**Highlights**

- Inflammation and oxidative stress may play a role in both depression and smoking.
- Inflammation includes raised pro-inflammatory cytokines and acute phase proteins.
- Oxidative stress includes decreased antioxidant levels and increased free radicals.
- The co-occurrence of depression and smoking increases activation of microglia.
- Depression and smoking may contribute to neuroprogressive pathways.
The shared role of oxidative stress and inflammation in major depressive disorder and nicotine dependence

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1. Introduction

Depressive disorder is highly comorbid with nicotine dependence. In the National Comorbidity Survey, nearly 59% of individuals with a life-time history of depression were current or past smokers, compared to less than 39% of those without a life-time history of depression (Lasser et al., 2000; Ziedonis et al., 2008). The comorbidity of nicotine dependence and depressive disorders can be explained either through common pathways or shared predisposing factors, such as genetic or environmental factors that may increase both smoking and depression. Smoking also appears to increase the risk for the development of mood disorders (Pasco et al., 2008; Pederson and van Soest, 2009; Ziedonis et al., 2008). Depressive and anxiety disorders are an overwhelmingly strong predictor of daily smoking (Patton et al., 1998). Pre-existing psychiatric disorders predict the subsequent onset of daily smoking and progression to nicotine dependence (Breslau et al., 2004).

People with current nicotine dependence exhibit greater prevalence and severity of several depressive symptoms compared to people with no history of nicotine dependence (Leventhal et al., 2009). Smokers with nicotine dependence have more severe depressive and anxiety symptoms and recover more slowly (Jamal et al., 2012) such that smoking worsens treatment prognosis (Dodd et al., 2010).

There is significant literature describing the pathways that may explain the co-occurrence of depressive disorder and nicotine dependence. The effects of diverse neurotransmitters, particularly glutamate, serotonin, and dopamine, have been demonstrated in both addiction and mood regulation. Dopaminergic agents such as the antidepressant bupropion have been used successfully for the relief of smoking withdrawal syndromes (Danovitch, 2011). Dopamine plays a key role in the regulation of mood and in depression (Berk et al., 2007a; Malhi and Berk, 2007).
Cigarette smoking is associated with decreased serotonin function (Malone et al., 2003), and there is extensive evidence of serotonergic abnormalities in depression (Stockmeier, 2003). Plasma levels of glutamate in patients with mood disorders were significantly higher than those in the control group (Hashimoto, 2011), and dysfunctional peripheral glutamate receptors are reported in depression (Berk et al., 2001).

There is also evidence that inflammatory pathways may link smoking and depression. Depressed smokers have higher levels of pro-inflammatory cytokines (PICs) than non-depressed smokers, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and acute phase proteins such as C-reactive protein (CRP) (Nunes et al., 2012).

Both depressive disorders and cigarette smoking are associated with increased levels of oxidative stress (Berk et al., 2011; Maes et al., 2011; Rytilä et al., 2006, van der Vaart et al., 2004). Oxidative stress results from an oxidant-antioxidant imbalance, as either an excess of oxidants and/or a depletion of antioxidants, leading to potential protein, lipid, carbohydrate, and deoxyribonucleic acid (DNA) damage (Sies, 1991, 1997).

This article focuses on inflammation and oxidative stress in nicotine dependence and depressive disorders. Inflammation and oxidative stress may interact to increase the risk of neuroprogression of these diseases. In this context, we used studies to provide a better characterization of the shared role of inflammation and oxidative stress in individuals with co-occurring disorders that affect neurotransmitters and that activate the hypothalamic-pituitary-adrenal (HPA) axis and microglial cells. This review article also discusses the fact that both nicotine dependence and depressive disorders both diseases with brain dysfunction by increase
the levels of inflammatory biomarkers, increase the production of oxidants, decrease the levels of antioxidants, alter mitochondrial function and modify gene function. Finally, this review provides some evidence for clinical practice.

2. Methods

A narrative review was performed to investigate studies showing explicit associations between depressive disorder, nicotine dependence, inflammation and oxidative stress. The sources used were identified in the electronic database Medline (PubMed) and were limited to English language articles published between January 2000 and July 2012. Using the MeSH (Medical Subject Headings), the following search terms were used: “depressive disorder” and “smoking” and “inflammation”, and “depressive disorder” and “smoking” and “oxidative stress”. Furthermore, review articles were searched, and other publications cross-referenced for additional published articles.

In this review, articles were excluded if inflammatory or immune abnormalities were accompanied by physical illnesses including diabetes, coronary artery disease, Crohn’s disease, rheumatoid arthritis, cancers, human immunodeficiency virus, and multiple sclerosis. These disorders are associated with an increased prevalence of major depressive disorder (MDD) (Benton et al., 2007). Medical comorbidities may include the following: cardiovascular disease, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, HIV infection, diabetes and metabolic syndrome; neurodegenerative and neuroinflammatory disorders, such as Alzheimer’s, Huntington’s and Parkinson's disorder, multiple sclerosis and stroke, conditions such
as the postpartum period, hemodialysis, interferon-induced depression and psychological stressors. All of these conditions are known to involve peripheral inflammation and cell-mediated immune activation (Leonard and Maes, 2012). Inflammation in depressive disorders is closely linked with behavioral parameters such as exercise, sleep, alcohol abuse, and nicotine dependence, as well as with medical comorbidities including coronary artery disease, obesity and insulin resistance, osteoporosis, and pain (Goldstein et al., 2009).

Pro-inflammatory cytokines and acute phase proteins, which normally coordinate the local and systemic inflammatory response to microbial pathogens, also appear to act directly on the brain where they can cause behavioral symptoms, including sickness behavior (Dantzer et al., 2008; Leonard and Maes, 2012; Maes et al., 2012a, 2012c).

The analysis also excluded depression in patients with hepatitis C receiving interferon alpha (IFN-α) treatment because it is associated with depression in 30%-50% of patients (Asnis et al., 2006; Raison et al., 2006). Articles focusing on patients with depression due to previous brain injury were also excluded. Prolonged microglial hyperactivity may lead to neuronal apoptosis and brain injury, which are commonly observed in neurodegenerative disorders such as Parkinson’s disease, Alzheimer’s disease and schizophrenia (Monji et al., 2009).

The exclusion criteria were based on the following Medical Subject Heading (MeSH) categories “not”: 1) carried out in “animals”; 2) depression due to medical diseases (“Cardiovascular Disease”, “Heart Failure”, “Neoplasm”, “Multiple Sclerosis”, “Dementia”, “Irritable Bowel Syndrome”, “Acquired Immunodeficiency Syndrome”, “Hepatitis”, and “Herpes”); 3) depression due to drug treatments (“Interferons”); and 4) depression due to brain injury.
3. Shared oxidative stress pathways and inflammatory markers in both depressive disorder and nicotine dependence

The selected articles matched inclusion criteria regarding involvement of inflammatory biomarkers and oxidative stress in both depressive disorder and nicotine dependence. This review excluded medical comorbidities and medicines that are associated with excess inflammation. The results are summarized in Table 1.

Table 1. Inflammatory markers and oxidative stress pathways in both depressive disorder and smoking

A small number of studies have examined shared inflammation and oxidative stress pathways in both depressive disorder and nicotine dependence. It is unclear if this association is causal or is due to confounding and bias or modulated by factors such as physical activity, weight, alcohol consumption and gender.

Elevated levels of circulating CRP have been found in depression and remained significant when controlling for sex, age, smoking status, physical activity, weight, as well as medication use and medical conditions influencing inflammation levels (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlanger, 2004; Liukkonen et al., 2006).

Many studies have confirmed that elevated levels of CRP predict an increased risk of development of depression (Almeida et al., 2007; Hamer et al., 2009a,b; Pasco et al., 2010) and precede the cognitive symptoms of depression (Gimeno et al., 2009). Smoking cessation does not reduce CRP (Asthana et al., 2010). Increased levels of CRP and the presence of clinically significant depressive symptoms can additionally be influenced by the presence of other factors, most notably poor physical health...
(Almeida et al., 2007) or weight gain (Hammer et al., 2009b) among men (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlanger, 2004; Liukkonen et al., 2006). However, the presence of high CRP has also been shown to be a risk marker for major depressive disorder in women (Pasco et al., 2010). In particular, female hormones may protect tissues; pre-menopausal women experience fewer and less severe adverse cardiovascular events when compared with men of similar age or with post-menopausal women (Vassalle et al., 2011).

Adults with depressive symptoms had higher rates of smoking, had greater sleep disturbance, and higher levels of interleukin 1 receptor antagonist (IL-1RA) and IL-6 compared with non-depressed individuals (Letho et al., 2010a). The pronounced secretion of the anti-inflammatory marker IL-1RA was thought to reflect the presence of compensatory mechanisms during a depression-related inflammatory state (Letho et al., 2010a).

Significantly elevated white blood cell counts were found among subjects with moderate and severe depression. Oxidative stress and a medical history of inflammatory diseases did not appear to mediate this association (Kobrosly and van Wijngaarden, 2010). However, other studies failed to find either lower levels of Natural Killer (NK) activity or increased IL-6 in depressed smokers compared to depressed nonsmokers or in depressed patients with and without a history of alcohol abuse or dependence (Pike and Irwin, 2006).

An association was observed between the severity of current depressive symptoms and increased levels of the inflammatory markers IL-6 and C-reactive protein (CRP). Genetic modeling found a significant genetic correlation between IL-6 and depressive symptoms. There were no significant differences due to zygosity and current smoker status (Su et al., 2009).
The inflammatory response appears to be greater in those who suffered childhood abuse (Miller and Cole, 2012), suggesting a cumulative effect of contributory risks on the immune system. This observation is compatible with the allostatic load model of illness (Kapczinski et al., 2008). Depression is part of a family of interrelated disorders in the affective disorders spectrum, including anxiety disorders and fibromyalgia, where alterations in mitochondria, inflammation and neurodegeneration are observed (Gardener and Boles, 2011).

Elevated levels of CRP, fibrinogen, and white blood cells are found in individuals who were both depressed and maltreated during the first decade of life (age 3-11 years). This association was not explained by correlated risk factors such as depression recurrence, low socioeconomic status in childhood or adulthood, poor health, or smoking. Depressed and maltreated individuals were more likely to smoke. In turn, smoking was associated with elevated mean levels of the inflammatory factors (Danese et al., 2008).

Adolescents with depressive or anxiety disorders have significantly higher levels of Interleukin-2 (IL-2), Interleukin 1 Beta (IL1-β) and Interleukin-10 (IL-10) compared to adolescents without depressive disorders. However, higher levels of IL-6 and Interferon-Gamma (IFN-γ) were significantly related to more severe self-assessed symptoms of anxiety and depression after adjustment for use of tobacco (snuff and smoking of cigarettes) or intake of tea, coffee, caffeinated soft drinks or beta stimulant asthma medication (Henje Blom et al., 2012). The depressed participants who smoked had higher depression scores and lower levels of MCP-1, MIP-1β, and IL-8 than healthy controls. Low chemokine levels may lead to increased neurotoxicity, neuronal loss, or both (Letho et al., 2010b).

One study demonstrated increased levels of immunologic and oxidative stress
markers among individuals with depressive symptoms who smoked. Levels of the oxidative stress marker $\gamma$-glutamyltransferase were positively correlated with the severity of depression, after adjustment for oxidative stress measures, sex (male or female), age, smoking status and physical activity (Kobrosly and Wijngaarden, 2010).

Serum levels of F(2α)-isoprostanes [8-iso-PGF(2α)], a biomarker of oxidative damage to lipids, were elevated in a group of depressed individuals, and this finding may represent a common pathophysiological mechanism by which depressed individuals become more vulnerable to atherosclerosis and its clinical sequelae (Forlenza and Miller, 2006; Yager et al., 2010). Depressed patients were significantly less educated and significantly more likely to be regular daily smokers (Yager et al., 2010).

Depression has also been shown to predict subsequent inflammation, but not vice versa. Patients with more persistent depression had higher subsequent levels of inflammatory markers (CRP, IL-6, and fibrinogen), but this association was also explained by unhealthy behaviors such as smoking, inactivity and obesity (Schroeder, 2011). Although research suggests that depression increases the risk for inflammatory markers in non-smokers, the majority of the studies cited in this review have reported an interaction between both major depressive disorder and nicotine dependence, which are highly comorbid, and the influence of oxidative stress and inflammatory markers in both conditions.

4. Inflammation and the involvement of neurotransmitters in both depressive disorder and nicotine dependence
The current understanding of the pathogenesis of depressive disorder has expanded significantly from the historical focus on the role of a monoamine deficit (e.g., noradrenaline and/or serotonin) and how that may be causally involved in the symptoms of illness (Baldessarini, 1975). Drugs that increase the synaptic availability of monoamines (serotonin, norepinephrine and dopamine) have been used to treat depression for more than 50 years.

The macrophage hypothesis suggests that depressive disorder is associated with innate immune system activation due to abnormal secretion of cytokines, such as IL-1 and interferon-alpha (IFN-α) (Smith, 1991). This notion has expanded to include the interrelationship between inflammation and oxidative stress and has been termed the inflammatory and oxidative and nitrosative stress (O&NS) theory of depression.

Inflammation might regulate brain functions, including neurotransmitter systems, neuroendocrine functions, synaptic plasticity, and the neural circuitry of mood (Salim et al., 2012).

The alterations of neurotransmitters by inflammation and oxidative stress suggest that antidepressant treatments may have an anti-inflammatory and antioxidant effect. Previous studies have reported that antioxidant activity normalizes during subchronic treatment with antidepressants and anti-inflammatory compounds. Furthermore, natural anti-oxidative stress substances may augment the efficacy of antidepressants or may have antidepressant efficacy (Maes et al., 2009, 2011, 2012b). Diverse treatments for mood disorders reduce oxidative stress and inflammation (Berk et al., 2011a). Antidepressants and lithium enhance ATPase activity, improving mitochondrial dysfunction and inflammation (Gardner and Boles, 2011).

The mechanisms underlying the association between nicotine dependence and MDD appear to involve neurotransmitter pathways that are linked to both conditions.
Monoamine oxidases catalyze the metabolism of dopamine, norepinephrine, and serotonin. Cigarette smoke inhibits the activity of monoamine oxidase type A (MAO A) and B (MAO B) (Benowitz, 2010).

Smoking also appears to be associated with dysfunction of the serotonergic system. Depletion of serotonin and lowered brain serotonin is associated with a higher risk for suicide and attempted suicide in smokers with depression. Acute administration of nicotine may result in the release of serotonin as well as dopamine, and chronic nicotine administration has been shown to decrease the concentrations and biosynthesis of serotonin. Impaired serotonergic function was found in smokers after fenfluramine challenge (Malone et al., 2003). The lowered MAO activity observed in the brain of smokers may contribute to addiction in that disorder (Talhout et al., 2007). Lowered MAO activity, which may play a role in central nervous system (CNS) serotonin metabolism, could modulate, in part, the link between cigarette smoking and suicidal behavior (Breslau et al., 2005).

Dopamine is a shared and robust biomarker for depressive disorder as well as smoking. Individuals with depressive disorder have a decreased turnover of homovanillic acid, the primary metabolite of dopamine (Berger et al., 1980, Lambert et al., 2000). Bupropion is an atypical antidepressant that helps to normalize noradrenaline and dopamine and is effective in smoking cessation and depressive disorder (Cox et al 2012).

Nicotine has diverse effects throughout the CNS, acting on multiple forms of nicotinic acetylcholine receptors. Nicotine can hijack synaptic plasticity mechanisms in key brain circuits, most importantly in the mesolimbic dopamine system, which is central to reward processing in the brain (Dani and Bertrand, 2007).
Neuroadaptation and tolerance involve changes in nicotinic receptors and neural plasticity, which could cause nicotine dependence (Benowitz, 2010). Addictive drugs elicit or modify synaptic plasticity in many of the key brain regions involved in addiction, and these synaptic modifications have important consequences (Dani and Bertrand, 2007). Self-reported measures of tolerance, loss of control, and other behaviors such as relapse during a quit attempt and withdrawal symptoms must be present for an individual to receive a diagnosis of tobacco/nicotine dependence (Fagerstron and Eiseemberg, 2012).

α4β2 receptors appear to be crucial to the effects of nicotine on mood and the development of dependency. Nicotine activates α4β2 receptors in the ventral tegmental area, resulting in dopamine release in the shell of the nucleus accumbens (Benowitz, 2010). Dopamine D2 and D3 receptors in the striatum are downregulated by smoking. Activation of dopaminergic neurons in the ventral tegmental area is enhanced by excitatory glutamatergic projections and inhibited by γ-aminobutyric acid (GABA) projections that are also stimulated by nicotine (Benowitz, 2008). Thus, stimulation of nicotine cholinergic receptors releases dopamine, glutamate, and GABA, which affects the development of neuroadaptation and increases levels of corticotrophin-releasing factor (CRF). These alterations may play a key role in withdrawal. The negative effect that typifies the response to nicotine withdrawal most likely results in part from a cascade involving increased levels of CRF. The release of CRF in the central nucleus of the amygdala causes anxiety and stress (Benowitz, 2010).

There is growing evidence that the glutamatergic system plays an important role in the neurobiology and treatment of depressive disorders (Berk et al., 2011a, 2011b). In nicotine dependence, the rewarding effect of nicotine can be attenuated by
5. Stress in individuals with depressive disorders and nicotine dependence

Nicotine dependence and depressive disorders could be linked by the role of stress in the activation of the HPA axis. Psychological stress can activate the HPA axis, inducing secretion of corticotrophin-releasing factor (CRF) and subsequent increases in adrenocorticotropic hormone (ACTH) and cortisol (Bateman et al., 1989).

Stressful life events (personal loss, infection, trauma, childhood maltreatment) and genetic vulnerability to stress may alter the HPA axis, which can activate the release of pro-inflammatory cytokines. The increased secretion of CRF, a key factor involved in the stress response, has been implicated in the pathophysiology of both nicotine dependence and depressive disorder. Patients with depressive disorders exhibit higher rates of CRF neuronal activation and increased levels of cortisol compared to age-matched controls (Nemeroff and Vale, 2005). In addition, many depressive symptoms can be induced by intracerebroventricular injections of CRF (Holsboer et al., 1992). Stressors facilitate the initiation of smoking, decrease the motivation to quit, and increase the risk of relapse. The role of brain stress systems in nicotine addiction indicates that CRF plays a pivotal role in nicotine addiction (Bruijnzeel, 2012).

Dysfunction of the HPA axis, with amygdala hyperfunction and decreased activity of the hippocampus (defective glucocorticoid-negative feedback), has been reliably observed in patients with depressive disorder (Pariante and Miller 2001), as
well as patients who suffered childhood sexual abuse (Heim et al., 2000; Nunes et al., 2010). Similar findings are observed in nicotine dependence (Rohleder and Kirschbaum, 2006).

A central tenet of the glucocorticoid cascade hypothesis is that excess glucocorticoid results in damage to key brain structures involved in HPA axis restraint, including, most notably, the hippocampus (Raison and Miller, 2003).

The pathways by which inflammatory cytokines produce depressive disorder include activation of the HPA axis, which causes microglial activation. This pathway is reactive to stressful life events, infection, trauma, toxins and immunogenetics. This activation releases pro-inflammatory cytokines and free radicals. These mediators are known to cause neuronal degeneration and decreased neurogenesis, which may be an important factor in the pathophysiology of depressive disorder (Moylan et al., 2012).

### 6. Epigenetic effects in both depressive disorder and nicotine dependence

Epigenetic modification of gene function may be related to depressive disorder and nicotine dependence. Chronic exposure to nicotine results in changes in gene expression and protein synthesis, including the generation of new synaptic connections, analogous to other forms of learning (Kauer and Malenka, 2007). The identification of single candidate genes associated with MDD and nicotine dependence has been difficult because of the likelihood that complex psychiatric illnesses are under polygenic influence and are associated with interactions between genetic variants and environmental exposures (Uher, 2009).

The importance of serotonin in the depression-nicotine dependence nexus indicates that pro-inflammatory cytokines may also affect serotonin
neurotransmission. Altered levels of cytokines are known to stimulate production of Kynurenine (KYN) from its precursor, tryptophan (TRP), and may thus potentially deplete TRP, leading to reduced levels of the TRP metabolite serotonin (Sublette et al., 2011).

The short (“s”) allele in the promoter region of the serotonin transporter gene (5-HTTLPR) is associated with lower transcriptional efficiency of the promoter compared with the long (“l”) allele. The hypothesis of a gene-by-environment interaction showed that childhood maltreatment predicted adult depression only among individuals carrying an “s” allele but not among l/l homozygotes (Caspi et al., 2003). This original observation has been replicated by many subsequent studies. Individuals with the “s” allele in the promoter region of the serotonin transporter gene (SLC6A4) are unusually vulnerable to the depressogenic effects of early life stress such as child abuse or neglect. Early life trauma and depression lead to chronic activation of the immune system and prolonged production of proinflammatory cytokines, as well as CRP (Saveanu and Nemeroff, 2012).

The serotonin pathway has been associated with smoking behavior, as well as several behavioral traits, such as neuroticism, novelty seeking and anxiety-related personality traits (Quaak et al., 2009). Genes involved in the serotonin pathway include insertion/deletion polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR), which has been linked to vulnerability to smoking and the ability to quit (Sieminska et al, 2008).

Genetic polymorphisms and the 5-HTTLPR variant are associated with smoking-related phenotypes and diminished serotonin neurotransmission. A polymorphism in the promoter region of the 5-HTTLPR gene modulates the mRNA and protein levels, such that allelic variants may influence nicotine dependence. The
presence of the short or long alleles appears to influence transcription regulation (Watanabe et al., 2011). Smoking is associated with epigenetic alteration of MAO-B by reducing methylation of its gene promoter. This alteration leads to increased production of MAO-B that persists long after smoking cessation (Launay et al., 2009).

7. Inflammation and oxidative stress are linked to central nervous system (CNS) dysfunction in both depressive disorder and nicotine dependence

7.1. Neuroprogression pathways in depression

Oxidative and nitrosative stress and inflammation are linked to neuronal cell injury or death, which contribute to the neuroprogression of depressive disorders, mediating changes in conjunction with genetic vulnerability and environmental factors (Figure 1). In neurons, N-methyl-D-aspartate (NMDA) receptor (NMDAR) activation and subsequent Ca\(^{2+}\) influx can induce the generation of nitric oxide (NO)-via neuronal NO synthase, which leads to nitrosative stress, synaptic damage, and neuronal loss (Nakamura, Lipton, 2011). The excessive accumulation of these free radicals causes damage and can lead to alterations in the structure and function of membrane fatty acids and proteins. Furthermore, free radicals can alter the activity of proteins residing in the cell membrane and can alter or damage DNA and mitochondrial function, leading to cell death via necrosis or apoptosis (Maes et al., 2011).

An increase in inflammation-induced apoptosis, together with a reduction in the synthesis of neurotrophic factors caused by a rise in brain glucocorticoids and a reduction in the neuroprotective components of the kynurenine pathway, contributes to the pathological changes that are postulated to cause neuronal damage. This effect
may predispose chronically depressed patients to neuroprogressive processes including dementia (Leonard and Myint, 2006).

The neurodegeneration hypothesis proposed that depressive disorder is a consequence of an imbalance between neuroprotective and neurodegenerative metabolites in the kynurenine pathway (Myint et al., 2007). Kynurenic acid (KYNA) is regulated by IDO (indoleamine 2-3-dioxygenase), which catalyzes the first step in the pathway, specifically the degradation from tryptophan to kynurenine (KYN). KYNA acts as a blocker of the glycine co-agonistic site of the NMDA receptor and as a noncompetitive inhibitor of the α7 nicotinic acetylcholine receptor, which has a role in cognitive disturbances. Depressive symptoms have been shown to be related to an increased ratio of KYN/KYNA (Müller and Schwarz, 2008).

Through stimulation of multiple inflammatory signaling pathways, including activation of nuclear factor kappa B (NF-κB) and p38 mitogen activated protein kinases (MAPKs), cytokines can activate IDO, which breaks down tryptophan (TRP), the primary precursor of serotonin, into quinolinic acid (QUIN), a potent NMDA agonist and stimulator of glutamate release (Miller et al., 2009).

Activation of NF-κB leads to an inflammatory response including the release of the pro-inflammatory cytokines. Once in the brain, cytokine signals participate in pathways known to be involved in the development of depression, including altered neurotransmitters such as serotonin and dopamine, activation of the HPA axis, and disruption of synaptic plasticity through alterations in relevant growth factors. NF-κB induction in the brain might contribute to alterations in neuronal growth and survival, especially through the induction of nitric oxide and, ultimately, oxidative stress, which has been shown to alter promoter function for several genes central to synaptic plasticity (Raison et al., 2006).
Microglia activated by excess inflammation, astroglial loss, and inappropriate glutamate receptor activation ultimately disrupt the delicate balance of neuroprotective versus neurotoxic effects in the brain, potentially leading to increased neurodegeneration and decreased neurogenesis (McNally et al., 2008). Biochemical factors including inflammatory, oxidative and nitrosative stress, mitochondrial dysfunction, epigenetic alterations, HPA axis dysregulation and disturbed neurotrophic function interact to cause cellular damage, stimulate apoptosis and decrease neuronal growth and survival (Moylan et al., 2012).

Mechanisms that may contribute to brain damage by oxidative and nitrosative stress are summarized in Figure 1. Genetic vulnerability and stressful life events activate CNS circuitry, including the HPA axis and pro-inflammatory cytokines (TNFα, IL-1, IL-6), which in turn lead to the release of IDO, which breaks down (TRP), the primary precursor of serotonin. Tryptophan–Kynurenine metabolism influences the ratio of KYN/KYNA (Müller and Schwarz, 2008), and this dysregulation of QUIN, a potent NMDA agonist, stimulates glutamate release. Glutamate release is associated with inhibition of BDNF, a decline in neuroprotective factors and increased oxidative stress (Miller et al., 2009).

Insert Figure 1

**Figure 1.** Oxidative and Nitrosative stress damage

Abbreviations: HPA: Hypothalamic-Pituitary-Adrenal axis; IDO: Indoleamine 2-3-dioxygenase; IL-1β: Interleukin 1 Beta; IL-6: Interleukin 6; KYN: Kynurenine; KYNA: Kynurenic acid; TNF-α: Tumor Necrosis Factor-Alpah

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7.2. Neuroprogression pathways in nicotine dependence
It is thought that smoking can predispose our brains to dementia or cognitive impairment by inflammatory, oxidative and nitrosative stress pathways. These same pathways lead to neuroprogression through exposure to free radicals and by inducing direct cellular damage and inhibition of mitochondrial bioenergetics. Oxidative and nitrosative stress can result from either increased production of reactive species from nitrogen (RNS, such as nitric oxide) or oxygen (ROS), which damage neurons and promote the release of glutamate. Activation of synaptic NMDA can result in physiological ROS and RNS production (Nakamura and Lipton, 2011). Oxidative and nitrosative stress is manifested as increases in lipid peroxidation end products, leading to protein, lipid, carbohydrate and DNA damage. Thus, these events constitute a vicious cycle, and any one of them could initiate neuronal cell death (Halliwell, 2006).

Chronic cigarette smoking also affects the synapse through reducing the expression of pre-synaptic proteins that may induce synaptic changes and other neuropathological alterations. These changes might serve as evidence of early phases of neurodegeneration and may explain why smoking can predispose brains to Alzheimer’s disease and dementia (Ho et al., 2012).

Cigarette smoking is known to be an important inducer of oxidative stress in multiple organs, including the brain (Rueff-Barroso et al., 2010). Several factors could explain the link between tobacco smoking and the higher risk of cognitive decline. For example, tobacco smoke and chronic lead exposure is a well-known risk factor for cognitive deterioration. Another ingredient of tobacco smoke, cadmium, also has neurotoxic properties. Furthermore, smokers have decreased levels of circulating antioxidants and increased levels of oxidative stress (Dome et al., 2010).

In cigarette smokers, there is an excess of pro-inflammatory cytokines such as
CRP, IL-1-β, TNF-α and IL-6 (Yanbaeva et al., 2007). Cigarette smoke increases TNFα, which can induce histone acetylation, pro-inflammatory gene transcription and oxidative stress. Smoking curiously impacts NF-κB by phosphorylating IκB kinase α (IKKα) and causing enhancement of target gene expression. IKKα also reacts to cigarette smoke and plays a role in regulating histone modification (Chung et al., 2011). The direct exposure to oxidative stress from cigarette smoke also contributes to additional endogenous oxidant formation through effects on the inflammatory immune response pathway (Swan and Lessov-Schlaggar, 2007).

Multiple studies have shown that current smoking is a risk factor for Alzheimer’s and Parkinson’s diseases (Dome et al., 2010). However, contradictory research has suggested that smoking may be protective against the development of neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease. In such cases, a local inflammatory response is sustained by microglial cells, which are associated with CNS nicotinic acetylcholine receptors and have recently been reported to inhibit TNF-α production in human macrophages as well as in mouse microglial cultures (de Simone et al., 2005).

Nicotine, on the other hand, may offer protective effects against dopaminergic cell damage induced by various neurotoxins and may also protect against aminochrome-induced toxicity in substantia-nigra derived RCSN-3 cells. These protective effects of nicotine may help to explain why smoking might reduce the incidence of Parkinson's disease (Muñoz et al., 2012).

There is an inverse relationship between cancer and neurodegeneration. The risk of Alzheimer's disease is lower among survivors of smoking-related cancers than among survivors of non-smoking-related cancers and cannot be explained by a survival bias (Driver et al., 2012).
In a meta-analysis of 43 studies, there was more evidence to suggest that smoking was associated with an increased risk for Alzheimer’s disease. Moreover, 11 of the 43 studies were conducted by researchers with tobacco industry affiliations, although these affiliations were often not disclosed. Studies with tobacco industry affiliations have generally suggested that tobacco protects against Alzheimer’s disease, whereas non-tobacco industry studies find that smoking is a risk factor for Alzheimer’s disease (Cataldo et al., 2010).

**7.3 Mitochondrial dysfunction may contribute to neuroprogression**

CNS functions strongly depend on efficient mitochondrial function because brain tissue has a high-energy demand. Mutations in the mitochondrial genome, defects in mitochondrial dynamics, generation and presence of ROS, protein aggregate-associated dysfunctions and environmental factors may alter energy metabolism and in many cases are associated with neurodegenerative diseases (Federico et al., 2012).

Oxidative stress and mitochondrial involvement may be major triggering factors in neurodegenerative disorders. Neurodegenerative disorders lead to cellular energetic depression (CED), which is characterized by a decreased cytosolic phosphorylation potential that suppresses the cell’s ability to do work and control intracellular Ca$^{2+}$ homeostasis and its redox state. If progressive, CED leads to cell death, whose type is linked to the functional status of the mitochondria (Seppet et al., 2009).

Mitochondria are responsible for the energy supply of cells. Mitochondria house the oxidative phosphorylation machinery, which enables aerobic ATP
generation, and multiple metabolic pathways, such as β-oxidation of fatty acids and the tricarboxylic acid and urea cycles. Indeed, over 90% of cellular energy generation takes place in mitochondria. In addition, mitochondria have important biosynthetic activities, control intracellular Ca\(^{2+}\) metabolism and signaling, regulate thermogenesis, generate most cellular reactive species from oxygen (ROS) and serve as gatekeepers of the cell for programmed cell death (apoptosis). Several events can compromise mitochondrial function and integrity. These include damage or mutation of mitochondrial DNA, increases in ROS and abnormal elevation of Ca\(^{2+}\) through NMDA (Manji et al., 2012). Mitochondrial dysfunction is associated with an increasingly large proportion of inherited human disorders and is implicated in common diseases, such as neurodegenerative disorders (Nunnari and Suomalainen, 2012).

There is a growing body of evidence to suggest that impaired mitochondrial function may affect key cellular processes, thereby altering synaptic functioning and contributing to the atrophic changes that underlie the deteriorating long-term course of major psychiatric illnesses such as mood disorders and schizophrenia. Because the brain is the body’s most metabolically active tissue, it is not surprising that the majority of mitochondrial disorders have a neurological phenotype (Manji et al., 2012).

Mitochondria are the key organelle involved in the control of two cellular processes: cell metabolism and cell death. The action of carbon monoxide (CO) on mitochondria is involved in cell death (Queiroga et al., 2012). Thus, in the case of CO-mediated oxidative stress exposure, neurons are especially sensitive to oxidative lesions, which could be the basis for later memory impairment (Garrabou et al., 2011). Evidence has shown that mitochondrial dysfunction in cells is induced by
tobacco smoke components. In particular, CO could be responsible for impaired mitochondrial function in smokers (Miró et al., 1999).

Mitochondrial dysfunction has been linked to neuron loss in ischemia, traumatic brain injury and neurodegenerative diseases (Monji et al., 2012). Smoking is associated with a decrease in neurogenesis, as well as white matter abnormalities in the brain. Chronic nicotine dependence is related to global brain atrophy and to structural and biochemical abnormalities in anterior frontal regions, subcortical nuclei and commissural white matter. Chronic nicotine dependence may also be associated with an increased risk for various forms of neurodegenerative diseases (Durazzo et al., 2010).

7.4. Autoimmune disorders may contribute to neuroprogression

It has been postulated that autoimmune dysfunction may be part of the cognitive impairment in MDD. It is noteworthy that humoral immunity dysfunction is frequently described in patients with depressive disorder, as indicated by increased autoantibody levels. MDD could be another autoimmune disease from the view of autoantibodies (Chen et al., 2009). High levels of autoantibodies were detected in serum of depressed patients (Laske et al., 2008; Maes et al., 1993, 2011, 2012a; Nemeroff et al., 1985).

7.5. Neuroimaging studies have demonstrated brain abnormalities
Nicotine-dependent depressive disorder could be conceptualized as a neurodegenerative disease because it is associated with impairment of synaptic plasticity, neuron loss and reduced neurogenesis (Manji et al., 2012).

Neuroimaging studies have demonstrated brain abnormalities that link nicotine dependence and depressive disorders, particularly involving portions of the prefrontal cortex. Magnetic resonance imaging has shown volume loss in regions of the orbitofrontal cortex and the medial prefrontal cortex in MDD, concordant with post-mortem-derived evidence of tissue loss. MDD patients with a family history of affective illness showed left hemisphere gray matter loss in a region immediately ventral to the genu of the corpus callosum—the subgenual anterior cingulate cortex (Savitz and Drevets, 2009).

Neuroimaging studies have also shown cigarette smoking to be associated with numerous structural brain changes, including a reduction in the integrity of the cerebral white matter microstructure (Gons et al., 2011) and reduced grey matter volumes in the prefrontal cortices (Brody et al., 2004; Zhang et al., 2011). Other brain abnormalities in cigarette smokers include ventricular enlargement and atrophy (Brody et al., 2004), as well as volumetric changes and atrophy (Brody et al., 2004; Gons et al., 2011; Zhang et al., 2011). One possible explanation may be the stimulating effect of nicotine on nicotine receptors expressed in oligodendrocyte precursor cells, which could result in microstructural alterations of white matter integrity in cigarette smokers, leading to cognitive decline (Gons et al., 2011).

8. Conclusions and implications for clinical practice
The depression-nicotine dependence nexus may increase the levels of inflammatory markers and oxidative and nitrosative stress. The exact pathways that underpin the common pathophysiology of both diseases are still not well defined. Some hypotheses have been postulated for common pathways for nicotine dependence and depressive disorders that have implications for neuroprogression. These pathways include alterations of neurotransmitters, HPA axis dysregulation, increased pro-inflammatory cytokines and levels of acute phase proteins, increased oxidative and nitrosative stress, decreased levels of antioxidants leading to damage to lipids, proteins, and DNA, microglia activation, mitochondrial dysfunction, and modification of gene function.

Smokers with serious mental disorders are at risk of dying prematurely, on average, 25 years earlier than the general population. Clinicians need to intervene to encourage their patients to cease smoking (Schroeder, 2011). Smoking is a risk factor in psychiatric disorders, in addition to causing a legion of other documented health problems. Aggressive targeting of smoking cessation must be a part of routine care (Berk, 2007b).

Patients with co-occurring depressive disorders and nicotine dependence in clinical practice are common; therefore, clinicians may have to treat these patients as having co-occurring disorders. This observation has clinical relevance because both disorders worsen the prognosis and could be regarded as neurodegenerative disorders.

In the future, anti-inflammatory treatments that promote neurogenesis and neuronal survival could be used by people with co-occurring disorders. Treatments with anti-inflammatory and antioxidant-target therapies, including diets, vitamins, omega-3 fatty acids, acetylsalicylic acid, cyclo-oxygenase, inhibiting inflammatory cytokines, minocycline and N-acetyl cysteine, may augment the clinical efficacy of
established agents and serve as novel treatments in depressive disorder and nicotine dependence.

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Table 1. Inflammatory markers and oxidative stress pathways in both depressive disorder and smoking

<table>
<thead>
<tr>
<th>Author / year</th>
<th>PICs / APP</th>
<th>Gender / age</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Henje Blom et al., 2012</td>
<td>IL-2, IL-4, IL-6, IL-10 TNFα, IFN-γ; IL-1β:</td>
<td>Adolescents with MDD or anxiety disorders.</td>
<td>Adjustment for the use of tobacco</td>
</tr>
<tr>
<td>2- Nunes et al., 2012</td>
<td>IL-1β, IL-6, TNFα, CRP</td>
<td>Men and Women (age 18- to 65 years) Depressive smokers (n = 77); Non-depressive smokers (n = 78)</td>
<td>Adjustment for the use of tobacco and BMI</td>
</tr>
<tr>
<td>3- Sublette et al., 2011</td>
<td>KYN, TRP, neopterin</td>
<td>Men and Women (age 18–73 years) Healthy volunteers (n = 31) Depressive with suicide attempt (n = 14) Depressive without suicide attempt (n = 16).</td>
<td>Adjustment for the use of tobacco and BMI</td>
</tr>
<tr>
<td>4. Pasco et al., 2010</td>
<td>CRP</td>
<td>Women (age 20 to 84 years) Depressive (n=151), Non-depressive(n=671)</td>
<td>Adjustment for the use of tobacco, physical activity , and BMI</td>
</tr>
<tr>
<td>5- Kobrosly and van Wijngaarden, 2010</td>
<td>CRP, GGTγ, vitaminC, bilirubin, uric acid platelet counts, WBC counts</td>
<td>Men and Women (age 20 to-80+ years) No/mild depression (n = 3080), Moderate depression (n = 705), Severe depression (n = 82)</td>
<td>Adjustment for the use of tobacco, Socioeconomic status and physical activity</td>
</tr>
<tr>
<td>7 Yager et al., 2010</td>
<td>8-iso-PGF(2α)</td>
<td>Men and Women (age± 28. years ) Depressed (n=73) non-depressed (n=72)</td>
<td>Adjustment for the use of tobacco, age, gender, years of education, physical activity, and BMI.</td>
</tr>
<tr>
<td>8- Letho et al., 2010a</td>
<td>IL-6, IL-10, IL-IRA</td>
<td>Men and Women (age ±50 years) Elevated depressive symptoms (n = 44) Non-depressed (n = 372)</td>
<td>Adjustment for the use of tobacco, physical activity, and BMI.</td>
</tr>
<tr>
<td>9- Letho et al., 2010b</td>
<td>MCP-1, MIP-1β, IL-8</td>
<td>Men and Women (age 53±. years) MMD(n=61), non-depressed (n=61)</td>
<td>adjusted for age, gender, BMI , smoking, and alcohol consumption</td>
</tr>
<tr>
<td>10- Hamer et al., 2009b</td>
<td>CRP , fibrinogen,</td>
<td>3609 men aged 60.5 ± 9.2 years. 2 years of follow up Depression at baseline and persistent</td>
<td>Adjustment for BMI ,smoking, alcohol, physical activity</td>
</tr>
<tr>
<td>11- Su et al., 2009</td>
<td>IL-6, CRP</td>
<td>188 male twins, age of 55 ± 2.75 years Past and Current depressive symptoms</td>
<td>Adjustment for tobacco (pack-years), marital status, and education</td>
</tr>
<tr>
<td>Study</td>
<td>Biomarkers</td>
<td>Participants</td>
<td>Control</td>
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<tr>
<td>12- Elovainio et al., 2009</td>
<td>CRP</td>
<td>Men and Women (age &gt;30 years)</td>
<td>Depressed and non-depressed</td>
</tr>
<tr>
<td>13- Danese et al., 2008</td>
<td>CRP, fibrinogen, WBC</td>
<td>Men and Women (age &gt;32 years)</td>
<td>Depressed-Only (n=673) Maltreated-Only (n=56)</td>
</tr>
<tr>
<td>14. Almeida et al., 2007</td>
<td>CRP</td>
<td>Older male Non depressive (n=5098) Depressive (n=340)</td>
<td></td>
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<tr>
<td>15. Pike and Irwin , 2006</td>
<td>NK, IL-6 , s IL-2R</td>
<td>Men (age non-depressed ±45, depressed ±42 years)</td>
<td>Depressed(n=25), Non-depressed(n=25)</td>
</tr>
<tr>
<td>17. Liukkonen et al., 2006</td>
<td>CRP</td>
<td>Men and Women (was born from 1st January and 31st December in 1966)</td>
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</tr>
<tr>
<td>18. Forlenza and Miller , 2006</td>
<td>8-OHdG</td>
<td>Men and Women (age ±28 years)</td>
<td>Depressed (n=84) Non-depressive (n=85)</td>
</tr>
<tr>
<td>19- Ford and Erlinger, 2004</td>
<td>CRP</td>
<td>Men and Women (age 18-39 years)</td>
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<tr>
<td>20. - Douglas et al., 2004</td>
<td>CRP</td>
<td>Men and Women (age 39 to 45 years)</td>
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<tr>
<td>21- Danner et al., 2003</td>
<td>CRP</td>
<td>Men and Women (age 17 to 39 years)</td>
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</tbody>
</table>

**Abbreviations:**
APP: Acute Phase Proteins; BMI: body mass index; CRP:C-reactive protein; GGTγ: γ-glutamyltransferase IFN-γ: Interferon-Gamma; IL-α: Interleukin 1 alpha; IL-1β: Interleukin 1 Beta; IL-1RA: Interleukin 1 Receptor Antagonist; IL-2: Interleukin-2; sIL-2R: soluble interleukin-2 receptor; IL-4: Interleukin-4; IL-6: Interleukin 6; IL-8:
Interleukin-8; IL-10; Interleukin-10; KYN: kynurenine; MCP-1: monocyte chemotactic protein; MDD: Major Depressive Disorder; MIP β: monocyte inflammatory protein Beta; NK: Natural Killer; O&NS: Oxidative & Nitrosative Stress; PICs: Pro-Inflammatory Cytokines; TNF-α: Tumor Necrosis Factor-Alpha; TRP: tryptophan; WBC: white blood cells; 8-OHdG: 8-hydroxy-2’deoxyguanosine, a biomarker of oxidative damage; 8-iso-PGF(2α): F (2α)-isoprostanes, a biomarker of lipid damage; ±, mean
Oxidative and Nitrosative Stress Damage

Genetic Vulnerability and Stressful Life Events

↑HPA

Pro-Inflammatory cytokines
↑TNFα, IL-1 - IL-6

↑IDO ↓Tryptophan ↓Serotonin
↑KYN/Kyna

↑Quinolinic Acid

NMDA receptor agonist

↓Glutamate

Damage to:
DNA
Proteins
Fatty acid

↑Oxidative Stress
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