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Review

Psychological co-morbidities in COPD: Targeting systemic inflammation, a benefit for both?

Charlotte E. Pelgrim[a,1], Julia D. Peterson[a,1], Harry R. Gosker[b], Annemie M.W.J. Schols[b], Ardy van Helvoort[b,c], Johan Garssen[a,d], Gert Folkerts[a], Aletta D. Kraneveld[a,e,*]

[a] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, the Netherlands
[b] NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Department of Respiratory Medicine, Maastricht, the Netherlands
[c] Nutrition, Metabolism and Muscle Sciences, Nutricia Research, Utrecht, the Netherlands
[d] Platform Immunology, Nutricia Research, Utrecht, the Netherlands
[e] Veterinary Pharmacology & Therapeutics, Institute of Risk Assessment Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands

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ABSTRACT

COPD is a chronic lung disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. Furthermore, COPD is often characterized by extrapulmonary manifestations and comorbidities worsening COPD progression and quality of life. A neglected comorbidity in COPD management is mental health impairment defined by anxiety, depression and cognitive problems. This paper summarizes the evidence for impaired mental health in COPD and focuses on current pharmacological intervention strategies. In addition, possible mechanisms in impaired mental health in COPD are discussed with a central role for inflammation.

Many comorbidities are associated with multi-organ-associated systemic inflammation in COPD. Considering the accumulative evidence for a major role of systemic inflammation in the development of neurological disorders, it can be hypothesized that COPD-associated systemic inflammation also affects the function of the brain and is an interesting therapeutic target for nutra- and pharmaceuticals.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death globally, representing a significant public health issue (Decramer and Vestbo, 2016; Musgrove et al., 2000). The majority of diagnosed COPD patients are 60 years or older, suggesting an increased risk of development upon aging (von Leupoldt et al., 2012). Genetic predispositions and infections at early ages may be influencing factors for the development of COPD in some individuals (von Leupoldt et al., 2012). However, development of COPD is considerably attributed to smoking and air pollution, with 80–90% of COPD cases caused by smoking (Mikkelsen et al., 2004). Furthermore, inhaling vapors of nicotine e-cigarettes and exposure to second-hand smoke have also been indicated to increase the risk for COPD development (Garcia-Arcos et al., 2016; Putcha et al., 2016).

COPD is characterized by persistent airflow restriction, which is associated with chronic pulmonary and frequently also systemic inflammatory responses (Decramer and Vestbo, 2016; Pauwels et al., 2001), which intensify with acute exacerbations of the disease (Lainscak et al., 2013). In a recent version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, disease severity is not only determined by airway obstruction, but by exacerbation frequency as well (Vogelmeier et al., 2017). Parenchymal degradation of airway tissue can occur (von Leupoldt et al., 2012), which is progressive and irreversible. The cardinal symptoms of COPD are difficulties with breathing (dyspnea), chronic cough, and sputum production (Decramer and Vestbo, 2016; Esser et al., 2016; Pauwels et al., 2001). Common comorbidities in patients with COPD include cardiovascular disease, sarcopenia, osteoporosis, and diabetes (von Leupoldt et al., 2012). Interestingly, extrapulmonary brain-related comorbidities, such as depression (Lee et al., 2017; Maurer et al., 2008; von Leupoldt et al., 2012; Yohannes and Alexopoulos, 2014a), anxiety (Maurer et al., 2008;

* Correspondence to: Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, the Netherlands.
E-mail address: a.d.kraneveld@uu.nl (A.D. Kraneveld).
[1] These authors equally contributed to the manuscript.

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von Leupoldt et al., 2012; Yohannes and Alexopoulos, 2014a), and cognitive problems (Baird et al., 2017; Doyle et al., 2017; Hu et al., 2018; Wen et al., 2018; Yohannes et al., 2017) are also common.

The onset of brain-related comorbidities in COPD patients can be very detrimental, as it has been related to worsening of symptoms and increased mortality (Chang et al., 2012; Dodd et al., 2013; Lou et al., 2014). The other way around, reduced efficacy of certain therapies have been indicated in patients with comorbidities of depression, anxiety and cognitive problems (Glassman, 1990; Ouellette and Lavoie, 2017; von Leupoldt et al., 2011). Therefore, there is a huge need to find an optimal therapy for treating COPD patients with mental health comorbidities.

The goal of this review is to provide a brief summary of the current findings on incidence and consequences of depression, anxiety and cognitive impairments in COPD, together with the current pharmaceutical interventions. The potential role of systemic inflammation relating these brain-associated comorbidities in COPD will be highlighted. In addition, the importance of treating brain problems in COPD with pharmacological and/or nutritional approaches will be discussed.

2. The prevalence of depression, anxiety and cognitive impairments in COPD

The prevalence of psychological problems in COPD patients has been explored by numerous research groups. As assessed in two meta-analyses, the prevalence of depression in COPD was found to be 24.6% and 27.1% while in non-COPD subjects the prevalence was 11.7% and 10.0% (Matte et al., 2016; Zhang et al., 2011). Additionally, four studies examining the prevalence of anxiety in COPD patients reported 9.1–28.2% of patients to have anxiety compared to only 4.1–6.1% of non-COPD subjects (Di Marco et al., 2006; Eisner et al., 2010; Hsieh et al., 2016; Lou et al., 2012). The consistency of investigations demonstrating a greater prevalence of anxiety or depression in COPD patients indicates that the association may be considered to be strong.

Many studies also showed an increased prevalence of cognitive problems in COPD. In a systematic review covering literature till 2010 from Schou and colleagues, a significant impairment in cognitive performance of COPD patients was found compared to healthy controls in 8 of the 14 case control studies (Schou et al., 2012). The prevalence of cognitive dysfunction in COPD patients is determined in multiple studies being between 17% and 56.7%, compared to 12–16.7% in healthy controls (Antonelli-Incalzi et al., 2006; Cleutjens et al., 2017a; Incalzi et al., 1993; Martinez et al., 2014; Ouellette and Lavoie, 2017; Roncero et al., 2016; Yohannes et al., 2017). Verbal memory, attention, processing speed, coordination and learning ability are shown to be the most influenced cognitive functions in COPD (Schou et al., 2012). The most recent studies also demonstrated that the total cognitive function scores of COPD patients were significantly lower compared to demographic-matched controls and worsened with the degree of airflow obstruction (Hu et al., 2018; Pierobon et al., 2017).

Although there is strong evidence for an increased prevalence of mental health symptoms in COPD, it is important to note that almost all studies that have investigated the prevalence of brain comorbidities in COPD did not include smoking control subjects. Smoking is a substantial risk factor as COPD smokers are more likely to develop brain comorbidities as opposed to non-smoking COPD patients (Armannsdottir and Jonsdottir, 2014; Goodwin et al., 2008; Luger et al., 2014; Mikkelsen et al., 2004). Therefore, it is crucial to include smoking controls in future studies.

3. Effects of depression, anxiety and cognitive impairments on COPD progression and management

The increased prevalence of depression, anxiety and cognitive problems in COPD patients is problematic as adherence to COPD treatment is affected by mental health complications (Kokturk et al., 2018), and worsened symptoms are observed in COPD patients with brain-associated comorbidities (Hilmarsen et al., 2014; Lou et al., 2014; Singh et al., 2016; Yohannes et al., 2016). Increased number of hospitalizations for exacerbations, decline in 6 min walking distance (6MWD), and decline in quality of life are observed in COPD patients with anxiety or depression (Hilmarsen et al., 2014; Yohannes et al., 2016). Additionally, there is an increased risk of mortality in patients displaying symptoms for anxiety and/or depression (Lou et al., 2014). The possible rationale for the detrimental effects these psychological disorders have on COPD progression could be due to 1) the reduction in treatment compliance in depressed patients, 2) the worsened perception of dyspnea in depressed and anxious patients which may lead to increased hospital admissions (Pumar et al., 2014; Regvat et al., 2011), and 3) the worsened ability of depressed and/or anxious patients to cope with a chronic disease (Pumar et al., 2014). Likewise, cognitive problems are associated with worsening of the disease progression. Impaired cognitive function was related to poor health status, increased rate of hospital admission, longer hospitalization and increased mortality (Chang et al., 2012; Dodd et al., 2013). This can be attributed to the fact that COPD patients with cognitive problems are often excluded from rehabilitation programs, are at higher risk of not completing the pulmonary rehabilitation program, and memory loss might result in lower therapy adherence and self-management as well (Yohannes, 2014; Cleutjens et al., 2017b).

Considering the severity of worsened symptoms, the treatment for such psychiatric and cognitive problems in COPD patients is a necessity (Kunik et al., 2005).

4. Current pharmacotherapies for COPD patients with brain-associated comorbidities

Investigations have been conducted to find effective treatment options for COPD patients with comorbidities of anxiety and depression (Hynninen and Nordhus, 2017; von Leupoldt et al., 2012). In this section, the current pharmacological therapies for treating anxiety, depression or cognitive problems are discussed.

4.1. Anxiety and depression

In general, serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin receptor agonists (azapirones), or benzodiazepines are prescribed to COPD patients with depression and anxiety (Majid and Nadeem, 2017). A majority of studies previously conducted involved SSRIs and TCAs.

Anti-psychotic medications are usually prescribed to COPD patients when mild to severe symptoms of depression and anxiety develop (National Collaborating Centre for Mental Health, 2009; Pumar et al., 2014; Yohannes and Alexopoulos, 2014b). A major problem with anti-psychotics in COPD patients is refusal of prescribed medication and nonadherence to medication due to the fear of adverse side-effects, denial of psychological symptoms, and misapprehension of anti-psychotics (Albrecht et al., 2016; Fritzsche et al., 2011; Yohannes et al., 2001).

4.1.1. Serotonin reuptake inhibitors

Serotonin reuptake inhibitors (SSRIs) appear as the first-line of treatment for anxiety and/or depression due to their equivocal effectiveness and low number of adverse side-effects compared to other drug classes (Majid and Nadeem, 2017; Pumar et al., 2014). Currently, there are very few studies examining the effect of SSRIs on depressed or anxious COPD patients. A study by Eisner and colleagues, composed of 28 patients, indicated an improvement in depression scores, 6MWD, and quality of life after three months of unblinded treatment with paroxetine relative to placebo (Eiser et al., 2005). In a double blind randomized control study (n = 15), a significant improvement in quality of life in paroxetine treated patients, relative to placebo, was

found after treatment with 20 mg for two weeks (Lacasse et al., 2004). Though, one third of patients discontinued the study due to adverse side-effects (Lacasse et al., 2004; Yohannes and Alexopoulos, 2014b). Fluoxetine improved symptoms of depression and anxiety in COPD patients: a randomized double blind control study composed of 42 patients with respiratory diseases indicated 67% of patients treated with 20 mg of fluoxetine to have a 50% reduction in depression scores and/or a score reached below 10, relative to 37% of placebo patients (Evans et al., 1997). Furthermore, a single blind study composed of seven depressed COPD patients found four patients to have a 50% reduction in Geriatric Mental Status Schedule scores after six months of treatment with 20 mg of fluoxetine. Of the initial 15 patients, five withdrew due to adverse side-effects (Yohannes et al., 2001). Sertraline has no significant improvements for symptoms of depression and anxiety, though this conclusion might not be reliable as the study design from these studies are very poor and lack proper controls (Papp et al., 1995; Smoller et al., 1998). Moreover, citalopram does not appear effective as a randomized double-blind placebo controlled study by Silvertooth and colleagues indicated no difference in Hamilton Anxiety Rating score between COPD patients treated with 20–40 mg of citalopram to placebo treated patients over a period of 12 weeks (Silvertooth et al., 2004). Currently, larger studies with reliable designs are necessary to make any conclusions regarding the effectiveness of SSRIs in COPD patients (Putman-Casdorph and McCrone, 2009). Furthermore, the prevalence of SSRI usage cannot be determined accurately if patients do not follow prescriptions. Thus, a current predicted percentage of COPD patients utilizing SSRIs/selective serotonin–norepinephrine reuptake inhibitors (SNRIs) (2.3%) (Wang et al., 2017) is likely not to be reliable and the accurate percentage is unknown.

4.1.2. Tricyclic antidepressants

Tricyclic antidepressants (TCAs) and SSRIs appear to be equally effective for treating symptoms of anxiety and depression in COPD patients, though TCAs should be secondary to SSRIs as there is potential for TCAs causing cardiac toxicity (Majid and Nadeem, 2017; Stage et al., 2006). If TCAs are prescribed, a lower dose will be given as the general population of COPD patients are elderly and the risk of adverse side-effects is larger in older patients (Stage et al., 2006). Nortriptyline improved symptoms of depression and anxiety in COPD patients treated incrementally with 0.25 mg/kg to 1 mg/kg body weight over a 12 week period (Borson et al., 1992; Yohannes and Alexopoulos, 2014b). The study was a double blind placebo control composed of 30 patients who were assessed by a physiatrist at the beginning and end of the trial (Borson et al., 1992; Yohannes and Alexopoulos, 2014b). Of the original 36 patients, three discontinued the trial due to adverse side-effects (Borson et al., 1992; Yohannes and Alexopoulos, 2014b). A placebo control study conducted by Gordon and colleagues indicated no difference between COPD patients treated incrementally with 25–100 mg of despiramine to the placebo control over an eight week period (Gordon et al., 1985; Yohannes and Alexopoulos, 2014b). Of the original 13, two patients withdrew from the study due to adverse side-effects while five others withdrew due to other problems (Gordon et al., 1985; Yohannes and Alexopoulos, 2014b). Doxepin was tested in a six week randomized placebo control study composed of 12 COPD patients (Light et al., 1986; Yohannes and Alexopoulos, 2014b). Patients were treated incrementally from 25 mg to 105 mg of doxepin, as tolerated, and compared with the placebo control group (Light et al., 1986; Yohannes and Alexopoulos, 2014b). No improvements in symptoms of depression and anxiety were indicated and three patients withdrew due to adverse side-effects (Light et al., 1986; Yohannes and Alexopoulos, 2014b). Protriptyline can cause severe adverse side-effects as a majority of patients withdrew from a trial due to anticholinergic side effects (Ström et al., 1995; Yohannes and Alexopoulos, 2014b). Interestingly, bupropion and nortriptyline have been reported to stimulate smoking cessation effectively, which is significant for COPD patients considering the large effect smoking has on progression of the disease (Wagena et al., 2005, 2001). Overall, to make any conclusions regarding TCAs, larger studies with reliable study designs are required (Putman-Casdorph and McCrone, 2009). Moreover, the prevalence of TCA usage, just like SSRIs, cannot be determined accurately if patients do not follow prescriptions. Thus, a current predicted percentage of COPD patients utilizing TCAs (3.3%) (Wang et al., 2017) is probably not reliable.

4.1.3. Benzodiazepines

Though benzodiazepines should probably be avoided in COPD patients due to the number of adverse side-effects, such as respiratory depression, cognitive impairments, anterograde amnesia, and addictive characteristics (Halvorsen and Martinussen, 2015; Stage et al., 2006), benzodiazepines are commonly prescribed to treat depression and anxiety in COPD patients. 69% of patients were found to be prescribed this type of drug in Norway during 2009 (Halvorsen and Martinussen, 2015). Using data from Ontario provincial healthcare administrative databases between 2004 and 2009, Vozoris and colleagues discovered 31.7% of COPD patients with no prior use of benzodiazepines to become new users of benzodiazepines during this time period (Vozoris et al., 2013). Additionally, in 2017 Wang and colleagues determined 34.9% of COPD patients to be prescribed benzodiazepine/non-benzodiazepines while only 2.3% were prescribed SSRIs/SNRIs and 3.3% were prescribed TCAs (Wang et al., 2017). This is alarming, considering the older aged population of COPD patients and that older age generally leads to altered pharmacokinetics, the risk for developing adverse side-effects is higher (Vozoris et al., 2013). Benzodiazepines should be a last resort and only utilized if previous anxiolytics fail (Stage et al., 2006). Furthermore, it is important to understand why benzodiazepines in general are being prescribed more often to COPD patients while SSRIs and TCAs appear as drug classes leading to less side-effects.

4.1.4. Azapirones

Azapirones are a class of drug displaying both anxiolytic and antidepressant properties. Though, they appear less effective in the clinic relative to SSRIs, TCAs, and benzodiazepines (Anderson and McAllister-Williams, 2015; Hidalgo and Sheehan, 2012; Za et al., 2011). A small number of studies have investigated the effectiveness of azapirones in COPD patients. In a randomized double-blind placebo control crossover trial (n = 16) the efficacy of 20 mg buspirone for two weeks was studied (Argyropoulou et al., 1993). Reduced symptoms of anxiety and depression were observed due to an increase in 6MWD and maximal exercise work rate (Argyropoulou et al., 1993). In contrast, a randomized double-blind placebo controlled crossover trial (n = 11) indicates no significant difference in State-Trait Anxiety Inventory scores between COPD patients treated with 30–60 mg of buspirone for six weeks and placebo control (Singh et al., 1993). Azapirones are linked with less drowsiness, psychomotor impairments, and potential for addiction relative to benzodiazepines (Guaiana et al., 2017; Imai et al., 2014). Though, there appears to be a lack of effectiveness in treating symptoms of anxiety and depression and they are currently rarely prescribed in the USA (Hidalgo and Sheehan, 2012).

4.2. Cognitive problems

Studies with pharmacological treatments for COPD patients to improve cognitive capacities do not exist. There are limited indications that airway-targeting therapies used in the treatment of COPD might improve cognitive function. Proper control of asthma, including the use of drugs commonly applied in COPD as well, was associated with improved cognitive function in elderly asthma patients (Bozek et al., 2010). Overlapping factors in asthma and COPD, such as the level of airway obstruction, systemic inflammation and extrapulmonary comorbidities, have been indicated to increase the risk of cognitive impairment (Dodd, 2015). In addition, Formoterol, a long-acting beta-2 agonist used to treat COPD, is shown to improve cognitive function in a

murine model of Down syndrome (Dang et al., 2014). However, its potential in improving cognitive function in COPD patients has not been elucidated yet. Overall, there are no pharmacological interventions for cognitive decline in COPD as this is still a neglected issue. Therefore, we present here possible pharmacological treatment options to target cognitive decline in COPD via two different neuronal signaling pathways.

4.2.1. Pharmacological targeting acetylcholine

4.2.1.1. Acetylcholine esterase inhibitors. COPD-associated chronic hypoxia is a known cause of impairment of the oxygen-dependent synthesis of neurotransmitters such as acetylcholine (Grant et al., 1982). This might be one of the pathological pathways of inducing cognitive decline in COPD patients. Acetylcholine esterase inhibitors, such as rivastigmine and galantamine, are frequently prescribed in patients suffering from dementia to enhance acetylcholine levels (Lao et al., 2018). However, recently it is reported that the use of acetylcholine esterase inhibitors in dementia patients suffering from COPD was associated with a higher risk of pulmonary exacerbations (Mahan and Blaszczyk, 2016). These side-effects can be explained by the fact that acetylcholine is a neurotransmitter involved in the autonomic regulation of airways, inducing bronchoconstriction and mucus production.

4.2.1.2. α7 nicotinic acetylcholine receptor agonists. Besides using pharmacological interventions to enhanced endogenous acetylcholine levels, agonists of α7 nicotinic acetylcholine receptors are a novel approach to treat cognitive impairments associated with Alzheimer's disease. In contrast to the acetylcholine esterase inhibitors, α7 nicotinic acetylcholine receptor agonists induce, through calcium influx and activation of second messenger systems, the release of neurotransmitters such as glutamate or gamma aminobutyric acid (D'Andrea and Nagele, 2006). α7 nicotinic acetylcholine receptor agonists have pro-cognitive effects in phase 2 or 3 clinical trials for Alzheimer's disease, however, the beneficial effect in COPD-associated cognitive impairments needs to be established. Of interest is the α7 nicotinic acetylcholine receptor as a pharmacological target to manage inflammation. Several studies indicate the vagal nerve as anti-inflammatory modulator via nicotinic anti-inflammatory pathway with a central role of α7 nicotinic acetylcholine receptors on immune cells (Jonge and Ulloa, 2007). With respect to the role of COPD-associated systemic inflammation and its possible role in inducing cognitive problems, α7 nicotinic acetylcholine receptor agonists could possibly be a double hits approach in COPD treatment. Future fundamental and clinical studies are essential to evaluate α7 nicotinic acetylcholine receptors as a target for the treatment of cognitive decline in COPD patients.

4.2.2. N-methyl-D-aspartate receptor antagonists

The excitatory neurotransmitter glutamate and its receptor, the cation channel N-methyl-D-aspartate (NMDA) receptor, play an important role in synaptic plasticity and regulation of learning and memory (Harvey and Shahid, 2012). Hypoxia-induced excessive release of glutamate results in sustained activation of NMDA receptors leading to neuronal damage and cells death, also referred to as excitotoxicity (Olney et al., 1971). Excitotoxicity has been studied as a novel target for the treatment of cognitive decline and NMDA receptor antagonists are expected to have neuroprotective effects. Inhibition of NMDA receptors ameliorated cognitive deficits in a chronic intermittent hypoxia hypercapnia animal model of COPD (Huo et al., 2014). The non-competitive NMDA receptor antagonist, memantine, is the only drug approved for the treatment of moderate to severe Alzheimer's disease and has not yet been tested in COPD-associated cognitive problems.

4.3. Concluding remarks pharmacotherapy brain comorbidities in COPD

Currently, studies are generally skeptical about the effectiveness of anti-psychotic medications in COPD patients (Yohannes and Alexopoulos, 2014a). This is most likely due to the rudimentary designs of the limited studies conducted, and difficulty of having COPD patients comply with anti-psychotics (Pumar et al., 2014; Yohannes and Alexopoulos, 2014a; Za et al., 2011). This is supported, though controversial, as a significant number of studies indicate an effectiveness of anti-psychotic medications in general populations (Fawcett and Barkin, 1998; Khan and Schwartz, 2005; Lebowitz et al., 1997; Roest et al., 2015). However, many anti-psychotics are also known to have side-effects, especially in the aging population. It has to be stressed that there are no recent studies on the effectiveness of anti-psychotics in COPD patients since 10 years ago. In order to make an accurate conclusion on the effectiveness of anti-psychotics in COPD patients with comorbidities of anxiety and/or depression, larger research trials with a meticulous study design are required (Yohannes and Alexopoulos, 2014b; Za et al., 2011). In addition, cognition enhancing drugs have not been tested and applied yet in COPD patients.

Understanding the mechanisms involved with the onset of depression, anxiety and cognitive impairments in COPD patients could aid towards improving current treatment strategies.

5. Mechanisms for increased prevalence of brain-associated comorbidities in COPD patients

Though increased occurrence of brain problems in COPD patients could be due to the emotional toll of simply having a chronic disease (Polsky et al., 2005; Pumar et al., 2014; Wilson, 2006), we believe that biological processes are involved. Possible causes are: systemic inflammation, hypoxia, oxidative stress, smoking, corticosteroid usage and the gut microbiome. Each mechanism appears to have an overlapping link with another, causing a very complex interaction between all mechanisms and the onset of depression, anxiety, and/or cognitive impairment in COPD (Fig. 1).

5.1. Brain pathology in COPD

Multiple clinical studies demonstrated several brain pathologies relating to cognitive impairment in COPD patients. Though, similar processes could also take place in brain regions involved in anxiety and depression. Functional magnetic resonance imaging revealed that functional connectivity in activated brain regions in the default mode network correlated well with cognitive and pulmonary functions (Hu et al., 2018). In a meta-analysis till 2016 a negative correlation between cognitive function and arterial partial pressure oxygen was shown (Wen et al., 2018). It has been appreciated that both periodic and continuous hypoxia in the brain caused by COPD have an important role in adversely affecting the metabolism of neurotransmitters in the central nervous system (Gibson et al., 1981; Thakur et al., 2010). Finally, white matter lesions in different brain regions are associated with loss of cognitive function (Ai et al., 2014) and, though brain pathology is relatively unexplored in COPD, white matter damage was shown to be consistent with ischemic pathology in COPD patients (Spilling et al., 2017). Taken together, impaired cognition in COPD is associated with the severity of the disease and white matter lesions e.g. neuronal damage in several brain regions.

5.2. Systemic inflammation

In recent years the role of inflammation in depression, anxiety and cognitive impairments has become more apparent (Allison and Ditor, 2014; Miller, 2009; Miller and Raison, 2016; Teunissen et al., 2003; Wilson et al., 2002; Yaffe et al., 2004). Patients diagnosed with depression display all fundamental symptoms of an inflammatory

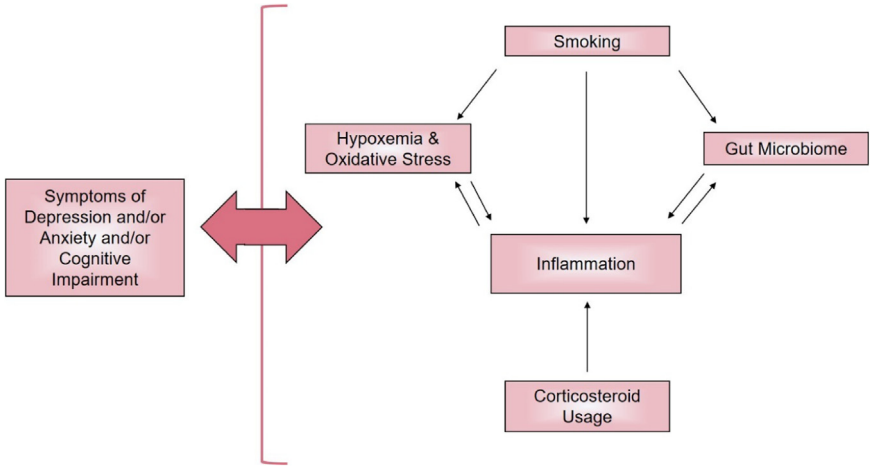

Fig. 1. Schematic representation of the interactions between each mechanism proposed for increased symptoms of depression, anxiety and/or cognitive impairment in COPD patients.

reaction, including increased expression of pro-inflammatory cytokines, pro-inflammatory cytokine receptors, and chemokines (Miller and Raison, 2016). In addition, studies have demonstrated the development of psychological and cognitive disorders after activation of the innate immune response and release of innate cytokines (Chen et al., 2008; Dantzer et al., 2008; Miller, 2009; Raison et al., 2006; Wilson et al., 2002). Administration of pro-inflammatory cytokines or their inducers into non-depressed individuals leads to symptoms of depression (Miller and Raison, 2016). In several diseases, such as metabolic syndrome and Alzheimer's disease, systemic inflammatory markers are related to cognitive impairment (Wilson et al., 2002; Yaffe et al., 2004). Even in healthy aging subjects, the levels of certain inflammatory markers, such as C-reactive protein (CRP), are correlated with cognitive performance (Teunissen et al., 2003). Induction of systemic inflammation in mice results in increased cytokine levels in the brain and cognitive impairment (Chen et al., 2008). Several pathways in which systemic inflammation is transmitted to the brain have been clarified (Allison and Ditor, 2014; Miller and Raison, 2016).

It has been demonstrated that plasma of COPD patients frequently contains increased levels of pro-inflammatory cytokines, such as CRP, interleukin (IL)-6, fibrinogen, activated leukocytes, and tumor necrosis factor alpha (TNF-α) (Eagan et al., 2010; Pumar et al., 2014; Sinden and Stockley, 2010). An association between plasma levels of soluble tumor necrosis factor receptor-1 and the diagnosis of depression in COPD patients was found (Eagan et al., 2010). Al-shair and colleagues found a positive correlation between plasma levels of TNF-α and depression scores in COPD patients (Al-shair et al., 2011). Last but not least, the cognitive functioning scores in COPD patients are reversely correlated with levels of CRP and fibrinogen (Crişan et al., 2014).

Enhanced systemic levels of cytokines in COPD are thought to originate from leakage from the lungs. However, the evidence for this theory in stable COPD characterized by systemic inflammation is not convincing. Several extrapulmonary organs and tissues are being recognized as other possible sources of inflammatory mediators in COPD. For example, adipose tissue is known to be an important production site of inflammation. Particularly in earlier stages of COPD, overweight and obesity are common (Agusti et al., 2010; Vozoris and O'Donnell, 2012). It has been shown that COPD patients with high plasma levels of CRP have greater adipose tissue macrophage infiltration compared to patients with low CRP levels (van den Borst et al., 2011). In addition, people with obstructive lung disease showed an increased abdominal fat area, which significantly contributed to IL-6 plasma levels (van den Borst et al., 2012). Furthermore, the gut is another possible source of inflammation in COPD. Inflammatory bowel disease (IBD) is a frequently observed comorbidity in COPD (Ekbom et al., 2008; Raj et al., 2008). At the same time, increased permeability of the small intestine and colon has been indicated in COPD patients (Rutten et al., 2014), thereby promoting gut inflammation. This "leaky gut" phenomenon is one of the characteristics of IBD as well (Michielan and D'Incà, 2015) and can promote the leakage of inflammatory mediators and aggravate systemic inflammation.

However, further research is necessary to conclude the relative contribution of different organs and tissues to systemic inflammation in COPD.

5.3. Hypoxemia

Hypoxemia is defined as reduced levels of arterial oxygen leading to increased levels of carbon dioxide in the body, which can cause confusion, altered consciousness, and mental slowing (Levenson, 2007). Considering that COPD involves degradation of alveolar capillaries and airflow restrictions, it is logical that COPD induces hypoxemia (Mikkelsen et al., 2004; Tuder et al., 2007). Hypoxia in the brains leads to oxidative stress, alterations of white matter, and alterations of endothelial cells, which can result in permanent cognitive defects and dementia (Levenson, 2007; Majid and Nadeem, 2017). Hypoxia modifies neuronal functions by altering the synthesis of neurotransmitters (Kumar, 2011). High levels of carbon dioxide may activate the respiratory center of the brain stem, triggering anxiety in attempt to alert the body for possible suffocation (Majid and Nadeem, 2017). Interestingly, the onset of depression has been demonstrated in COPD patients experiencing hypoxemia (Mikkelsen et al., 2004). In addition, hypoxemia can enhance systemic inflammation (Andelid et al., 2015; Eagan et al., 2010; Mikkelsen et al., 2004), as hypoxemia has been demonstrated to induce nuclear factor κB, the master regulator of cellular inflammatory responses resulting in systemic inflammation (Kent et al., 2011). Andelid and colleagues found hypoxemia after COPD exacerbations to be associated with systemic neutrophilic activity (Andelid et al., 2015). Moreover, it is hypothesized that hypoxia of adipose tissue in obese COPD patients might be an important source of systemic inflammation (Trayhurn et al., 2008). Indeed, chronic hypoxia in mice resulted in increasing circulating levels of IL-6 together with changes in the metabolic profile of adipose tissue (van den Borst et al., 2013). Hypoxemia-associated oxidative stress is a potential organic mechanism for the onset of depressive symptoms (Rose and Sharafkhaneh, 2017). Supporting this, Forlenza and colleagues found increased serum levels of a biomarker for oxidative damage, 8-hydroxy-2'-deoxyguanosine, in depressed patients (Forlenza and Miller, 2006). Translating this phenomenon to COPD, increased levels of oxidative stress have also been found in COPD patients (Drost, 2005; Kirkham and Barnes, 2013;

Rahman et al., 1996). Oxidative stress regulates inflammation in COPD (Rahman, 2006), and decreased levels of the antioxidant glutathione are found after severe and very severe exacerbations (89.2% and 52.3% respectively) relative to stable COPD (Drost, 2005). Taken together, hypoxemia and oxidative stress, directly and/or indirectly through associated systemic inflammation, might be involved the onset of brain-associated comorbidities in COPD patients.

5.4. Smoking

A bidirectional relationship between smoking and the development of depression and anxiety is well established (Mathew et al., 2017). Smoking contributes to the development of COPD and many patients with COPD continue this habit due to addiction (von Leupoldt et al., 2012). Not only does smoking accelerate the progression of COPD, but as expected COPD smokers are more likely to develop depression and anxiety than COPD non-smokers (Armannsdottir and Jonsdottir, 2014; Goodwin et al., 2008; Luger et al., 2014; Mikkelsen et al., 2004). Torres and colleagues demonstrated a higher prevalence of depression and anxiety in COPD patients who are/were smokers (30.2% and 66.9%, respectively) compared to COPD patients who had never smoked (20.5% and 34.6%, respectively) (Torres et al., 2016). Smoking, even secondhand exposure to smoke, is an established risk factor for cognitive decline and substantially increases the risk of Alzheimer's disease (Anstey et al., 2007; Cataldo et al., 2010; Chen et al., 2012; Llewellyn et al., 2009). The causal link between lifelong cigarette smoke exposure in COPD patients and memory loss is evident.

The mechanisms behind the onset of depression, anxiety and cognitive impairments in smokers/COPD patients are the activation of nicotinic acetylcholine receptors, hypoxia, dysregulation of the hypothalamic–pituitary–adrenal system, or inflammatory effects of smoking (Brusselle et al., 2011; Jensen, 1991; Markou, 1998; Pumar et al., 2014). Patients with anxiety and/or depression are at a higher risk for developing COPD due to an increased prevalence of smoking in depressed and/or anxious patients (Garcia-Arcos et al., 2016; Pumar et al., 2014). Thus, it is important to have the proper controls when assessing the relationship between smoking and the onset of depression and anxiety in COPD patients, as it is likely that these psychological disorders were already present in these patients before smoking. Nevertheless, the high occurrence of depression and anxiety in COPD patients is partially due to smoking.

5.5. Usage of corticosteroids

Corticosteroids are proposed to enhance the development of depression and/or anxiety (Majid and Nadeem, 2017; Russo et al., 2013). Corticosteroids alone or in combination with long-acting β2 agonists are used to decrease pulmonary inflammation (Singh et al., 2002), however, the usage of steroids in COPD patients leads to increased symptoms of depression (Gift et al., 1989). Interestingly, decreased symptoms of anxiety were found in mice with a deleted corticotrophin releasing hormone receptor after stress induction (Timpl et al., 1998) and, in humans, dose-dependent effects of corticosteroids were found on symptoms of depression, anxiety and cognitive problems which disappeared after discontinuation of the therapy (Brown and Chandler, 2001). Although the underlying mechanisms are not fully understood, there is evidence for the adverse impact of excess corticosteroids on hippocampal volume and function (Brown, 2009; Herbert et al., 2006). Contradictory to this, Hyun and colleagues have indicated no significant difference in depression and anxiety scores in COPD patients after treatment with inhaled corticosteroids, long-acting β2 agonists, or long-acting muscarinic antagonists using multivariate general linear mixed model analyses (Hyun et al., 2016). Therefore, further investigations are needed to elucidate this contradiction (Russo et al., 2013).

5.6. The gut microbiome

The gut microbiome is crucial for shaping the immune system and plays an important role in inflammatory processes (Clemente et al., 2018; Han et al., 2012). Many studies have demonstrated that smoking modulates the gut microbiome in both humans and rodents (Savin et al., 2018). Gut dysbiosis is linked to impairments in brain function in several neurodegenerative diseases, such as Parkinson's disease (Perez-Pardo et al., 2017c), and is believed to be involved in the development of behavioral and cognitive impairments (Oriach et al., 2016; Rogers et al., 2016). In addition, the microbiota can regulate the kynurenine pathway by modulating tryptophan availability, and changes in this pathway have been linked to anxiety, depression and cognitive decline (Kennedy et al., 2017). Although the gut microbiome in COPD patients has not yet been compared to healthy individuals, there are indications that gut function and immunity are disturbed in COPD (Shukla et al., 2017). Patients with COPD are two to almost four times more likely to have inflammatory bowel disease (IBD) and show increased intestinal permeability (Ekbom et al., 2008; Raj et al., 2008; Rutten et al., 2014). IBD is accompanied by dysbiosis in the gut, representing a shift toward a pro-inflammatory microbiome (Loh and Blaut, 2012). It is believed that gut inflammation in IBD is driven by an inefficient immune response to bacterial antigens, largely regulated by the gut microbiome (Abraham and Cho, 2009). Maintaining a healthy gut microbiome is strongly dependent on the host's diet (Clemente et al., 2018; Oriach et al., 2016). In addition, antibiotic use is known to cause dysbiosis in the gut (Francino, 2016) and this antibiotic-induced dysbiosis has been associated to the development of cognitive impairment in a recent study in mice (Fröhlich et al., 2016). Considering that an insufficient and unhealthy nutritional intake has been observed in COPD patients (van de Bool et al., 2014) and that COPD patients are often exposed to antibiotics, evaluation of the gut microbiome in COPD would be valuable to get a better understanding of the pathways involved in brain comorbidities in COPD.

6. Future outlook: novel treatment approaches for brain-associated comorbidities in COPD

From the previous sections, it can be concluded that inflammation most likely plays a central role in the development of depression, anxiety as well as cognitive decline in COPD. Therefore, targeting inflammation in alleviating brain-associated comorbidities in COPD may be a novel promising future outlook.

6.1. Anti-inflammatory drugs

Malignant melanoma patients given interferon alpha treatment displayed symptoms of a psychological disorder later along their therapy, who were responsive to anti-depressants (Capuron, 2002; Musselman et al., 2001). TNF-α receptor knock-out mice exhibited anti-depressant phenotypes and a reduction in anxiety after stimulation with a viral infection relative to wild type mice (Miller, 2009; Silverman et al., 2007). Certain classes of anti-depressants reduce or increase inflammation levels in depressed men (Vogelzangs et al., 2012). Additionally, a meta-analysis indicated that treatment with the anti-inflammatory drug celecoxib, had decreased symptoms of depression without increasing the risk of developing adverse side-effects in depressed patients (Köhler et al., 2014). In the future, certain classes of anti-inflammatory medications or other anti-inflammatory strategies may focus on treating symptoms of depression and anxiety (Miller and Raison, 2016).

As cognitive decline is also observed in non-hypoxemia COPD patients, it is hypothesized that a chronic systemic inflammation could affect the central nervous system (Kakkera et al., 2018). Therefore, anti-inflammatory drugs could be an option for treatment of cognition problems in COPD as well. Roflumilast, a Food and Drug

Administration (FDA)-approved phospodiesterase-4 inhibitor for the treatment of COPD for its potential anti-inflammatory and bronchodilator effects (Chong et al., 2017), improves memory in healthy young adults (Van Duinen et al., 2018) as well as in a rodent model for Alzheimer's disease (Smith et al., 2009). However, it needs to be established whether this effect is mediated via targeting immune cells or cells in the central nervous system (Spina, 2008).

Considering COPD is associated with higher levels of pro-inflammatory cytokines in patient blood (Eagan et al., 2010; Pumar et al., 2014; Sinden and Stockley, 2010), anti-inflammatory medications may be significantly useful in treating COPD patients with comorbidities of depression and/or anxiety as well as cognitive decline.

6.2. Nutritional modulation of inflammation

A potential successful approach for the treatment of COPD could be nutritional interventions. Advantages of nutritional interventions above of pharmacological treatment are that one nutritional supplement can target various systems, and that multiple dietary compounds may synergistically improve health by reducing inflammation, with less side-effects. Apart from this, it is well known that insufficient dietary intake and dietary deficiencies are common in COPD, which may negatively affect disease progression including brain comorbidities (Janssens et al., 2010; van de Bool et al., 2014, 2012). For example, severe vitamin D deficiency has been strongly associated with the occurrence of exacerbations and hospitalizations in COPD patients (Malinovschi et al., 2014), which in turn have been related to the induction and aggravation of mental health comorbidities in some COPD patients.

6.2.1. Dietary interventions affecting inflammation and/or brain function

Omega-3 poly-unsaturated fatty acids (N-3 PUFAs) are known to reduce inflammation in health and disease (Calder, 2015; Li et al., 2014). A meta-analysis by Li and colleagues indicated the potential of N-3 PUFAs to reduce the inflammatory factors CRP, IL-6 and TNF-α (Li et al., 2014). N-3 PUFAs incorporate into membrane phospholipids of cells involved in inflammation thereby improving membrane homeostasis and maintaining a regulated inflammatory response (Burri et al., 2012; Calder, 2008). Importantly, dietary N-3 fatty acid intake is associated with a lower risk of depression (Grosso et al., 2016). However, the effects of N-3 PUFAs on cognitive function, especially in adults, still remains inconclusive (Rangel-Huerta and Gil, 2017).

Some specific nutritional concepts are effective in improving mood and cognitive function in various diseases characterized by chronic inflammation, especially in the brain. For example, a combination of N-3 PUFAs, uridine, cofactors and vitamins elicits favorable effects in Alzheimer's disease. This nutritional concept improved cognitive function in preclinical studies (Jansen et al., 2014, 2013; Wiesmann et al., 2013), and specifically target the typical pathology in the brain (Broersen et al., 2013). Clinical studies suggest that this nutritional supplement has mostly beneficial effects on cognitive functioning in mild Alzheimer's disease (Scheltens et al., 2012, 2010) as opposed to a more advanced stage (Shah et al., 2013). These effects are related to a decline in hippocampal atrophy (Soininen et al., 2017). Furthermore, this diet enhances synapse formation and function (van Wijk et al., 2014), thereby improving neuronal signaling and functional connectivity in the brain, and reduces anxiety-like behavior in two different mouse models of Alzheimer's disease (Jansen et al., 2014, 2013). A diet containing a comparable combination of nutrients was effective in a Parkinson's disease model as well. The diet not only enhanced cognitive functioning (Perez-Pardo et al., 2017a), but could improve gut barrier function and reduce gut inflammation as well, as shown by a reduction in T-cells in the gut (Perez-Pardo et al., 2017a, 2017b). Interestingly, extending this diet by adding prebiotics was even more effective by restoring cognitive and gut functions, and gut inflammatory status almost to those observed in healthy animals (Perez-Pardo et al., 2017a). Considering these favorable effects on mood and cognition of this nutritional concept, including at least these nutrients in the treatment of brain-related comorbidities in COPD could be of importance.

As described above, there are several studies that have examined the efficacy of separate nutritional components in COPD. However, nutritional strategies including multiple different nutrients may be more effective in synergistically targeting different organs and tissues. A recent study by van de Bool and colleagues investigated the efficacy of a nutritional supplementation enriched with leucine, vitamin D and N-3 PUFAs in COPD patients (van de Bool et al., 2017). For four months, 81 COPD patients had to take two or three portions of either the nutritional supplement or placebo daily in addition to supervised high intensity exercise training. Solely the nutritional supplemented group improved HADS depression scores, suggesting this supplementation ameliorates symptoms of depression in COPD patients (van de Bool et al., 2017).

Although it is reasonable to believe that certain dietary components, such as N-3 PUFAs and prebiotics, may improve brain-related comorbidities in COPD, the number of studies supporting this is still limited. Investigations in animal models of COPD should be an important step into elaborating the most effective nutritional compounds in modulating mood and cognition.

6.2.2. Dietary anti-oxidants

The reduced anti-oxidant capacity associated with COPD exacerbations and/or smoking indicates a potential role for anti-oxidant therapy to dampen oxidative stress and consequent systemic inflammatory response in COPD (de Boer et al., 2007). Moreover, neurological diseases also are associated with oxidative stress and reduced anti-oxidant capacities in the brain (Patel, 2016). Dietary anti-oxidant supplementation with vitamin C, vitamin E, β carotene or polyphenols have been shown to improve lung function in limited set of studies and more robust clinical trials are needed in COPD (McGuinness and Sapey, 2017). Likewise, improvement of cognitive performance and mood by vitamin C and E supplementation or N-acetylcysteine treatment has been reported in elderly and depressed patients, respectively (Popa-Wagner et al., 2013; Xu et al., 2014). Currently, there are no clinical data regarding the effect of anti-oxidant therapies on COPD-associated brain problems.

6.2.3. Dietary modulation of the gut microbiome

Nutritional substances shown to positively modulate health, and especially brain function, via the gut microbiome are prebiotics. Prebiotics are non-digestible fibers stimulating the growth of certain favorable bacteria in the gut (Gibson and Roberfroid, 1995). Prebiotics improve gut barrier and immune function, and shift the gut microbial composition towards a more beneficial and protective one (Looijer-van Langen and Dieleman, 2009). In rats, prebiotics increase levels of specific signaling molecules in the brain important for neuronal survival and protection (Savignac et al., 2013). In the gut, prebiotic fibers are converted into short-chain fatty acids (SCFAs) by commensal bacteria (den Besten et al., 2013). SCFAs, such as butyrate, are known to have anti-inflammatory properties (McLoughlin et al., 2017), and improve gut microbial composition (den Besten et al., 2013). In several animal models representing cognitive impairment, SCFAs enhance cognitive function (Arnoldussen et al., 2017; Govindarajan et al., 2011; Kilgore et al., 2010). In an animal model of COPD, prebiotics supplementation reduced inflammation in the lungs and right ventricle heart hypertrophy (Verheijden et al., 2011). Besides prebiotics, nutritional intervention with probiotics – as live microorganisms that when administered in adequate amounts, confer a health benefit on the host – can be an approach to target the gut-brain axis. Cryan and colleagues introduced the term ‘psychobiotics’ that exert anxiolytic and antidepressant effects characterized by changes in emotional, cognitive, and neuronal systems (Dinan et al., 2013). Though most research is based on rodent models, results indicate that neuronal (enteric nervous system-vagal nerve-CNS) as well as immunological pathways play an important role in the psychobiotics-brain axis finally resulting in mental

health improvement (Sarkar et al., 2016).

However, efficacy of prebiotic and/or probiotic supplementation in improving mood and cognitive function in COPD still needs further investigation.

7. Challenges

A major problem surrounding the therapy options mentioned above is that, in general, only 31% of COPD patients with anxiety and/or depression are currently being treated for these psychological disorders (Kunik et al., 2005). Moreover, to date no specific cognition improving strategies are put in place for COPD patients. Considering the dampening effect the brain-associated comorbidities have on COPD, this is a problem and thus a challenge. This lack of treatment may be attributed to the point that it is not the specialty of the primary care provider to notice, diagnose, and treat brain problems (Rose and Sharafkhaneh, 2017). The problems with treatment compliance in COPD patients suffering from brain-associated comorbidities may also play a role (Albrecht et al., 2016; Fritzsche et al., 2011; Hynninen and Nordhus, 2017; Yohannes et al., 2001). Patients may also fear to confess symptoms of depression and/or anxiety to a professional due to the negative stigmatisms associated with mental health disorders (Majid and Nadeem, 2017). Home care givers may or may not enhance patient compliance depending on their view of mental and cognitive health problems (Dooley and Kunik, 2017). Additionally, resources to identify psychological disorders are generally lacking (Rose and Sharafkhaneh, 2017). Thus, improving screening instruments, the view of mental and cognitive disorders with home caregivers and patients, and healthcare providers' cognition of the high frequency of brain disorders in COPD is very important (Cleland et al., 2007; Kunik et al., 2005; Majid and Nadeem, 2017).

In the future, anti-inflammatory pharmacological or nutritional interventions may be used for treating brain comorbidities in COPD due to the increasing evidence for the major role of inflammation in mental health problems. However, although it is very likely that systemic inflammation may play a role in (the development of) brain-associated comorbidities in COPD, not every COPD patient shows signs of systemic inflammation (Agustí et al., 2012). Therefore, it is important to elucidate whether patients, in which systemic inflammation is observed, also show (more) symptoms of psychological and cognitive impairment.

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