with antidepressants and placebo regarding depression and anxiety scores and pulmonary physiological parameters (either 6MWD or dyspnea scale) [25–27].

However, it is suggested that improvement in physiological functions in COPD patients found in our study is not attributed to the type of antidepressant molecule but to treatment of depression and anxiety per se as there is no documented or suggested link between serotonin reuptake inhibition and COPD improvement, though this may be an issue for further studies.

Several mechanisms may explain the link between depression and anxiety and functional impairment in patients with COPD and hence may explain improvement in COPD status with treatment of depression and anxiety. First, anxiety may increase disability in COPD by increasing vigilance for, and amplification of, distressing respiratory sensations. The tendency to misinterpret potentially threatening stimuli, a characteristic of many anxiety disorders, would lead anxious COPD patients to avoid any activity that might produce these sensations. Second, repetitive experiences with hypoxia and hypercapnia in COPD might sensitize neural circuits that control fear responses, to overreact subsequent episodes of hypoxia and hypercapnia. These reactions would again lead to avoidance of physical activity and limit exercise performance. Third, patients with higher anxiety may be more emotionally sensitive to unpleasant somatic sensations, which would lead to greater distress even with a normally tolerable level of these symptoms. All the mentioned mechanisms create a vicious circle in which dyspnea leads to anxiety, which produces a rapid and shallow breathing pattern, leading to air trapping and hyperinflation, creating further dyspnea and exercise limitations [28–30]. Moreover, a concurrent depressive disorder may bring the patient into a vicious circle: the depressed mood reduces the patient's ability to cope with the physical symptoms, which become less tolerable. The psychosocial effects of the disease may be enforced by the influence of the depressed mood. Breathlessness on exertion also often leads to a sense of anxiety further compounding activity avoidance. This leads to the well-known deconditioning cycle of activity avoidance [20].

In summary, depression and anxiety have a considerable role in impairment of the physiological state of COPD patients and should be thoroughly searched for. Treatment of depression and anxiety in COPD is recommended as it is associated with a significant improvement in pulmonary physiological parameters, measured by improvement in pulmonary function tests and dyspnea scale, besides improvement in quality of life. Further studies in this issue on larger scales are recommended.

Conflict of interest

None declared.

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