ORIGINAL ARTICLE

THE ROLE OF CHRONIC INFLAMMATION IN THE DEVELOPMENT OF DEPRESSION IN COPD PATIENTS

Vania Tryanni 1 , Hamzah Shatri1,3, Dika Sinulingga1, Vinandia Irvianita1, Edward Faisal1, Rudi Putranto1, Gurmeet Singh2, Ceva W. Pitoyo2
1 Psychosomatic and Palliative Division, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
2 Respirology and Critical Care Division, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia
3 Clinical Epidemiology in Department of Internal Medicine, Faculty of Medicine Universitas Indonesia- Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

COPD is one of the most prevalent disease and the prevalence is still increasing. Depression is one of the most prevalent comorbid found in COPD and associated with increase mortality and reduced quality of life. The linked between booth of them can't be fully elucidated. One of the theories is chronic inflammation. Increase inflammatory state is associated development of depression to some pathway, and there is direct link between serotonin-inflammation. COPD is a well-known inflammatory state with same increasing inflammatory state. There are also similar characteristics between depression with inflammatory stated and depression in COPD such as atypical symptom and resistance to therapy. Studies also proved that there were increase in cytokine especially IL-6 , IL-2 and IFN gamma in COPD -Depression.

Keyword: COPD, Depression, Chronic Inflammation

ABSTRAK

PPOK adalah salah satu penyakit kronik tersering dan satu satu nya yang angka-nya terus meningkat. Depresi adalah salah satu komorbiditas tersering yang ditemukan pada PPOK yang menyebabkan peningkatan mortalitas dan kualitas hidup. Hubungan antara keduanya masih belum diketahui dengan jelas. Salah satu teorinya adalah peran dari inflamasi kronik. Peningkatan kondisi inflamasi diketahui menyebabkan kejadian depresi lewat jalur serotonin – inflamasi. PPOK sendiri adalah penyakit inflmasi dimana perubahan status inflamasinya mirip pada kondisi depresi. Depresi dengan status inflamasi tinggi dan depresi pada PPOK juga memiliki kesamaan klinis yaitu gejala yang atipikal dan resistensi terhadap pengobatan. Beberapa studi telah menemukan peningkatan sitokin pro inflamasi seperti IL-6, IL-2 dan IFN gamma. Studi lebih lanjut diperlukan.

Kata Kunci: PPOK, depresi , inflamasi kronik

Correspondence :
Hamzah Shatri MD, Division of Psychosomatic and Palliative medicine, Department of Internal Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo National General Hospital.
Jl. Diponegoro No 71, Jakarta 10430, Indonesia
Email: hshatri@gmail.com

How to cite this article :
THE ROLE OF CHRONIC INFLAMMATION IN THE DEVELOPMENT OF DEPRESSION IN COPD PATIENTS

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressively incapacitating multisystem disease that worsens the patient's physical and psychosocial functioning, and still incurable. Preserving quality of live, prevention of exacerbation and maintaining residual pulmonary function was the mainstray purpose of COPD treatment. Patient with COPD tend to have many comorbidities. During investigation from the last two decades, it was known that COPD patient with three or more comorbidities are more likely to be frequently hospitalized and may die prematurely compared with COPD patients without comorbidities.[i] One of the most common comorbidities are depression and anxiety. COPD patients 3-10 fold have higher case of mood disorder compare to normal population.[ii]For depression itself almost half of COPD patient have significant depression symptoms , and about 20% will meet psychiatric criteria for major depressive or dysthymic disorder. [iii] Study by Shcnieder et.al found that incidence of depression in COPD group are 16.2 / 1000 person versus 9.4/ 1000 person. They also found that those with severe COPD twice more likely to develop depression.

Mental health-related disorders are the leading causes of increased disability and impaired quality of life in older people worldwide. Specifically, mood disorders, such as major depression, dysthymias (chronic depressive symptoms of mild severity), minor depression and anxiety disorders (generalised anxiety disorder, phobias and panic disorders) are common in patients with COPD. [iv]Depression with COPD is associated with poorer treatment adherence, decreased HRQL, greater disability and increased mortality, exhibit self-reported functional limitations, poorer exercise tolerance and higher frequency of acute exacerbations. [v]

COPD and depression have bidirectional effect as depression may be both a cause and a consequence of COPD. However, the exact mechanisms linking COPD with depression and anxiety have not been identified and probably multifactorial and varies between patients. Several pathologic systemic processes could contribute to the development of anxiety and depression in both direct and indirect ways. COPD causing increase chronic low-grade inflammation, hypoxemia , more vigilant to respiratory sensation and react to this sensation and will increase anxiety. It also led to feelings of frustration, helplessness, and hopelessness in patients as they struggle with the impact of COPD on their physical, psychologic, and social functioning. [vi] This article will elaborate the role of chronic inflammation in the development of depression in COPD population.

Chronic Inflammation and Depression

Immune Finding in Depression

There are growing evidence of association between a systemic immune activation, comprising abnormality in inflammatory markers, immune cell numbers, and antibody titers with major depressive disorder (MDD). There are couple of literature that find proinflammatory cytokines and acute phase proteins are increased in MDD patients, with a fairly unanimous consensus of increases in IL-6, TNF, and C-reactive protein (CRP) in the blood of MDD patients compared to healthy controls. With increasing technology in the measurement of cytokine there are several other cytokines that have been evaluated. A relatively recent meta-analysis of 82 studies including 3,212 MDD patients and 2,798 healthy controls reveals increased levels of IL-6, TNF, IL10, sIL-2, C-C motif ligand (CCL)2, IL-13, IL-18, IL-12, IL-1RA, and soluble TNF receptor (sTNFR)2, whereas the level of interferon-g (IFN-g) is reduced. [vii]But there is large heterogeneity which influenced by the cytokine

component studied, and due to the absence of consideration of the clinical course , illness duration, comorbidity, medications, fasting status, smoking, assay methodology, or body mass index (BMI) . Beside increase pro inflammatory cytokine, there are also increase in anti-inflammatory cytokine.

Not all MDD patient will have increased inflammation. Increased inflammatory state is associated with atypical symptom of depression [viii], suicidal, and newly treated patients. Patient with increased inflammatory state tend to have non melancholic threat, and the other way around. Specific type of cytokine also play role, where TNF associated with atypical feature and IL-6 associated with acute exacerbation. Furthermore high concentration of IL-6 , CRP ,and TNF also associated with more severe symptom and chronicity. These feature are consistent with Chamberlain finding that showed patient with proinflammatory stages showed resistance to therapy and poor response to antidepressant.[ix] The increased pro-inflammatory stated maybe caused by activation of monocyte and macrophages that caused elevation of IL-6 and IL-1 beta. Where increase of sIL-2R is produced d by activated T cells would serve to downregulate T cell activation. There are also increased number of leukocytes, neutrophils, and monocytes and CD4/C8 with decrease CD8 and increased CD4. But the increased of CD 4 can't overcome the reduce response of T Cell and NK cell and causing the net effect of immunosuppression. [x]Both of the process, increased cytokine production and cell immunosuppression can occur in the same individual, and influenced by age and depression stages.

Caused of increased inflammation in Depression

There are several factors that causing increase inflammation in MDD patient. First are epigenetic malformation. There are several genes that have been most replicated such as polymorphism in gene encoding such as IL-1b, IL-6, IL-10, TNF, MCP1/CCL2, CRP, and phospholipase-A2 (PLA2). The contribution of these each polymorphism to MDD remains difficult to determine. For example, polymorphism in IL-1Beta whether causing increased or decreased production of IL-1Beta associated with more severe depressive symptom. This discrepancy might be due to the facts that not all depressed patients exhibit inflammation, and the environmental factors and gene-environment interactions are likely more important than pure genetic factors to account for depression. But Al together showed that epigenetic polymorphism associated inflammatory genes in MDD.

There is epidemiological link between psychiatric and autoimmune diseases. There is an increased risk of autoimmune diseases (rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus) in depressed patients, on the other way patients with autoimmune diseases have some of the highest rates of comorbid depression.

There are several mechanisms that linked depression and chronic inflammation. First one is mediated by activation of HPA axis and SNS. HPA axis was activated by stress and known to be immunoregulatory. This axis will release ACTH and causing release of cortisol and SNS activation which will release catecholamines. Both cortisol and catecholamines regulate inflammation, acting as immunosuppressants, inhibiting leukocyte trafficking and activation, as well as inflammatory cytokine production, even causing apoptosis in some Th subset. Depression is often associated with hypercortisolemia and glucocorticoid resistance. Stress, particularly in early life, including maternal stress during the intrauterine period, affects glucocorticoid sensitivity via epigenetic mechanisms,

turning down the sensitivity of the immune system to cortisol

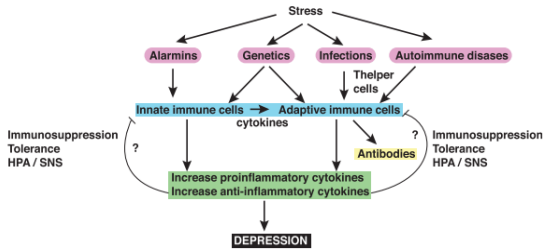

Figure 1 Diagram of Potential Immune

These changes in the communication between the HPA axis and immune system lead to increased rates of inflammatory and metabolic diseases in survivors of childhood abuse and neglect, as well as increased depression. Depression will cause increased sympathetic and lower parasympathetic tone. Parasympathetic tone act as mediator to sickness behavior. Its activation was caused by increase macrophage and dendritic cell in perineural sheath of vagus nerve. Sickness like behavior also associated with depression symptom

Second is mediated by TLR-4 (tumor like receptor). TLR-4 are a major class of receptors that detect DAMPs and PAMPs and are critical for the innate immune response. It was found that mice with knockout TLR 4 are resistant to depression behavior, proofing its role in depression. Moreover TLR-4 MRNA is elevated in the peripheral and CNS in MDDD patient. Its level also reduced in successful treated patient. TLR-4 can be induced by lipopolysaccharides (LPS) dan causing cytokine production dependent and induction of depressive like behavior. Upon recognition and activation, TLR4 will activates glycogen synthase kinase-3 (GSK3) that activates NF-kB to promote proinflammatory cytokine production. Newer ligand is found to activate TLR-4 such as alarmins: high-mobility group box 1 protein (HMGB1), adenosine triphosphate (ATP), or Myeloid-related protein 8/14 (Mrp8/14, also called S100A8/9). Alarmin will produce under psychological stress .. Activated TLR 4 will active inflammasome pathway that is not always require. Inflammasome will increase caspase-1 that is responsible of pro IL-1 Beta and Prol IL-18 cleavage. Mice deficient caspase will be resistance to depressive like behavior

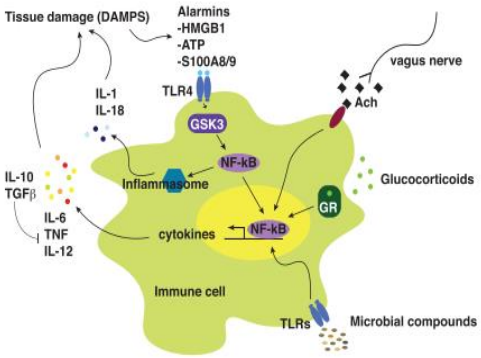

Figure 2 Multiple Mechanisms May Contribute to the Dysregulation

As we know, the Monoamine Hypothesis, is the most well-known hypothesis for pathophysiology of depression. Based on this hypothesis, depression is caused by deficiency of monoamine especially serotonin in the nerve cell gap. Chronic inflammation can suppress hippocampal neurogenesis ,and activate HPA axis. It also activate indoleamine 2,3-dioxygenase, an enzyme that decomposes tryptophan to kynurenine and will inhibit biosynthesis of tryptophan to serotonin. Inflammatory cytokine also activate the serotonin transporter , contrary to the action of antidepressant and reduce serotonin in the synaptic cleft. As a result of activation of the tryptophan–kynurenine pathway, the production of neurotoxic substances with excitatory amino

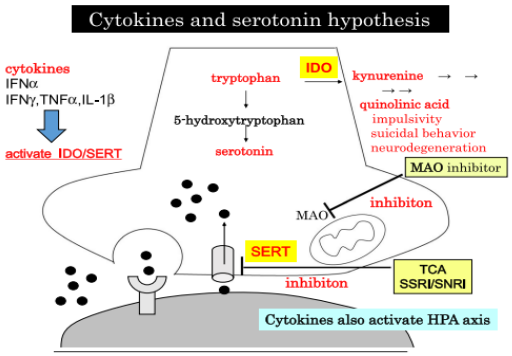

Figure 3 Cytokines and serotonin hypothesis.

Serotonin; HPA, hypothalamic–pituitary–adrenal axis; IDO, indoleamine 2,3-dioxygenas;

acid receptor stimulating action, such as quinolinic acid, is increased, resulting in increased impulsivity and suicide-related behavior (Figure 1), It has been reported that quinolinic acid actually shows a high level in the cerebrospinal fluid of a suicide attempter, and decreases in correlation with a decrease in suicidal ideation over time. Furthermore, in chronic inflammation, glutamate metabolism by astrocytes is not well carried out, and glutamate in the intercellular space is in an excessive state[xi]

Chronic Inflammation and COPD

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation, that affecting the lung parenchyma and peripheral airways. This process will caused progressive and irreversible airflow obstruction. COPD development is promoted by persistent pulmonary inflammation in response to several stimuli (e.g., cigarette smoke, bacterial and viral infections, air pollution, etc.). [xii] There are increased number of macrophages and neutrophil the sputum of COPD patient as a response to to chemotactic mediator released by epithelial cells in response to insult. These processes causing increase in CD 8 and reduced CD4. There also increased chemokines such as CXCL9, CXCL 10 , and CXCL 11 that causing increased migration. In COPD patient. There are also increased eosinophilic basic protein without increased cell, indicating that maybe the eosinophil already degranulating. Bacterial colonization is suspected to influence theses processes. *Hemophilus influenzas* but no other bacteria , is associated with increased inflammation. This process causing a similar response to senescence associated secretory phenotype with increased of IL- 1β, TNF- α, IL- 6, CXCL8, CXCL10, MMP- 2, MMP- 9 and TGFβ, suggesting that the inflammation seen in COPD lungs may reflect cellular senescence in lungs.[xiii] Plasminogen activator inhibitor-1 (PAI- 1) is a characteristic mediator of SASP and is increased in the sputum and lungs of COPD patients. [xiv]

Insults to the airway epithelial cells from cigarette smoking, oxidative stress, bacteria or viruses will activate neutrophilic inflammation via nuclear factor- κB (NF-κB) and p38 mitogen- activated protein kinase (MAPK) signaling, causing release in neutrophilic mediators, including neutrophil chemoattractant CXCL1 and CXCL8 that will activate neutrophil. This pathway also activate and attract Th 17 or ILC 3 and will release IL 17 then release IL 6 that are a potent pro inflammatory cytokine. Activation of NF-kB will increase TNF Alfa that maintained neutrophil. Neutrophil will release MMP that will induce mucus secretion . Moreover neutrophil will increase oxidative stress that will further inflammation. This kind of inflammation called neutrophilic and it characterized by resistance to steroid. To overcome this problem , many other drugs of choice are made. One of which is roflumilast, that reduces neutrophilic (and eosinophilic) inflammation resulting in lower exacerbations rate when using as add-on. However, its dose is limited by side effects, such as diarrhea, headaches and nausea, so its clinical effect is limited.

Depression and COPD

Previous studies already showed that patient with COPD has twice risk to developed MDD, and there must be linked those two. First booth of them is based on chronic inflammation. COPD chronic inflammation produce many pro inflammatory cytokines such as IL-6 and TNF alfa. These condition also associated with decrease responsiveness to glucocorticoid that increase risk to poor functioning of immune system. Booth of them is a well-known cytokine that has a major role in development of MDD. Depression in COPD and depression with increase inflammatory state tend to have atypical symptom. Last is booth of them did not responde well to anti-depressant. As one of meta-analysis showed that use of anti-depressant showed insignificant benefit to improve QOL. All of these reasons give biological plausibility of chronic inflammation as main caused of depression in COPD.

Unfortunately, the evidence is still variable. One from the oldest in 2015 by Rybka[xv] ,involved 45 patients from four different groups. There are 13 patients with COPD and depression, 16 patients with COPD alone, 15 Patients with recurrent depression disorder (rDD) and 19 healthy control from several center in Poland. Depression was assessed by Beck Depression Inventory (BDI) with cut off > 13 , that was assessed a week before enrolment. Patient with other commodities was excluded from the study. All COPD patients were treated with usual drugs , with around 42% received inhaled glucocorticoid. All depressed patient also still in their usual medication with 60 % were treated with SSRI, 35 % with SNRI, and 15 % with TCA. All blood samples were taken and was examined for cell surface phenotype expression. They also examine concentrations of IL-2, IL-6, IL-8, and IL-17 using ELISA method. These studies showed that COPD, depression, and COPD with comorbid depression are associated with increased IL-6 levels when compared with healthy controls 42.2 ± 1.87, 40.9 ± 2.12, 41.7 ± 1.31, and 33.2 ± 1.23 pg/ml, respectively (p\0.05). Concentrations of IFN-c were significantly increased in COPD= DS patients when compared with controls (24.3 ± 1.49 and 17.8 ± 0.70 pg/ml, respectively, p= 0.05). IL-2 levels were highest in COPD + DS (3.20 ± 0.389 pg/ml) and differed significantly when this group was compared with controls (2.20 ± 0.184 pg/ml), p B 0.05). These findings suggest that T helper cell 1-derived cellular immune activation may play significant role in developing depressive symptoms in COPD patients.

Latest study by Strollo in 2021, they are looking for association of chronic inflammation and depressive symptom in COPD patient. They do secondary analysis from two different large cohort called SCCOR (N-220) and COPDGene(N= 745). They defined COPD as evidence of airway obstruction (FEV1/FVC <0.7), they evaluated depression using Beck Depression Inventory II (BDI-II) and the Hospital Anxiety and Depression Scale (HADS). From booth of the studies only IL-6 data were available. They found that depression was detected in around 14% of COPD patients. Booth cohort showed that depressive symptom was associated with higher with smoker, more severe obstruction, and more severe symptom. In COPD gene cohort they found that depressive symptoms was associated with lower 6 minutes walking test that represent daily activities. In this cohort, there are higher population of more severe symptom (GOLD III-IV) compared to SCCOR.

One parameter was consistent that is increased IL-6. Increased IL -6 was found to be independent risk factor for depressive symptom even after adjusting with other comorbidity. . Increase IL-6 found to increase depressive symptom in COPD patient with OR form SCCOR cohort is 1.7 (

1.07- 2.68; p=0.024) and COPDGene 1.152 (1.13 -2.04, p= 0.006).

Lu et al found that IL-6, CRP and depressive symptoms were independently associated with decreased FEV1% predicted and FEV1/FVC in a large Singaporean population. [xvi]Although most participants did not meet the threshold for airflow obstruction, this study supports the relationship between inflammatory markers, particularly IL-6, and depressive symptoms. Al-shair et al[xvii] investigated the relationship of inflammatory markers and depressive symptoms in a small British cohort with moderate COPD.21 They did not find an association between IL-6 and depression in COPD but did conclude that TNF-α is linked with depression. The small size of the population and patient characteristics may have influenced the results.

One proposed mechanism suggests that depressive symptoms in subjects with COPD may be differentially modulated by factors such as systemic inflammation and respiratory symptoms at different levels of airflow obstruction. At mild to moderate airflow obstruction, systemic inflammation may be the dominant contributor to depressive symptoms when there is a lower overall degree of respiratory limitation. In the populations with more severe airflow obstruction, persistent respiratory symptoms and activity limitation may drive depression independent of systemic inflammation. Alternatively, there may be a distinct endotype of individuals who are predisposed to producing higher levels of inflammatory biomarkers which subsequently mediate depression.

Treatment Consideration

As stated, before depression associated with increase inflammation tend to be resistant to antidepressant. Same like in depression in COPD patient, used of antidepressant showed no significant benefit. Last meta-analysis in Cochrane in 2018 by Pollok et.al [xviii], involved 171 patients from two RCT did not found any significant benefit in depressive symptom after treatment with SSRI (SMD 0.75, 95% CI -1.14 to 2.64; P = 0.44; I2 = 95%). Use of TCA showed benefit in reducing depressive symptom (MD -10.20, 95% CI -16.75 to -3.65; P = 0.007) but no benefit to improving QOL, dyspnea symptom , change in FEV1 , change in exercise tolerance, change in hospital utilization, or cost-effectiveness. It is noteworthy that this is a very small study involving only 30 patients.

Other approach was used to help reduce depressive symptom in this population. Many studies was held and showed variable result. There is a Cochrane meta-analysis by pollok et.al[xix] involving 13 RCT with total of 1500 participants looking the benefit of variable psychological intervention from supportive psychotherapy or CBT with various method. There was a small effect showing the effectiveness of psychological therapies in improving depressive symptoms when compared to no intervention (SMD 0.19, 95% CI 0.05 to 0.33; P = 0.009; 6 studies, 764 participants), or to education (SMD 0.23, 95% CI 0.06 to 0.41; P = 0.010; 3 studies, 507 participants). We rated the quality of evidence as very low. Two studies compared psychological therapies plus a co-intervention versus the co-intervention alone (i.e. pulmonary rehabilitation (PR)). The results suggest that a psychological therapy combined with a PR program can reduce depressive symptoms more than a PR program alone (SMD 0.37, 95% CI -0.00 to 0.74; P = 0.05; 2 studies, 112 participants). As secondary outcome, this study also look for benefit in quality of life and hospital admission and showed significant benefit but only from one studies. Owing to the nature of psychological therapies, blinding of participants, personnel, and outcome assessment was a concern.

This review showed a big role of chronic inflammation in the development of

depression, whether in normal population of COPD. So it make sense to use anti-inflammatory drugs to reduce depressive symptom. As stated before that TNF-Alfa and IL-6 hold major role in the development of depression. There is a meta-analysis by Bavaresco et.al[xx] in 2019 found 4 relevant studies involving 152 patients. They found no significant reduction of depressive symptom represent using HAM-D with weighted mean difference was 1.90 (95% CI: −1.80, 5.60). There wasn't any adverse effect reported. All of the studies using infliximab as adjuvant, with other anti-depressant as the main drugs. Infliximab was administered with dose of 5mg/kg at baseline, week 2 and week 6.

Usage of anti-IL-6 was not well studied like TNF Alfa , there are one study by Knight et.al[xxi] that administer anti IL-6 to patients undergone hematopoietic stem cell transplantation as a prevention method to prevent depression. Tocilizumab was administer one day before allogeneic HCT. The primary outcome included depressive symptoms at 28 days post HCT. They found that using tocilizumab was associated with higher depression symptom in day 28 ($\beta = 5.74$; 95% CI 0.75, 10.73; $P = 0.03$). Even after adjustment for baseline depressive symptoms, propensity score, and presence of acute graft-versus-host disease (grades II–IV) and other baseline covariates ($\beta = 4.73$; 95% CI 0.64, 8.81; $P = 0.02$).

There are some reasons to explain this result, it is believed that tocilizumab is not cross the blood–brain barrier. Second it is possible that blockade of peripheral receptors alone results in excess unbound peripheral IL-6 available to exert its action centrally.

Reference

[i] Hegerl U, Mergl R. Depression and suicidality in COPD: understandable reaction or independent disorders? Eur Respir J 2014; 44: 734–743.

[ii] Marc Decramer, Rennard S, Trosster T, et.al. COPD as a Lung Disease with Systemic Consequences – Clinical Impact, Mechanisms, and Potential for Early Intervention. 2008. COPD: Journal of Chronic Obstructive Pulmonary Disease, 5:235–256

[iii] Lecheler L, Richter M, Franzen DP, et al. The frequent and underrecognised co-occurrence of acute exacerbated COPD and depression warrants screening: a systematic review. Eur Respir Rev 2017; 26: 170026 [https://doi.org/10.1183/16000617.0026-2017].

[iv] Fritzsche A, Clamor A, von Leupoldt A. Effects of medical and psychological treatment of depression in patients with COPD – a review. Respir Med 2011; 105: 1422–1433.

[v] Yohanes A, Kaplan , Hanania, Anxiety and Depression in Chronic Obstructive Pulmonary Disease: Recognition and Management. The Journal of Family Practice and Cleveland Clinic Journal of Medicine. doi: 10.3949/ccjm.85.s1.03

[vi] Pumar M, Gray C, Walsh J. Anxiety and depression—Important psychological comorbidities of COPD. J Thorac Dis 2014;6(11):1615-1631

[vii] Ko¨ hler-Forsberg, O., N Lydholm, C., Hjorthøj, C., Nordentoft, M., Mors, O., and Benros, M.E. 2019. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. Acta Psychiatr. Scand. 139, 404–419

[viii] Lamers, F., Milaneschi, Y., de Jonge, P., Giltay, E.J., and Penninx, B.W.J.H. 2018. Metabolic and inflammatory markers: associations with individual depressive symptoms. Psychol. Med. 48, 1102–1110.

[ix] Chamberlain, S., Cavanagh, J., De Boer, P., Mondelli, V., Jones, D., Drevets, W., . . . Bullmore, E. (2019). Treatment-resistant depression and peripheral C-reactive protein. British Journal of Psychiatry, 214(1), 11-19. doi:10.1192/bjp.2018.66

[x] Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and

Inflammation: Double Trouble. Neuron. 2020 Jul 22;107(2):234-256. doi: 10.1016/j.neuron.2020.06.002. Epub 2020 Jun 17. PMID: 32553197; PMCID: PMC7381373.
[xi] Monji A. Inflammation in psychiatry especially focused on depression. Clin Exp Neuroimmunol. 2021;12:107–110
[xii] Poto R, Lofferdo S, Palestra F et,la. Angiogenesis, Lymphangiogenesis, and Inflammation in Chronic Obstructive Pulmonary Disease (COPD): Few Certainties and Many Outstanding Questions. Cells 2022, 11, 1720. https://doi.org/10.3390/cells11101720
[xiii] Barnes PJ. Senescence in COPD and its comorbidities. Annu Rev Physiol. 2017;79:517-539.
[xiv] Barnes PJ. Inflammatory endotypes in COPD. Allergy. 2019;74:1249–1256.
[xv] Rybka J, Korte , Malinoswaka et.al. The links between chronic obstructive pulmonary disease and comorbid depressive symptoms: role of IL-2 and IFN-c. Clin Exp Med .2016. 16:493–502
[xvi] Lu Y, Feng L, Nyunt MS, Yap KB, Ng TP. Systemic inflammation,
depression and obstructive pulmonary function: a population-based
study. Respir Res. 2013;14:53. doi:10.1186/1465-9921-14-53
[xvii] Al-shair K, Kolsum U, Dockry R, Morris J, Singh D, Vestbo J. Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. Respir Res. 2011;12:3. doi:10.1186/1465-9921-12-3
[xviii] Pollok J, van Agteren JEM, Carson-Chahhoud KV. Pharmacological interventions for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD012346. DOI: 10.1002/14651858.CD012346.pub2.
[xix] Pollok J, van Agteren JEM, Esterman AJ, Carson-Chahhoud KV. Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD012347. DOI: 10.1002/14651858.CD012347.pub2.
[xx] Bavaresco, D. V., Uggioni, M. L. R., Ferraz, S. D., Marques, R. M. M., Simon, C. S., Dagostin, V. S.,da Rosa, M. I. 2020. *Efficacy of infliximab in treatment-resistant depression: A systematic review and meta-analysis. Pharmacology Biochemistry and Behavior, 188, 172838.* doi:10.1016/j.pbb.2019.172838
[xxi] Knight, J.M., Costanzo, E.S., Singh, S. *et al.* The IL-6 antagonist tocilizumab is associated with worse depression and related symptoms in the medically ill. *Transl Psychiatry* **11**, 58.2021. https://doi.org/10.1038/s41398-020-01164-y