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# Evaluation of Safety of Nortriptyline in Patients with Chronic Obstructive Pulmonary Disease

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## ABSTRACT

***Background**: Patients with severe chronic obstructive pulmonary disease (COPD) have a poor quality of life and limited life expectancy, frequently resulting in depression that enhances their symptoms. This depressive state might need medical intervention; however, the safety of antidepressant drugs in these patients with poor respiratory function is not clear.*

***Materials and Methods**: Thirty-four subjects with concomitant COPD and depression as well as 34 controls with COPD without depression were enrolled in a single blind controlled study. Nortriptyline was prescribed to the first group and placebo to the second. Spirometric and gas analysis findings were compared before and after a three-month course of trial.*

***Results**: Pulmonary function tests and gas analysis recordings did not show any deterioration after nortriptyline administration. Two deaths occurred during the study period, one in study group due to respiratory infection and the second in control group because of Pulmonary Thromboembolism (PTE).*

***Conclusion**: Nortriptyline is a safe medication to be used in COPD patients when indicated.* ***(Tanaffos 2003; 2(8): 41-48)***

***Key words**: Chronic Obstructive Pulmonary Disease (COPD) - depression - Tricyclic antidepressant(s)- Nortriptyline*

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most frequent chronic lung disease in developed countries (1). Epidemiologic surveys in the United Kingdom (2), Italy, Spain (3), and most of developed countries (4) have demonstrated that approximately 10% of the adult population present with chronic cough and sputum production accompanied with spirometric signs of airflow obstruction. Chronic obstructive pulmonary disease (COPD) afflicts an estimated 14 to 20 million people in the United States and is the fourth leading cause of death for Americans (5). Prevalence of the disease is not greatly different in developing countries, either in urban or rural areas (6-7).

The economic costs of the disease are estimated at almost $40 billion annually in the United States. Social costs include significant disability as reflected

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in; poorer emotional functioning, decreased social-role functioning, impaired activities of daily living, and limited recreational pastimes (1). Several studies indicate that the incidence of depression and anxiety disorders increases in patients with COPD. About 40% of COPD patients in general medical practice were estimated to suffer from depressive disorders compared to 13% of total patients (8).

To continue their strenuous breathing, these patients need their ventilatory drive and muscle strength to be preserved. Thus, prescribing anti-depressants with its potential neuromuscular blockade and possible mucus retaining effects can result in hypoventilation, increased arterial $CO_2$ pressure ($PaCO_2$), decreased arterial $O_2$ pressure ($PaO_2$), and possibly respiratory insufficiency. A few of recent studies have demonstrated short and safe course of tri-cyclic antidepressants in COPD (9); however, their long term effects have not been adequately elucidated.

The purpose of this study was to evaluate long term effects of nortriptyline in patients with moderate to severe COPD who needed anti-depressant pharmacotherapy.

## MATERIALS AND METHODS

***Subjects:***

The "Medical Ethics Committee at Isfahan University of Medical Sciences" approved the protocol and methods. All patients signed the protocol consent forms. Two-hundred-seventy-six patients with COPD who were referred to a pulmonary clinic were screened in order to enroll 34 patients into the study. The selected cases had to meet all the study criteria included complaints regarding their coexisting depression.

Meanwhile another group of 34 COPD patients matched by age and severity of the illness as defined by gas analysis findings, without symptoms of depression, were enrolled to be considered as control group.

Based on a pilot study by one of the authors, sample size was estimated, the change in the lowest nocturnal $PO_2$ observed in 14 COPD patients was 7.1±6.0%, Mean ± SD. Our trial was originally planned for 25 patients per treatment group to achieve at least 90% power to detect a 7% difference based on a two-sample t-test with a SD of 6%, but to cope with possible losses in patient follow ups, the population was increased to 34 patients in each group.

The baseline demographic and respiratory characteristics are summarized in Table 1.

**Table 1**. Demographic characteristics and baseline respiratory parameters

| Characteristic | Nortriptyline cases | controls | P |
|---|---|---|---|
| Male/female | 20/16 | 14/18 | 0.28 |
| Age/years (Mean ± SD) | 63.41±11.11 | 60.37±11.82 | 0.68 |
| FVC/liters (Mean ± SD) | 2.12±0.88 | 2.28±0.98 | 0.57 |
| $FEV_1$/liters(Mean ± SD) | 1.32±0.70 | 1.52±0.81 | 0.69 |
| $PaO_2$/mmHg (Mean ± SD) | 58.24±7.25 | 60.29±8.84 | 0.35 |
| $PaCo_2$/mmHg (Mean ± SD) | 42.25±3.93 | 40.61 | 0.47 |

FVC = Forced Vital Capacity

$FEV_1$ = Forced Expiratory Volume at first second of expiration

$PaO_2$ = Pressure of arterial $O_2$

$PaCo_2$ = Pressure of arterial $Co_2$

The diagnosis of COPD was followed by the "American Thoracic Society" definition (1).

Diagnosis of depression was based on a rather loose criteria. In fact, all patients with any of the following symptoms were considered to be depressed:

- Depressed mood most of the day, particularly in the morning
- Markedly diminished interest or pleasure in almost all activities nearly every day (anhedonia); either indicated by the subjective account or observations made by others
- Insomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Impaired concentration, indecisiveness
- Recurring thoughts of death or suicide

This study included both male and female patients between the age of 41 and 82 years. The $FEV_1$ was needed to be < 65% of predicted, and relative stability of symptoms was required. The patients were excluded if significant (as determined by an investigator) non pulmonary or pulmonary disease other than COPD was present. Specific exclusions were elevated liver or renal function laboratory values (greater than two times normal values), a myocardial infarction within 6 months, and any respiratory viral infections within 6 weeks of study.

Patients had to take their current medications including theophylline preparation, inhaled or oral corticoseroids, inhaled beta agonists, and/or ipratropium bromide.

***Study Design:***

The study was a 3-month, single-blind , placebo controlled, two-arm parallel group design, in which the physician knew the type of medication, but the patient didn't.

In the initial 4-week screening process, all patients in the two groups underwent pulmonary function study and arterial blood gas (ABG) analyses. Later, depressed patients were enrolled into a 12-week treatment phase using nortriptyline (Nortrilene) tablets 25 mg at bedtime. The control group received a placebo tablet with similar shape and color. Any of the cases or controls who developed exacerbation of COPD were considered as treatment failure and left the group, while those who did not follow the course for any reason including intolerance to the medication were excluded from the study.

Pulmonary function tests (PFT) and ABGs were repeated at the end of the 12-week period.

***Statistics***

All comparisons between two groups (PFT, ABG, symptom scores, etc.) were performed using independent samples t-test, while paired sample t-test was used to make a comparison within the groups before and after intervention.

Statistical package for the social sciences (SPSS version10; SPSS Chicago ILL) was used for all statistical analyses.

Because of multiple comparisons, statistical significance is claimed at level 0.01 vs. the two-sided alternative.

## RESULTS

Overall, spirometric parameters and blood gas analysis during the study period showed minimal improvements in those patients taking nortriptyline as compared with the control group; however, this improvement was clinically minimal with questionable statistical significance ($p>0.01$)

The results of comparisons are summarized in Table 2.

**Table 2.** Comparisons between respiratory parameters before and after intervention for nortriptyline cases and controls.

| Parameter | Nortriptyline cases | | | Control group | | |
|---|---|---|---|---|---|---|
| | Before | After | p | Before | After | p |
| FVC/lit (Mean ± SD) | 2.11±0.88 | 2.27±0.84 | 0.017 | 2.28±0.98 | 2.32±0.96 | 0.35 |
| $FEV_1$/ lit (Mean ± SD) | 1.32±0.70 | 1.45±0.70 | 0.027 | 1.52±0.81 | 1.55±0.79 | 0.52 |
| PEFR/ lit (Mean ± SD) | 3.46±1.53 | 3.88±1.95 | 0.024 | 3.76±1.98 | 3.89±1.84 | 0.26 |
| $FEF_{25-75}$ | 0.83±0.69 | 1.01±0.85 | 0.013 | 1.00±0.78 | 1.06±0.77 | 0.25 |
| $PaO_2$ | 58.24±7.25 | 59.30±7.35 | 0.011 | 60.29±8.94 | 58.24±12.98 | 0.29 |
| $PaCo_2$ | 42.25±3.93 | 41.03±7.04 | 0.23 | 40.62±4.41 | 40.54±3.44 | 0.80 |
| PH | 7.38±0.037 | 7.38±0.037 | 0.09 | 7.38±0.039 | 7.38±0.037 | 0.55 |

The changes in the most important respiratory parameters are best illustrated by a scattero-gram of the follow-up observations (vertical-axis) vs. the baseline observations (horizontal-axis) for each patient (Figs 1 to 3). The vertical distance between the two groups of dots represents the improvement or deterioration associated with treatment with nortriptyline at a given baseline value. The amount of change varies depending on the baseline value at which the comparison is made.

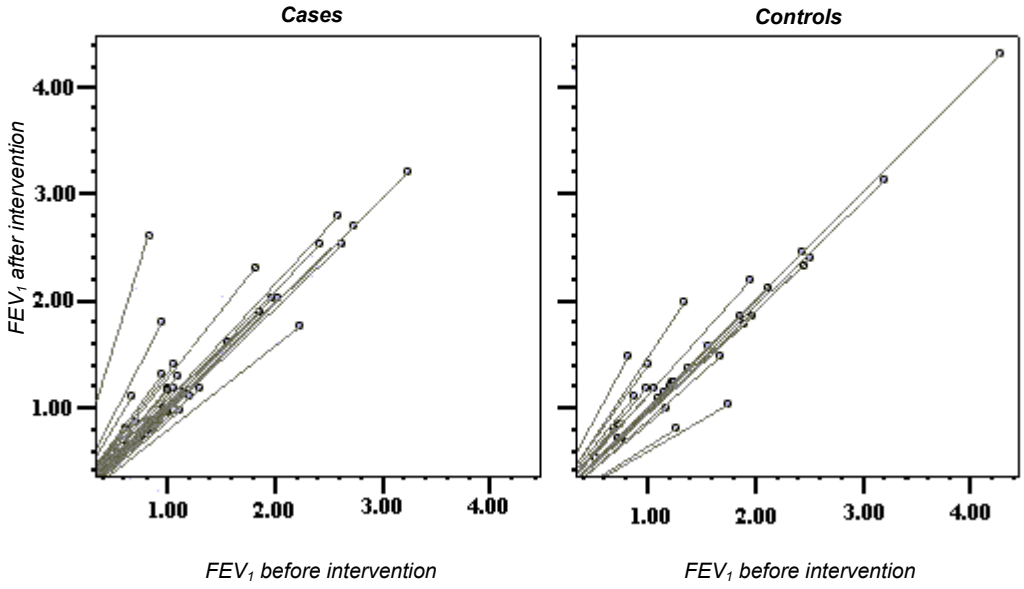


**Figure 1.** Comparisons between measured $FEV_1$ before and after intervention in cases and also in controls

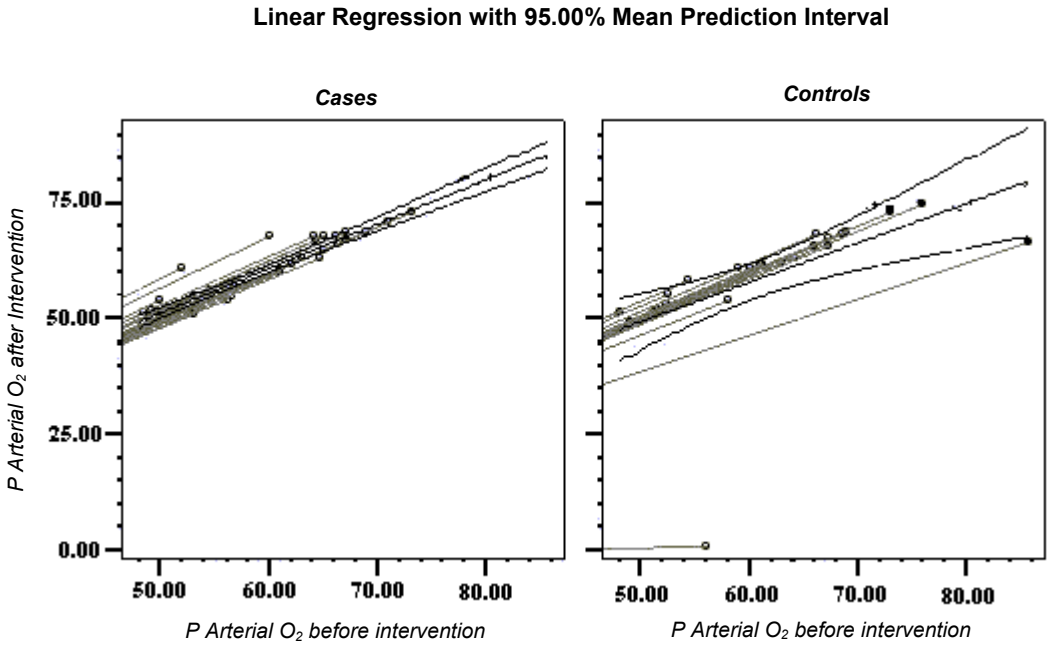


**Figure 2.** Comparisons between measured $PaO_2$ before and after intervention in cases and also in controls

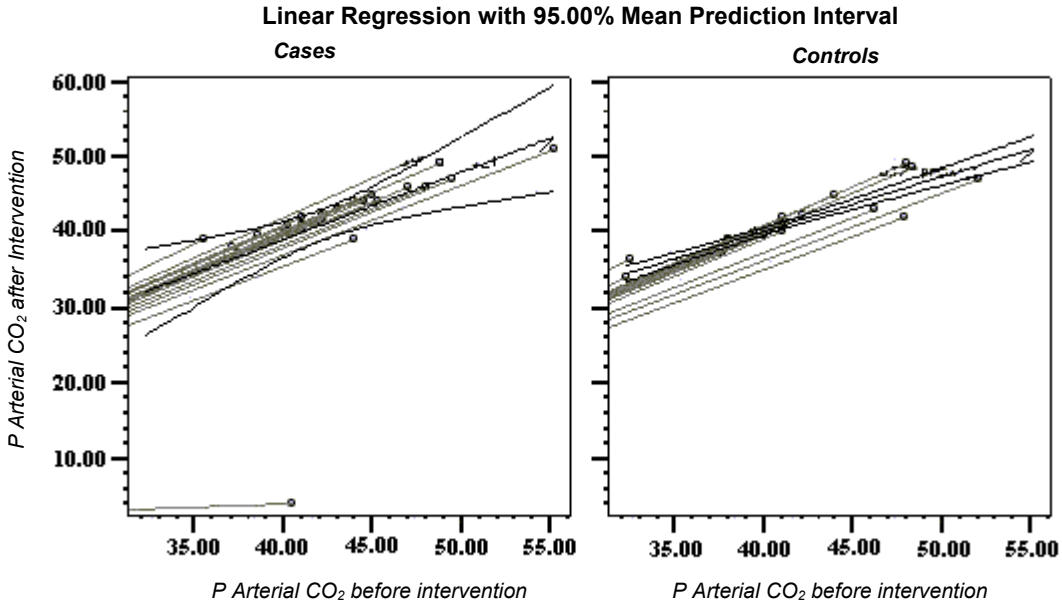


**Figure 3**. Comparisons between measured $PaCo_2$ before and after intervention in cases and also in controls

During the study period, five patients (three from the nortriptyline group and two controls) experienced exacerbation resulting in their hospitalization. Two patients (one case and one control) expired during the study period; their deaths were related to respiratory infection and pulmonary thromboebolism respectively.

## DISCUSSION

Ormel and co-workers (10) have reported that depressive symptoms contribute more to functional disability, poor health perception, and poor well-being, rather than many chronic medical conditions. Patients with both chronic obstructive pulmonary disease and depression are more functionally disabled than those with either COPD or depression alone (11). Furthermore, patients with both conditions use greater resources, more primary care services, and more emergency care than patients with COPD without depression (11). Researches on patients with coronary artery disease have shown that both anxiety and depression have a significant effect on physical functioning over 12 months. However, little attention has been paid to patients with COPD and concomitant psychopathology, despite findings that less than 40% of the variance in exercise tolerance is explained by any physiological measure of pulmonary function. Previous studies of COPD patients have indicated that there is no relationship between functional status and psychiatric co-morbidity. However, more recent studies have indicated a significant relationship between functional status of COPD patients and the presence of anxiety or depression and have not recommended therapeutic intervention for depression (12-13). Furthermore, several studies indicate that pharmacotherapy of depression or anxiety in COPD patients improves functional capacity (14-15). Therefore, finding antidepressant drugs that can be safely used in the mentioned situation might be of great importance.

The antidepressants such as nortriptyline and bupropion have been reported as effective agents in stimulating smoking cessation (16, 17, 18). The mechanism by which nortriptyline acts as smoking cessation aid is unknown. Since smoking cigarettes is the major risk factor for developing COPD (19), and smoking cessation is the main preventive measure in reducing the decline in lung function observed in patients at all stages of COPD (17), the use of antidepressants in the treatment of these patients needs further attention.

To our knowledge, this is the first study concerning the safety of nortriptyline in COPD patients. Our study clearly discloses the long term safety of nortriptyline in COPD patients without any deterioration in pulmonary parameters as compared with control group.

The study outcomes also show minimally improved respiratory parameters in cases taking nortriptyline during the study period. These increments with borderline statistical significance are minimal changes that are not clinically significant; therefore, we cannot consider them as routine medications for COPD management. However, this minimal increment can ensure the physicians to manage their depressed COPD patients with more confidence.

## CONCLUSION

Treatment with nortriptyline antidepressant medication is clinically safe and may be followed by significant improvement in the functional status of COPD patients. It is imperative that clinicians treat not only the medical illness but also the concomitant psychological symptoms in order to optimize the patient's quality of life.

## REFERENCES


1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global Strategy for the diagnosis, management, and Prevention of Chronic Obstructive Pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. ***Am J Respir Crit Care Med*** 2001; 163(5): 1256-76.
2. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. ***Thorax*** 2000; 55(12): 1000-6.
3. Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? ***Chest*** 2003;123(5): 1684-92.
4. Cydulka RK, Rowe BH, Clark S, Emerman CL, Camargo CA Jr; Marc Investigators. Emergency department management of acute exacerbations of chronic obstructive pulmonary disease in the elderly: the Multicenter Airway Research Collaboration. ***J Am Geriatr Soc*** 2003; 51(7): 908-16.
5. Petty TL. Scope of the COPD problem in North America: early studies of prevalence and NHANES III data: basis for early identification and intervention. ***Chest*** 2000; 117 (5 Suppl 2):326S-31S.
6. Golshan M, Barahimi H, Nasirian K. Prevalence of chronic bronchitis and chronic respiratory symptoms in adults over the age of 35 years in Isfahan, Iran in 1998, Respirology 2001; 6(3):231-5.
7. Golshan M, Esteki B, Dadvand P. Prevalence of self-reported respiratory symptoms in rural areas of Iran in 2000. ***Respirology*** 2002; 7(2): 129-32.
8. Gift AG, McCrone SH. Depression in patients with COPD. ***Heart Lung*** 1993; 22(4): 289-97.
9. Lewis L; Optimal treatment for COPD, Patient Care; 2000; 34: 60-74.
10. Ormel J, Kempen GI, Deeg DJ, Brilman EI, van Sonderen E, Relyveld J. Functioning, well-being, and health perception in late middle-aged and older people: comparing the effects of depressive symptoms and chronic medical conditions. ***J Am Geriatr Soc*** 1998; 46(1): 39-48.
11. Doll H, Grey-Amante P, Duprat-Lomon I, Sagnier PP, Thate-Waschke I, Lorenz J, et al. Quality of life in acute exacerbation of chronic bronchitis: results from a German population study. ***Respir Med*** 2002; 96(1): 39-51.
12. Wagena EJ, Huibers MJ, van Schayck CP. Antidepressants in the treatment of patients with COPD: possible associations between smoking cigarettes, COPD and depression. ***Thorax*** 2001; 56(8): 587-8.
13. Kim HF, Kunik ME, Molinari VA, Hillman SL, Lalani S, Orengo CA, et al. Functional impairment in COPD patients: the impact of anxiety and depression. ***Psychosomatics*** 2000; 41(6): 465-71.
14. Mitchell-Heggs P, Murphy K, Minty K, Guz A, Patterson SC, Minty PS, et al. Diazepam in the treatment of dyspnea in the "Pink Puffer" syndrome. ***Q J Med*** 1980; 49(193): 9-20.
15. Papp LA, Weiss JR, Greenberg HE, Rifkin A, Scharf SM, Gorman JM, et al. Sertraline for chronic obstructive pulmonary disease and co-morbid anxiety and mood disorders. ***Am J Psychiatry*** 1995; 152(10): 1531.
16. Hall SM, Reus VI, Munoz RF, Sees KL, Humfleet G, Hartz DT, et al. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. ***Arch Gen Psychiatry*** 1998; 55(8): 683-90.
17. Prochazka AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D. A randomized trial of nortriptyline for smoking cessation. ***Arch Intern Med*** 1998; 158(18): 2035-9.
18. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. ***N Engl J Med*** 1997; 337(17): 1195-202.
19. Jorenby DE, Leischow SJ, Nides MA, Rennard SJ, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. ***N Engl J Med*** 1999; 340(9): 685-91.