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Use of Benzodiazepines in Treatment of Depression and Anxiety in Patients with Chronic Obstructive Pulmonary Disease. Trends, Controversies and Alternatives

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is primarily affecting the lungs but is also associated with a number of accompanying conditions known as comorbidities. Depression, anxiety and insomnia are very common among older people and especially those with COPD. Treatment of these conditions is often related to prescription of benzodiazepines, a class of drugs which is highly addictive and has adverse effects on the respiratory function. Despite of the known harms and controversial benefits, the use of benzodiazepines in the general population and in COPD patients is increasing. In this article are discussed the mechanisms of coexistence of anxiety and depression in COPD patients and the use of benzodiazepines in their treatment: trends of prescription, indications and harmful effects. The use of this group of medications is a matter of debate and suggests further use of alternative treatment, more specific personalized therapeutic approach and non-pharmacological interventions.

Keywords: COPD, benzodiazepines, anxiety, depression, non-pharmacological treatment

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is now one of the top three causes of death and chronic morbidity worldwide and 90% of these deaths occur in low- and middle-income countries[1]. In the beginning of the 20th century, COPD was the fifth leading cause of death also in high-income countries and is estimated to be major cause of disability adjusted life years[2]. COPD patients very often have a variety of concomitant chronic conditions that can influence the prognosis or complicate the treatment. Comorbidities contribute to the disease severity and are evenly distributed irrespective of the GOLD stage of obstruction[2]. Among the most common comorbidities of COPD are depression, anxiety and insomnia, which lead to worsened quality of life and more severe symptoms[3]. The evidence about optimal approaches for managing depression and anxiety in COPD patients remains unclear and largely speculative. Patients with COPD may receive benzodiazepines (BZD) for several reasons, including treatment of insomnia, mood disorders, and refractory dyspnea, all of which are common problems in COPD[4].

Despite all the possible side effects, BZD use is high in COPD especially in elderly patients with severe disease. A population-based cohort study found that new benzodiazepine use occurred in about one-third of older adults with COPD[5]. Furthermore, a study conducted in Norway showed that almost 70% of 5,380 COPD patients treated in hospital during 2009, were dispensed with BZD during the following 12 months[6]. The use of BZD is increasing in attempt to reduce symptoms of depression and anxiety in COPD patients.

The scope of this review article is to consider the burden of anxiety and dyspnea in COPD patients, the evidence-based indications for prescribing benzodiazepines, and the interface between the two. The article considers non-benzodiazepine and non-pharmacological approach of treating these accompanying conditions.

2. Depression and anxiety in COPD: prevalence and mechanisms:

Mental health conditions are leading cause of increased disability and worsened quality of life in elderly patients. Mood disturbances, especially depression, anxiety and insomnia are common in COPD patients[7]. Anxiety is a major concern for people with COPD and it is not only present during acute exacerbations of COPD, but for many people there is a background level of chronic anxiety. The prevalence of depression and anxiety differs widely, depending on the studied population and the used methodology. Anxiety in COPD patients is often related to clinical depression and some studies report seven times higher risk for development of clinically manifested anxiety in depressed COPD patients[8]. There is overlap of the symptoms of both conditions, such as fatigue, weight changes, insomnia and difficulties in the concentration. In patients with stable COPD the prevalence of clinical depression is between 10-42% and the prevalence of anxiety varies in the range of 10-19%[9]. The prevalence of these conditions in advanced disease is even higher. Systematic review in severe COPD reports prevalence of depression between 37% and 71% and prevalence of anxiety 50-75%, which is comparable or even higher than the prevalence of these conditions in other advanced diseases like neoplasms, CHF and AIDS[10].

SUGGESTED RISK FACTORS AND MECHANISMS

The mechanism of depression and anxiety in COPD is still not completely understood, as the relationship is complex. Both are often associated with younger age, female sex, cigarette smoking, increased airflow limitation (lower forced expiratory volume in 1 s (FEV1)), cough, worse health-related quality of life and cardiovascular disease antecedents[11].

Smoking is a major risk factor for COPD but also has a complex impact on mental health. Large multinational study reports 23.7% prevalence of major depression in smokers compared to 6.2% in non-smokers and also a significantly higher risk for developing depression among smokers[12]. Another study suggested some genetic association between smoking and depression. In this study the variations of serotonin transporter gene, SLC6A4, responsible for nicotine dependence, were shown to affect COPD pathogenesis suggesting genetic predisposition to depression in these patients[13].

Suggested interrelating mechanism of COPD and depression is hypoxia which develops in severe COPD and during exacerbations. A proposed mechanism for the neurological and psychiatric changes is the decreased level of oxygen in the periventricular and subcortical regions of the brain. This leads to damage in the white matter and vascular endothelium - changes similar to those observed on MRI in patients with depression[14].

Another possible mechanism relating depression and COPD is the “overspill” theory, where it is suspected that inflammatory markers spill over into the general circulation causing systemic inflammation. In support of that, markers such as sTNFR-1 (soluble tumor necrosis factor alpha receptor-1) have shown a strong association with depression rates in patients with COPD[14]. A large study from the Bergen cohort showed significant relation between inflammatory markers and depression which is supporting the common inflammatory pathogenic theory[15]. However, the ECLIPSE study did not find significant association between inflammatory markers and depression[11]. This theory needs further evaluation.

Risk factors for developing depression are shown on table 1.

Strong associations	Mixed or weak associations
Severe dyspnea	FEV1
Quality of life	Low BMI
Long-term oxygen treatment	Significant comorbidity
Exacerbations	Age
Fixed airflow limitation	Gender
Living alone	Social status
Non-supportive family	Smoking

3. Benzodiazepines (BDZ)

Benzodiazepines are a class of medications which were first described in 1955 and were available to prescribe in clinical practice, as sedatives and anxiolytics in the 1960's. Widespread prescription that followed made benzodiazepine one of the most widely prescribed classes of medications by the mid-1970s. This widespread use was subsequently reflected in very high levels of dependence[16]. Benzodiazepines work on the γ-aminobutyric acid (GABA) A-receptors. GABA-A receptors have a large number of distinct subunits allowing for a huge number of receptor combinations, some of which are used by benzodiazepines. GABA-A benzodiazepine receptors are high-affinity binding sites in the central nervous system through which clinical effects are generated[17]. Clinical effects include the use as sedatives/hypnotics, anxiolytics, muscle relaxants, amnesiacs and anticonvulsants. The most widely used indications for prescribing oral benzodiazepines in the general population include insomnia or night-time sedation and anxiety[18]. In elderly patients, greater sensitivity to benzodiazepines is seen, particularly because of reduced clearance of the drug[19].

EFFECTS OF BENZODIAZEPINES ON THE RESPIRATORY FUNCTION IN COPD PATIENTS

Studies dating back some decades ago have linked BZD with a variety of adverse respiratory physiology outcomes in COPD, including decreased minute ventilation, hypoxemia and/or hypercapnia, dulling of central respiratory drive and chemoreceptor responsiveness to hypercapnia, and decreased respiratory muscle strength[20-22]. More recent works suggest that while benefitting several parameters of good sleep, benzodiazepines may cause a slight increase in transcutaneous carbon dioxide pressure[23]. Benzodiazepines affect the upper airways and patency may be lost in people who are snorers, but have not yet experienced obstructive sleep apnea (OSA). In these patients OSA can be induced following BZD administration[24].

INDICATIONS FOR PRESCRIBING BENZODIAZEPINES IN COPD PATIENTS

Anxiety is the most common reason for prescribing BZD in COPD patients. For generalized anxiety disorder and social anxiety disorder, there are meta-analyses that support the use of benzodiazepines, although longer term use is not a registered indication and benzodiazepines are relatively poorly tolerated[24]. Usually for social anxiety disorders in adults, when cognitive behavioral therapy was not successful, then the pharmacotherapy of choice is a selective serotonin reuptake inhibitor (SSRI), not a benzodiazepine[25].

Another common reason for prescribing BZD in COPD patients is insomnia. The prevalence of insomnia in the general population is with rates of around 10%. These rates are increased 2.5-fold in people with COPD, making this a significant problem, with prevalence rising with age[26]. In the community setting, there are meta-analyses that support the short-term use of benzodiazepines to help initiate sleep, deliver longer sleep and improve subjective evaluation of sleep[27].

The use of BZD in treatment of chronic dyspnea is not supported by available evidence, although they are limited[28]. Taking into account the harmful effects with no predictable benefits and no predictable subpopulations which are likely to benefit, there is no role for benzodiazepines as a first-line therapy for chronic breathlessness, alone or in combination with regular, low-dose morphine[29].

4. Prescribing benzodiazepines in COPD patients: trends and risks

As mentioned above, BZD are widely prescribed in the general population in high-income countries. A register based Danish cohort study identified 950,767 incident BZRA users, of whom 15% and 3% became long-term users for more than 1 or 7 years, respectively. These percentages were highest for individuals who initiated Z-drugs – Zopiclone and Zolpidem (17.8% and 4%) [30]. Prescribing increases with age, with estimates of up to one-third of older people with COPD in Ontario using benzodiazepines[5], e.g. more than 20% of people 65–69 years of age, rising to more than 30% of people aged over 85 years of age[31]. Study from Norway showed even higher rates of BZDP prescription from up to 70% in COPD patients after hospital discharge and follow up[6]. As COPD and benzodiazepine prescribing are highly prevalent across the community and both increase with age, it is likely that a large number of people with COPD will be prescribed benzodiazepines.

One large study from the US explored trends in prescribing of benzodiazepines across the population over a 12-year period to the end of 2010[32]. The study found out that BZD were 1.5-fold more likely to be mentioned in the consultation of people with COPD than in people without the disease. Furthermore, when comparing the first and last 4-year periods in this study, and adjusting for age, sex and race, the adjusted prevalence of mentioning a benzodiazepine increased 2.26-fold in people with COPD. Using one of the large databases in USA (the National Ambulatory Medical Care Survey) and assessing more than half a million consultations, there were increases in the number of outpatient consultations where benzodiazepines were

prescribed across the years 1993 (2.6%) to 2010 (4.4%)[33]. One-third of these prescriptions were written for people over the age of 65 years.

There are certain concerns regarding benzodiazepine use in people with COPD and some studies have looked at possible harms. In five studies included in a meta-analysis, there were no adverse effects on the respiratory parameters measured, except for a slight increase in transcutaneous carbon dioxide pressure during sleep[34].

A Swedish study conducted by Ekström et al. explored the prescribing of benzodiazepines in people on the Swedish register for long-term oxygen therapy (LTOT). The study among 2249 patients found out that BZD were associated with higher rates of hospital admission and higher rates of death, with a dose response relationship apparent[35].

Vozoris et al. conducted a large study among 177,355 people with COPD, which explored the prescribing patterns across a large dataset from Ontario, Canada[5]. All people had COPD and, compared with those not prescribed benzodiazepines (n = 126,997), there was an increase in all-cause mortality at 30 days after prescription of benzodiazepines. Possible explanations include that these people had more advanced disease and were receiving these medications for symptoms closer to the end of life care.

A nationwide case–control study in Taiwan in which 2434 controls were matched for sex, age and date of enrolment with people prescribed benzodiazepines from a comprehensive national health insurance database, demonstrated that, overall, the introduction of benzodiazepines was associated with a higher risk of respiratory failure . This risk doubled when people used two or more benzodiazepines or a combination of benzodiazepines with other centrally acting medications[36].

5. Alternative treatment approaches and benzodiazepines replacement

Current guidelines for treatment of COPD (GOLD, NICE) do not recommend the regular use of BZD in COPD patients and this treatment is only mentioned in the context of palliating end-stage disease[16]. For sleep disorders, including insomnia, evidence based approaches in people with COPD include the use of antidepressants[37] and non-benzodiazepine sedatives (without compromising respiratory function) [38]. There is also new emerging evidence, which show that there is a potential of melatonin for treating insomnia in COPD patients [39, 40]. The three indications for benzodiazepines in people with COPD (anxiety, sleep disorders and chronic breathlessness) can be managed with non-pharmacological interventions and other classes of medications with better long-term outcomes [16].

NON-PHARMACOLOGICAL TREATMENT OF ANXIETY AND DEPRESSION IN COPD PATIENTS

Cognitive-behavioral therapies (CBT)

These therapies are indicated as first-line treatment for long term anxiety. The NICE guidelines recommend the usage of low-intensity psychological interventions (self-support programs) and high-intensity psychological interventions (individual or group cognitive-behavioral therapy) depending on the severity of the mental symptoms[41]. Both individual and group therapy psychological interventions are useful in promoting more adaptive coping in COPD patients. The treatment focuses on changing an individual's thoughts (cognitive patterns) in order to change his or her behavior and emotional state. Therapists attempt to make their patients aware of these distorted thinking patterns that fuel anxiety and depressive symptoms and change them (a process termed cognitive restructuring) [42]. Therapy focuses on helping patients discover alternative solutions and promote more adaptive coping styles in order to overcome adversities and effectuate operational techniques to address their problems[43]. Studies have found that a single two-hour session of CBT can reduce depressive symptoms in mild depressed COPD patients[44]. A recent meta-analysis which included 16 randomized controlled trials, found out significant improvements in anxiety, depression, quality of life, and emergency room visits in COPD patients treated with CBT. However, fatigue, exercise capacity, self-efficacy, and sleep quality were not impacted[45].

Pulmonary rehabilitation (PR)

According to the American Thoracic Society and the European Respiratory Society, pulmonary rehabilitation is an evidence-based multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities[46]. PR should be offered to all COPD patients irrespective of disease severity, since they all get improvements[47], from mild COPD[48] to severe and very severe lung disease[49, 50] Emphasis should be given to exercise training with respect to patients with mild-to-moderate disease, but for patients with severe-to-very severe COPD, PR programs should be tailored mostly toward dyspnea management and psychological support [50].

It has been shown that PR has beneficial effects on psychological symptoms via different mechanisms: changes in the monoamines central function; up-regulation of the hypothalamic-pituitary-adrenal axis; increased secretion of endogenous opioids and reduced systemic inflammation[51]. In addition, behavioral mechanisms associated with exercise activities operate synergistically to produce reductions of symptoms. Such mechanisms include active distraction from worrying thought patterns (rumination), increase of self-efficacy by providing patients with a meaningful mastery experience, and provision of daily pleasant events and regular social contact and support [52, 53]. The majority of PR programs have a primary exercise focus in order to recondition the legs and other peripheral muscles, making them more efficient as to oxygen needs, and thereby requiring relative less breathing to satisfy these oxygen requirements[51]. PR programs also teach breathing control exercises to patients and educate them in recognizing an impending dyspnea attack and preventing it, or controlling it, so they lose their fear of exerting themselves[54].

A recent meta-analysis of 11 studies showed that in COPD patients compared with usual care, pulmonary rehabilitation conferred significant benefits of a moderate magnitude for anxiety symptoms (SMD, -0.53; 95% CI, -0.82 to -0.23) and large magnitude for depression symptoms (SMD, -0.70; 95% CI, -0.87 to -0.53)[55]. Thus, PR provides significant, clinically relevant benefits on anxiety and depression symptoms in COPD patients.

Finally, the strategies of discontinuing BZD in patients which are already established on long term BZD use include tapering the dose, psychological support and a brief intervention which consist of advice, either verbal or written. Each of these approaches is better than routine care alone at successfully changing patterns of benzodiazepine use[56, 57]. Pulmonary rehabilitation may be of benefit for discontinuing BZD in COPD patients. Further studies are needed in this direction.

6. Conclusion

Despite the current recommendations for treatment of COPD and the established harmful effects of BZD on population level, the use of these drugs is increasing, especially in the middle and high income countries. For some types of anxiety and for insomnia, benzodiazepines may provide symptomatic benefits in some people in the short-term. Any symptomatic benefits need to be estimated carefully in the population with COPD, especially with regard to the risk of exacerbations of COPD, respiratory tract infections, and short- and intermediate-term mortality. There is no evidence that support the use of BZD for treatment of chronic dyspnea. Non-pharmacological treatment of insomnia and anxiety/depression are preferred alternative.

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