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RESEARCH ARTICLE

GENERAL REVIEW ON DEPRESSION ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT

The COPD condition experience co-morbid symptoms of cardiovascular disease, diabetes meleitus, anemia, depression, anxiety, GERD, obstructive sleep apnoea, cachexia, muscle wasting and osteoporosis. Depression is the major co-morbidity in COPD and are associated with poor prognosis. The occurance of depression in a community have a strong relationship with low level of education, poor socio-economic condition and advance in age. COPD exacerbations have a negative impact on pulmonary functions, health related quality of life and patient survival. Frequent exacerbations are more seen in depressive patients than in normal patients. Severe dyspnoea, progressive irreversible condition and associated hypoxia may be responsibe for the organic causes of depression in severe COPD patients. Simple questionnaires are used to diagnose depression in COPD patient. Antidepressant drug therapy are effective in the treatment of moderative severe depression in patients with COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease, which can be prevented and treated. The COPD is characterized by persistent limitations in airflow that are progressive. The COPD is associated with an enhanced chronic inflammatory response in airways of the lungs to noxious particle or gases. COPD will be the third most common cause of death by 2020 (Tsai yi-Tzung *et al*., 2013). The prevalence of physiologically defined COPD in adult aged ≥40 yrs is 9-10% (Halbert *et al*., 2006) and that for the elderly patients was found to be 72% (De Sajal, 2011).

Etiology

Several factors are associated with COPD condition. Tobacco smoking is considered to be the primary cause for COPD (Vaart.H.vander *et al*., 2004). Smoking results in pulmonary hyperactivity, which causes persistent airway obstruction.90% of the individuals with smoking habit are likely to get COPD. In non-smokers, about 20% of COPD cases are due to passive smoking. Individuals having the habit of smoking marijuana, cigar and water pipe can also confer the risk of COPD (McKay *et al*., 2012; Wagena *et al*., 2001). Destruction of lung tissues are seen in individual with COPD condition, having the habit of smoking. The destruction may be due to mediation by neutrophils, when exposed to smoking (ProfitaMirella *et al*., 2010; Tatcher *et al*., 2005). Genetics play an important role in the development of COPD. The inherited risk factor of COPD is alpha-1-antitrypsin(AAT) deficiency. (Yang Ping *et al*., 2008) The AAT deficiency can be defined as a genetic disorder that contributes to the risk in developing COPD specifically emphysema. AAT is a serine protease inhibitor and is an acute phase reactive protein. (Yang Ping *et al*., 2008; Barr *et al*., 2009)Other factors that can lead to risk for COPD are air pollution, occupational exposure, exposure to irritants like sulphurdioxide, noxious gas, organic dust and history of respiratory infections.

Pathophysiology

In obstructive bronchiolitis, the poor airflow is due to the breakdown of lung tissues and small airway diseases. Severe destruction of small airways can leads to the formation of larger air pockets called bullae. The bullae will replace the lung tissue, leading to a disease condition called bullous emphysema. In COPD inflammations are seen both in the peripheral airways and in lung parenchyma. (Murry *et al*., 2012; Losano *et al*., 2012) The inflammatory cells involved in COPD includeneutrophil, granulocytes, macrophage and two types of white blood cells. Individuals with smoking habit have

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additional T cell lymphocyte involvement. In some individual with COPD, eosinophilinvolvement in mediating inflammation are also seen. In addition these cell responses are activated by inflammatory mediators like chemotactic factors (Tatcher *et al*., 2005).Other processes involved in lung damage include, oxidative stress produced by high concentration of free radicals in individuals with smoking habit. The oxidative stress will activate Endothelial Growth Factor(EDGF) and stimulate mucin synthesis in airway epithelial cells(Takeyama Kioshi *et al*., 2001). The airway get narrowed due to inflammation and scarring within them can lead to inability in breathing. Narrowing of the arteries in the lung tissues are seen when the oxygen level are low for a longer period. These changes results in increased blood pressure in the pulmonary arteries, leading to cor-pulmonale. (Weitzenblum Emmanuel, 2003)

Signs and symptoms

The most common symptoms of COPD are sputum production, shortness of breath and productive cough. These symptoms are present for a longer period of time and typically worsen over time. The evidence for chronic bronchitis are confirmed, when individual with cough symptoms exist for more than three months in a year and continued for more than two years with sputum production. In chronic bronchitis, the shortness of breath will worsen on exertion, and chest tightness are not common. Individuals with obstructed airflow may have wheezing or decreased sounds, when heard on a stethoscope. A barrel chest is a characteristic sign of COPD patients.

Diagnosis of COPD

The spirometry can be used for measuring the amount of airflow obstruction present and is generally performed after the use of a bronchodilator, to open up the airways. The main components used in diagnosis include; forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio. The ratio less than 70% will confirm the disease. Mortality has been an important outcome in patient with COPD and FEV1 is regarded as the most important predictor in mortality rate. (Oga Toru *et al*., 2003) The severity of COPD is diagnosed by using mMRC shortness of breath scale. The scale is grouped in to grade; 1-only strenuous activity, 2-vigorous walking, 3-with normal walking, 4-after few minutes of walking, 5-while changing cloth. GOLD grade severity FEV% predicted mild, moderate, severe, very severe or chronic respiratory failure. The COPD can be also diagnosed from medical history, physical examination, ABG analysis, chest X ray, sputum analysis and CT scan. (Mathew.L.Mintz *et al*., 2011) (Table-1)

Prevention of COPD

The most cases of COPD are potentially prevented by decreasing the exposure to smoke and polluted air. Smoking cessation is the only measure to slow down the worsening of COPD. The measures to stop the smoking habit can be done by participating in smoking cessation program by the use of medications like nicotine replacement therapy, bupropion or verenicline (Wagena *et al*., 2001). Individuals with COPD should avoid the exposure to occupational dust, organic dust and chemicals. The preventive measures have to be taken for reducing the exposure to environment for the workers engaged in industries like coal mining, construction and stone masonry, which otherwise can lead to development of COPD. The measures taken for maintaining occupational health include; creation of public policy, educating the workers and management about the risk and checking for the early signs of COPD. Both indoor and outdoor air quality should be improved for preventing COPD or to slow the worsening of the COPD condition. Exposure to smoke from cooking and heating fuels can be reduced by applying proper ventilations in houses. (ProfitaMirella *et al*., 2010)

Complications of COPD

The pulmonary arterial pressure get increased due to decrease in the vascular bed space (due to lung congestion). In some cases the pressure get increased, leading to corpulmonale (right ventricular atrophy) with consequent heart failure. In advanced stages of COPD, there is poor cerebral oxygenation and increased Pa CO_2 level leading to hypoxia and respiratory acidosis. If the condition progress, will result in complete respiratory failure.

Management of COPD

The COPD symptoms are treatable and its progression can be delayed. The goal for treating COPD include reduction in the rate of progression of disease, improvement in physical, physiological well beingness and finally reducing the mortality rate. (Mathew.L.Mintz *et al*., 2011)

Non pharmacological therapy

The non pharmacological therapy for managing COPD is to minimize the exposure to polluted air, smoking cessation and avoiding other irritants will slow the rate of decline in FEV1 in COPD patients. The pulmonary rehabilitation programs are an integral component in managing COPD and should include exercise training along with smoking cessation, breathing exercise, optimal medical treatment, psychosocial support and health education. The rehabilitation can improve patient health status and quality of life. Patients with severe chronic hypoxia can be treated by oxygen therapy. The supplement of oxygen therapy can reverse hypoxia, particularly at night and during exercise. Patients with severe emphysema, the lung volume reduction surgery (LVRS) are beneficial to the patient. The patient who receive LVRS and pulmonary rehabilitation showed a greater improvement in lung function and quality of life. (Mathew.L.Mintz *et al*., 2011) The substantial weight loss are reported in both hospitalized and non hospitalized COPD patients. The decreased caloric intake and increased energy expenditure spend in breathing are the two possible explanations for the weight loss. The result of malnutrition can decrease the respiratory muscle function leading to depression of the immune function (Sergio Alcolea *et al*., 2007).

Pharmacological treatment for COPD

The bronchodilators are the primary medication used in COPD condition. There are two major types of bronchodilators namely, β-agonist and anti-cholinergic which can be further grouped into long acting and short acting forms. They reduce shortness of breath, wheezing and exercise limitation, resulting in improved quality of life. β-agonist stimulate β2 receptors located in the lungs and relaxes muscles in the airways and increase the air flow to the lungs. The anti-cholinergic drugs in hibitsmuscarinic receptor activity, there by relaxes the bronchial smooth muscles and increases air flow to the lungs.

Corticosteroids are usually used both by inhalation and orally administered tablet form for treating and prevent acute exacerbations. Long term treatment with steroids can cause significant side effects like osteoporosis, increased susceptibility to infection, hyperglycemia, cardiovascular collapse. Long term use of antibiotic specifically those belonging to macrolide class like erythromycin will reduce the frequency of exacerbations. Methyl xanthenes like theophylline are used as a second line agent for treating COPD. Mucolytics are also recommended for treating COPD condition. (Table 2-3)

Table 1. Spirometric classification of COPD

Stage I : mild	FEV1/FVC < 0.70
	FEV1 ≥ 80% predicted
Stage II : moderate	FEV1/FVC < 0.70
	50% ≤ FEV1< 80% predicted
Stage III : severe	FEV1/FVC < 0.70
	30% ≤FEV1< 50% predicted
Stage IV: Very severe	FEV1/FVC < 0.70
	FEV1< 30% predicted or FEV1< 50% predicted plus chronic respiratory failure

Table 2. Classification of Drugs used in COPD patients

Category	Example
Anticholinergics	• Ipratropium bromide
	• Tiotropium bromide
B-agonists (sympathomimetics)	• Salmetrol
	• Formoterol
	• Salbutamol
Methylxanthines	• Theophylline
	• Aminophylline
Corticosteroids	• Prednisolone
	• Budesonide

Table 3. Pharmacologic Therapy For Stable COPD (SA-short acting, LA- long acting, ICS-inhaled corticosteroids, PDE-phosphodiesterase)

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments
A	SA anticholinergic or SA b2 agonist	LA anticholinergic or LA b2 agonist or SA b2 agonist and SA anticholonergic	Theophyllin
B	LA anticholinergic or LA b2 agonist	LA anticholinergic and LA b2 agonist	SA b2 agonist and/or SA anticholinergic Theophylline
C	ICS+LA b2 agonist or LA anticholinergic	LA anticholinergic and LA b2 agonist or LA anticholinergic and PDE-4 inhibitor or LA b2 agonist and PDE-4 inhibitor	SA b2 agonist and/or SA anticholinergic Theophylline
D	ICS+ LA b2 agonist and/or LA anticholinrgic	ICS+ LA b2 agonist LA anticholinergics or ICS+LA b2 agonist PDE-4 inhibitor or LA anticholinergics and LA b2 agonist or LA anticholinergic and PDE-4 inhibitor	Carbocysteine SA b2 agonist and/or SA anticholinergic Theophyllin

Management of exacerbations

Exacerbations can be characterised based on the worsening of the patient's respiratory symptoms, that is beyond normal day to day variations and need to have a change in medication. Treatment options:

- Oxygen therapy
- Bronchodialators
- Systemic corticosteroids
- Antibiotics

Comorbidities seen in COPD

The COPD condition experience co-morbid symptoms of cardiovascular disease, diabetes mellitus, anaemia, depression, anxiety, GERD, obstructive sleep apnoea, cachexia, muscle wasting and osteoporosis.(Martinez H. Carlose *et al*., 2014)

Cardiovascular diseases

The most common spectrum of cardiovascular diseases seen with COPD include cerebrovascular disease, CHF, arrhythmias, CAD, atrial fibrillation and interstitial heart disease (IHD)(Martinez H. Carlose *et al*., 2014).

Diabetes and metabolic syndrome

Individuals having both COPD and diabetes, the risk of death is higher within 5 yrs, especially when they are recovering from an exacerbation. Inhalation of high dose of corticosteroids are also associated with a higher frequency of diabetes related hospital admission and the higher glucose levels (Martinez H. Carlose *et al*., 2014)

Osteoporosis

The osteopnoea and osteoporosis are increased in patients with COPD. The prevalence of osteoporosis are seen with severity in COPD. The association of COPD and osteoporosis are stronger in men than for women and include a rapid progression of bone loss, particular when individual have vitamin D deficiency (Martinez H. Carlose *et al*., 2014).

Cachexia and muscle wasting

Low body mass index (BMI) and weight loss are common in many chronic diseases; however, in COPD low weight are due to disproportionate loss of fat-free tissue, especially muscle

mass. The association between cachexia in COPD individuals and specific genetic polymorphisms within genes related to fat mass and obesity.The potential interventions including the use of mechanical ventilation, nutritional supplementation anabolic steroids and growth hormone releasing factor such as ghrelin are effective for these condition (Martinez H. Carlose *et al*., 2014).

Anemia

Anemia in COPD shares mechanisms with other anemia of chronic disease with persistently elevated interleukin interfering with the response to erythropoietin. The erythropoietin level was found to be higher in COPD patients having anemic condition compared to individuals with normal hemoglobin count. (Martinez H. Carlose *et al*., 2014)

Obstructive sleep APNOEA

The population based studies have identified sleep apnea among COPD patients with a frequency slightly higher than the general population. Clinical findings which indicates the presence of COPD include pulmonary hypertension or right sided heart failure, whose etiology is unknown. (Martinez H. Carlose *et al*., 2014)

Gastro esophageal reflux disease (GERD)

The prevalence of GERD is more in COPD than in general population. According to research databases, the incident of GERD diagnosis was found to be higher in individuals with established COPD. (Martinez H. Carlose *et al*., 2014)

Anxiety and depression

The patient diagnosed with COPD are at risk in developing depression and gradually increases the intensity after the diagnosis.(Martinez H. Carlose *et al*., 2014) In past two decades it was observed that, patients with COPD with three or more co morbidities, can lead to frequent hospitalization and may even die prematurely compared to COPD patients without co morbidities. Among the co-morbidities, anxiety and depression contribute to a substantial burden to COPD related morbidity, notably by impairing quality of life and reducing adherence to treatment. Untreated and under recognized depression and anxiety symptoms in patients with COPD have serious effects on physical functioning and in social interaction, were there is an increase in fatigue and health care utilization(Martinez H. Carlose *et al*., 2014; Schnell Kerry *et al*., 2012).

Depression in COPD

Depression is the major co morbidity in COPD and are associated with poor prognosis. The prevalence of depression varies widely in different populations which could be attributed to different ethnicity, different cultural backgrounds and heterogeneous demography of the study populations and different screening tools (Khaled *et al*., 2009). The occurrence of depression in a community have a strong relationship with low level of education, poor socio economic condition and advance in age. (Negi Harish *et al*., 2014) The cumulative prevalence of depression in COPD was found to be 72 % (De Sajal, 2011). One fifth of the patients with COPD have severe symptoms related to depression, with severity in COPD condition (Negi Harish *et al*., 2014). An increased experience of dyspnoea are likely to be a contributing factor leading to anxiety. Smoking has been associated with nicotine addiction, and the factors that contribute to smoking may also predispose to anxiety and depressive disorders. (Kochhar *et al*., 2007) Depression is another example for chronic illness that cause significant morbidity and mortality rate. Depression is a leading cause of disability worldwide and an increases the impairement of physical and psychological conditions in persons with COPD. The depression will adversely affect the functional mobility, symptom burden, the ability to tend to daily tasks and mortality rate (Schane E. Rebecca *et al*., 2008). COPD exacerbations have a negative impact on pulmonary function, health related quality of life and patient survival. Frequent exacerbations are more seen in depressed patients than in normal patients. Frequent exacerbations lead to more frequent hospitalizations and thereby increases the healthcare cost (Afonso *et al*., 2011; Mohammed zeeshanRazal *et al*., 2013; Quint *et al*., 2008). The quality of life of a chronically ill patient may be particularly complicated by concurrent depressive disorder which may bring the patient into a dicious circle. The depressive mood lowers the force needed to cope with chronic disease and the physical symptoms become less tolerable. Mislabeling depressive symptoms as side effects of COPD may lead to under detection and under treatment in general practice. (Hill *et al*., 2008)

Etiologies of depression in COPD

There is significant evidence supporting the increased prevalence of depression in patients with COPD, but depression is not a homogenous entity because they are multiple contributing etiologies for the depressive symptoms. To manage these co-morbidity in a effective way is by understanding the potential contributors, that causes depression (Hill *et al*., 2008). Several factors contribute to the development of depression in patients with COPD. Severe dyspnoea, progressive irreversible condition and associated hypoxia may be responsible for organic causes of depression in severe COPD. In addition advanced age, low socio-economic condition and the chronic nature of the disease also result in social isolation which can lead to more depression. Even after adjusting the severity of COPD, depression is responsible for fatigue, shortness of breath and disability. (De Sajal, 2011) Chronologically the earliest risk may be a genetic predisposition to depression, followed by the environmental assaults imposed by the respiratory illness itself and finally the direct neuropsychiatric effects of chronic respiratory disease (Norwood.J. Rachel, 2007). Smoking associated depression is highest among people who try to quit smoking. Depression in COPD is a heterogeneous entity with a potentially composite etiology including genetic predisposition, environmental loses and stresses, as well as direct damage to the brain mediated by the physiologic effect of chronic respiratory illness. As such the relationship between depression, COPD and smoking are not linear but rather interconnected with each element influencing the others to different degrees in any given patient at any given time. Over the course of their lifetimes COPD patients may experience multiple exposures, that increases the risk for development of depression (De Sajal, 2011).

Mechanism of depression in COPD

The exact pathophysiological mechanism of depression in patient with COPD is unknown. It is currently assumed that

depression of COPD patients is likely to have multi dimensional with physiological, psychological and psycho-social contributors. Elevated levels of inflammatory biomarkers IL-6 and C-reactive protein accounts for the association of depressive symptoms with pulmonary obstruction. In addition there are biological, behavioral and social factors that may contribute to an increase in physical disability and social isolation in patients with COPD (Goodwin *et al*., 2012). The inter relationship between smoking, depression and/or anxiety and COPD is not clear. Smoking increases the risk and severity of COPD which make the daily activities effortful and stressful and increases the risk of depression or anxiety in patients with COPD. (Khaled *et al*., 2009)

Diagnosis of depression in COPD

Detection of depression in patients with COPD by a simple questionnaire will help the respiratory physicians to diagnose it and appropriate treatment or referral can be suggested. Patient health questionnaire-9 (PHQ-9) is a part of the primary care evaluation of mental disorders (PRIME MD) and utilizes a semi structural psychiatric interview using the diagnostic and statistical manual of mental disorder (4^{th} Edition) (DSM IV) criteria for assessing the severity and functional impairment due to depression. In PHQ-9, the patients are asked to report each of the nine depressive symptoms during the previous two weeks. (De Sajal, 2011; Kochhar *et al*., 2007) Hamilton depression scale is also used to diagnose depression in COPD patients.

Role of Antidepressants in COPD

Treatment of depression in COPD particularly by cognitive behavioral therapy have a positive impact on quality of life. Tricyclic Antidepressants have a positive impact on mood and COPD, but side effects limit their use. Physical rehabilitation along with use of Antidepressants may have a positive impact on mood disorders (Wilson Ian, 2006; Panagioti Maria *et al*., 2014). Antidepressants may have differential effects on depressed COPD patients when compared with non COPD depressed patients. The selection of antidepressants with regard to minimize the drug interactions and optimization of medical management of COPD due to small benefit/risk ratio are important in depression treatment. Evidence suggests that antidepressant drug therapies are effective in the treatment of moderate to severe depression in older patients with chronic physical illness as compared to placebo. However the efficacy of antidepressants in depressed COPD patients are inadequately investigated from published articles. (FritzscheAnja *et al*., 2011) Antidepressant medication aims to regulate the neurotransmitter systems in the brain that are associated with depression. Tri cyclic Antidepressants (TCA) are successfully used for decades and their antidepressant effect is initiated by inhibiting the reuptake of neurotransmitters serotonin, nor adrenaline and dopamine from synaptic cleft.(Stage B. Kurt *et al*., 2006) The increase in available neurotransmitters enhances the synaptic cleft transmission and are suppose to adjust the deficiency of second messengers that underline depression mechanisms. Today Selective Serotonin Reuptake Inhibitors (SSRI) are the most commonly prescribed antidepressant drugs. They act on serotonin transporters and enhances the concentration of serotonin in the synaptic cleft by inhibiting the reuptake into presynapse. In contrast to TCA they are more selective, since they do not act on other monoamine transporters. Comparing the TCAs and SSRIs, it was observed that SSRIs have fewer side effects like sedation, dizziness and anticholinergic symptoms, which will enhance patient compliance.(Manen *et al*., 2002) Depression should be treated according to usual depression treatment guidelines as there is no evidence that depression should be treated differently in the presence of COPD. It was estimated that more number of patients are diagnosed with both depression and COPD. More studies should be done to manage the depression associated with COPD in reducing the mortality rate.

Association between COPD, Depression and cigarette smoking

Smoking is a risk factor shared by depression and COPD. Smoking is the main cause of COPD in 80-90% of cases. It is the single most important way of affecting the outcome in patients at all stages of COPD, and is the only evidence based treatment which has been provided to slow down the development of disease by preventing further deterioration in lung function. Smoking cessation is the only intervention at this time to affect long term decline in Forced expiratory volume in one second (FEV1). It is difficult for an individual to stop smoking especially when the attempt to stop is being hampered by the co-existence of a psychiatric disorder. (Manen et al., 2002) The effectiveness of smoking cessation programmes can be influenced by the co-existence of depression or other psychiatric disorders. Both depression and depressive symptoms are independently associated with failure to quit smoking and relapse. The attempt to quit smoking and maintain abstinence from smoking might be hampered by the co-existence of depression. The rate of depression is significantly higher in active smokers of COPD patients compared to healthy persons. The association of depression and COPD is possibly due to lifetime nicotine dependence. Studies shows that smoking increases the levels of pro-inflammatory cytokines including IL-6, Tumor Necrosis Factor alpha (TNF-α) and C-reactive protein. Recent studies have reported that depressed smokers showed higher levels of TNF-α, IL-6 and CRP compared to non-depressed smokers. (Manen *et al*., 2002)

Conclusion

The review have shown that COPD is a class of chronic obstructive disorder that has clear influence on the quality of life. The main reason behind evolution of COPD is cigarette smoking. The review also elaborated the association of depression and COPD. The review also suggest to identify the etiologies behind the association and different co-morbidities and complications associated with COPD.

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