

# A review of etiologies of depression in COPD

Rachel J Norwood

National Jewish Medical and Research  
Center, Denver, CO, USA

**Abstract:** There is significant evidence supporting an increased prevalence of depression in patients with COPD, but that depression is not a homogenous entity because there are multiple contributing etiologies for the depressive symptoms. Additionally the relationship between COPD and depression is neither exclusively linear, nor unidirectional. “Early onset” depression is defined as depression that develops prior to the diagnosis of COPD, often during an individual’s youth. This is often reflective of a genetic vulnerability to depression which increases adolescents’ risk for developing addiction to nicotine, setting up a life-long exposure to tobacco – the single greatest risk factor for the development of COPD. When COPD does develop it brings with it attendant losses, particularly in level of independent function and self image that contribute to a “reactive” depression that is not distinct from the losses experienced by those suffering with other chronic illnesses. Lastly there is increasing evidence through magnetic resonance imaging (MRI) and biochemical markers that systemic, physiologic changes associated with COPD have direct effects on the brain’s vasculature that have also been associated with depression in the elderly, termed “late onset” depression. The conclusion is that the presence of depression in a COPD patient does not reflect a single pathologic pathway. Rather the two disorders each contribute to the morbidity of the other. This review discusses the evidence supporting each of these contributors and suggests that an understanding of these varying elements can direct healthcare interventions.

**Keywords:** COPD, depression

## Introduction

A review of epidemiologic studies demonstrates a prevalence of co-morbid depression in a range of 6%–80% of COPD patients, with an average among the majority of the strongest studies of approximately 40%. This compares to a rate of 15% in the general population (Light et al 1985; van Ede et al 1999; Yohannes 2000; Aydin and Ulusahin 2001; Kunik et al 2005). In cardiac patients the range is 15%–23% (Carney et al 1997; Ariyo et al 2000; Ziegelstein 2001) and in cancer patients over a range of 13%–38% (Kathol et al 1990). In a cluster of studies that have compared depressive disorders across diverse chronic illnesses, COPD patients suffer from depression with greater frequency and a greater chronicity of the mood symptoms (Kurosawa 1983; Katon and Sullivan 1990; Evans et al 1999; Cruess et al 2003). Evidence suggests, however, that the depression experienced by COPD patients is not a homogenous entity. To manage this co-morbidity as effectively as possible it is important to first understand the potential contributors to an individual patient’s depression. Chronologically the earliest risk may be a genetic predisposition to depression, followed by the environmental assaults imposed by the respiratory illness itself and finally the direct neuropsychiatric effects of chronic respiratory disease. The goal of this review is to explore each of these elements to help inform clinical management of this patient population.

## Genetics

In the psychiatric literature the heritability of a vulnerability to depression has been well established. First-degree relatives of individuals with major depression are 2 to

Correspondence: Rachel J Norwood  
National Jewish Medical and Research  
Center, 1400 Jackson Street, Denver,  
CO 80206, USA  
Tel +1 303 398 1763  
Fax +1 303 270 2115  
Email norwoodr@njc.org

3 times as likely to develop depression when compared to the first-degree relatives of controls. This increased risk is also supported by adoption and twin studies. The latter show a concordance rate of 50% in monozygotic twins, 10%–25% in dizygotic (Kaplan and Sadock 1988; Sullivan et al 2000; Kendler et al 2006). The age at which this increased risk manifests varies widely from individual to individual, but is often already evident in adolescence (Eley et al 2004). This vulnerability plays a role in the eventual development of COPD in that adolescents and young adults who are depressed or have a history of depression are more likely to progress in their use of and dependence on nicotine (Breslau et al 1993; Ferguson 1996; Patton et al 1996). The genetic underpinning of this vulnerability has recently gained increased support with the finding that the likelihood of an adolescent's smoking progressing from initial nicotine exposure to regular smoking was doubled by each additional copy of an identified allele (DRD2A1) for a subtype of a dopamine receptor. The presence of depressive symptoms magnified the effect (Audrain-McGovern et al 2004). These data would suggest that smoking interventions that have been implemented in adults – such as the administration of antidepressants – might also be useful to help adolescents stop smoking, but there is currently very limited evidence for any effective interventions in this population. Certainly this is an area that warrants further research.

Smoking, COPD and depression are interrelated in a sort of trinity, with depression playing a role in the initiation and maintenance of smoking, smoking leading to the development of COPD and COPD, in turn, contributing to the genesis of depression. Because of depression's role in the development of nicotine dependence, it might also be considered a risk factor for COPD. In adults, continued smoking increases the morbidity and mortality experienced in COPD. A history of either recent or distant depression has been associated with diminished success in smoking cessation, more persistent withdrawal symptoms and an increased likelihood of recurrence of the depression if nicotine is discontinued (Covey et al 1997, 1998; Covey 1999). The application of antidepressant therapy in smokers who endorsed some level of depressive symptoms did increase abstinence rates up to three months out from quit dates (Hitsman et al 1999), a finding consistent with previous reports (Hurt et al 1997; Hall et al 1998; Niaura et al 2001). There is suggestion that the benefits from the application of antidepressants is not exclusively due to the relief of depressive symptoms but potentially because the vulnerability to nicotine dependence and to depression share a common genetic source, possibly one that defines

some characteristic of the dopamine pathways (Lerman and Berrettini 2003).

## The impact of chronic illness

The responses to the question of why depression arises so frequently in COPD reflect an evolving understanding of the complex relationships between these two disease entities. Early theory held that depression in chronic illness was a “reaction” to the losses imposed by the illness – an understandable grieving (Agle and Baum 1977). Since that time both the reactions and the losses have been more clearly defined. Loss of functionality is a strong mediator of the development of depression in chronic illness, with an attributable risk measured at 34% (Dunlop et al 2004). Functional impacts may include decreased mobility, inability to carry out prior occupational activities, shifted roles within the family constellation and decreased ability to physically participate in previously enjoyed recreational activities. Another common insult to self-image that COPD patients struggle with is the use of supplemental oxygen. In fact, this insult often contributes to patients' reluctance to utilize oxygen therapy (Earnest 2002). The psychological losses attached to each of these insults are first the loss of the phenomenon itself and secondly of the emotional or material benefits derived from it.

A second factor in a patient's ability to adjust to the burden of illness is the patency of internal coping mechanisms including self-efficacy and sense of mastery. The stronger patients' sense of mastery or ability to impact the daily experience of their illness, the lower is their risk for depression (Brown 1986, Holahan and Holahan 1987). In a cohort of 208 severe COPD patients their level of perceived self-efficacy and functionality had a greater impact on variability in perceived quality of life than either objective or subjective pulmonary function (Kohler et al 2002).

A third influence on a patient's resilience in the face of the stress of dealing with a chronic illness is their perceived level of social support. Overall the greater the level of perceived social support the less likely a patient will report symptoms of depression (McCathie et al 2002). In a study of 719 elderly individuals with a variety of chronic medical issues both strong social supports and effective personal coping strategies were associated with favorable effects in reducing levels of depression. In addition, for the 280 subjects in this study with lung disease (asthma, chronic bronchitis or emphysema), “diffuse” relationships, those that were defined as less intimate, community-based relationships, were helpful in “buffering” the negative effects of the illness (Penninx et al 1998). Associated with higher reports of depressive symptoms across

all groups was patients' receipt of "instrumental support" – tangible assistance with disease management. The suggested interpretation is that receiving high levels of instrumental support reinforces feelings of dependence and helplessness, countermanding feelings of self-efficacy and mastery (Penning and Strain 1994). A single study focusing on determinants of depression in COPD patients found that the risk of depression was significantly increased for subjects who lived alone, who had poor reversibility of FEV<sub>1</sub> on spirometry and those who suffered severe functional impairment (van Manen et al 2002).

These studies suggest that educating patients and caregivers in strategies that maximize independence, encouraging patients to develop and nurture their support systems and to participate in effective rehabilitation can help with both the physical and the psychosocial aspects of COPD. Certainly COPD can impose staggering losses on COPD patients and many of these same losses occur in other chronic illnesses, yet COPD patients demonstrate higher rates of depression. The explanations for this disparity include the early vulnerability posited by genetics studies and the longitudinal physiologic effects of chronic respiratory disease.

## COPD effects on the CNS

Magnetic resonance imaging (MRI) is a non-radiological imaging technique that offers detailed study of soft tissues. In the T2-weighted MRI scans CSF and other areas of acute anoxia or elevated fluid content, such as that seen with edema, appear white. These sites of increased signal are termed hyperintensities (Yudofsky and Hales 1992). Multiple studies have noted an increased prevalence of these hyperintensities in subcortical areas in the brains of elderly subjects, collectively called subcortical hyperintensities (SH). The concentration of these subcortical lesions increases with advancing age but they are not universally associated with clinical pathology, appearing in imaging studies of both clinically compromised and healthy elderly subjects (Grafton et al 1991; Guttmann et al 1998). When present, SH are typically seen in the deep white matter, periventricular areas, the basal ganglia, the thalamus and the pons. These areas are particularly vulnerable to vascular insult because they are in identified "watershed" or border zones of vascular supply. Considering all sites, the odds-ratio of finding SH increases by approximately 5% per additional year of age (Coffey et al 1992). While the lesions are seen in individuals without clinical disease, the prevalence and severity of SH do increase with cardiovascular risk factors as well as with a high burden of medical co-morbidity (Awad et al 1986; Brown et al 1992). The differential diagnosis for the lesions includes

malignancies, infarcts and multiple sclerosis as well as less clinically apparent, although still pernicious, conditions typically associated with aging. These include arteriosclerosis and the diminution of autoregulation of blood pressure and subsequent aberrations in blood flow (Campbell and Coffey 2001). In the absence of identified cerebrovascular disease, other factors that have been associated with greater SH burden on MRI include clinically silent stroke, elevated systolic blood pressure and lower forced expiratory volume in 1 second (FEV<sub>1</sub>). When these factors are controlled for, smoking also emerges in positive association with SH (Longstreth et al 1996).

Several studies have found that the concentration of SH is also elevated in elderly patients with depression, with an even higher prevalence among the subset of patients whose depression developed after their 5th decade (Krishnan et al 1988, 1993; Figiel et al 1991; Coffey et al 1993; Howard et al 1993; Lesser et al 1996). In a meta-analysis a common odds ratio of 3.2 (95% CI 2.11–4.82) was found for the presence of SH in all patients with major depression (Videbech 1997). While not consistent across studies, there is some evidence that when compared to individuals who developed depression prior to 40 years of age, a higher concentration of SH is seen in older depressed subjects (Salloway et al 1996).

The concept of "vascular depression" was developed as a putative explanation for elders' increased vulnerability to depression. Evidence supporting the concept includes literature showing that cerebrovascular disease often predates the onset of the depression; the increased prevalence of depression in individuals who also suffer from hypertension or coronary artery disease; and an increased finding of depressive symptoms in patients with vascular dementia when compared to those with non-vascular Alzheimer's disease. Accumulating MRI evidence that shows a high concentration of SH in elderly, depressed patients, and the localization of those lesions in areas at increased risk for vascular compromise, strengthen the argument (Alexopoulos et al 1997a, 1997b). Contrasting studies in late onset depression have found a smaller association with SH but a stronger one with decreased total brain volume, preserving the concept of structural damage albeit with a different manifestation (Rainer et al 2006).

Attempts have been made to identify a constellation of clinical factors that help with the identification of late-onset depression. Late-onset depression has been found to be more refractory to treatment with antidepressants (Coffey et al 1988; Hickie et al 1995), associated with a greater degree of patient apathy (Krishnan et al 1995) and less often associated with a family history of depression (Fujikawa et al 1994; Krishnan et al 1997). Additionally, patients are

less likely to achieve and sustain remission of their depressed symptoms (Fujikawa et al 1994; Taylor et al 2003). Relevant to clinical management, the concentration of SH has been associated with more problematic side effects in response to somatic treatments including delirium and parkinsonism with medications and ECT (Figiel, Coffey et al 1989; Figiel, Krishnan et al 1989; Fujikawa et al 1996).

There is strong evidence of an association between SH and late-onset depression, as well as between COPD and an increased severity of SH (van Dijk et al 2004). A portion of this increase may be accounted for by the subjects' smoking history. Smoking has been shown to be cytotoxic to endothelial cells and, as is discussed further below, this intravascular damage is a likely contributor to the observed SH (Blann and McCollum 1993). Smoking has also been shown to increase the risk for permanent brain injury following exposure to what might, in the absence of a smoking history, have been a transient ischemic insult (Wang et al 1997). The fundamental insult in ischemia is a failure to deliver sufficient oxygen to the site of involvement and that insufficiency can be caused by either hypoperfusion or hypoxemia. By the very nature of the disease process COPD is associated with chronic, if often subclinical, hypoxemia. The consequences of chronic hypoxemia include both impaired cognitive function and depression, although the evidence supporting the latter is less robust (El-Ad and Lavie 2005; Ozge et al 2006). In a comparison of cognitive function between healthy subjects, COPD patients and patients with Alzheimer's disease (AD) with mild hypoxemia the AD patients had the worst performance, with the COPD patients showing significant impairment relative to the normals (Kozora et al 1999). Imaging studies demonstrate that worse hypoxemia in COPD is associated with decreased perfusion of anterior cortical and subcortical areas and decreased performance on cognitive testing relative to normals (Antonelli et al 2003). Most studies of hypoxemia and depression arise from the sleep apnea literature where one of the primary identified sequelae of recurrent nocturnal hypoxemia is depressed mood (Aloia et al 2004).

It should be noted that depression itself has been identified as a risk factor for cerebrovascular insult, and so may contribute to the formation of lesions manifesting as SH. The severity of depressive symptoms is predictive of stroke after controlling for a host of variables including measured blood pressure (Simonsick et al 1995), smoking, body mass index, hypertension or diabetes (Everson et al 1998). A large, longitudinal study of 6095 stroke-free individuals followed for an average of 16 years found that after adjusting for multiple previously identified risks for stroke (age, gender, ethnicity,

systolic blood pressure, alcohol use, serum cholesterol level, diabetes and heart disease) being in the top third of measured depression levels increased the risk of stroke over the duration of the study period by 50%–106% when compared to subjects in the lowest third. The relative risk for stroke due to depression was roughly equivalent to a 40-point increase in systolic blood pressure (Jonas and Mussolino 2000).

Finally, there is growing evidence that depression and COPD impose similar microvascular and biochemical insults that would be expected to contribute to the accumulation of SH. Both depression and chronic respiratory disease have been associated with processes that jeopardize the microvasculature of the brain. In depression this has been evidenced by significantly elevated biomarkers of oxidative damage. Levels of 8-hydroxy-2'-deoxyguanosine were directly correlated with the severity of the depression and with the level of the resultant oxidative damage was correlated with the chronicity of the depression (Forlenza and Miller 2006). Oxidative stress has also been associated with biochemical alterations in the cell membrane and function of erythrocytes in patients with mental illness. These cell membrane aberrations are thought to interfere with effective transduction of neurotransmitter signaling (Ponizovsky et al 2003). In a treatment study depressed patients were noted to have deranged oxidant and antioxidant defense systems at baseline. After treatment with antidepressants depression measures improved and oxidative stress was reduced (Khanzode et al 2003).

In both COPD and depression there is evidence for increased platelet activation that may potentially lead to thrombotic insult to the microvasculature, the type of injury to which the narrow perforating arteries of the brain are particularly vulnerable. In COPD the synthesis of a marker of platelet activation was significantly elevated and inversely related to arterial oxygen tension (Davi et al 1997). In a comparison of depressed patients and controls, the patients demonstrated increased platelet activation at baseline as well as increased platelet reactivity (Musselman et al 1996). In a small study of depressed patients treatment with the antidepressant sertraline diminished a pre-treatment elevation in platelet activation (Markovitz et al 2000).

## Conclusion

COPD is a chronic, progressive disease and as such exerts an escalating burden over time. As the size of the elderly population grows, the number of people suffering with this debilitating disease is certain to increase. In spite of the high prevalence of COPD, treatment continues to be primarily symptomatic and rates of functional impairment and mortality have not significantly



decreased in the past several decades. While our understanding of the disease continues to progress, our ability to halt, or better still reverse, the progression of the disease has not. Improved management of morbidity must then become a parallel goal and one of the areas with the greatest potential for improvement is the management of patients' co-morbid depression. Depression in COPD is a heterogeneous entity with a potentially composite etiology including genetic predisposition, environmental losses and stressors, as well as direct damage to the brain mediated by the physiologic effects of chronic respiratory illness. As such, the relationships between depression, COPD and smoking are not linear but, rather, interconnected with each element influencing the others to different degrees in any given patient at any given time. Over the course of their lifetimes COPD patients may have experienced multiple exposures that increase their risk for the development of depression. The advantage to recognizing the inter-dependent relationship of these contributing factors is the corollary recognition that effective intervention in any one of them will have a cascading, positive impact on the others. Effectively targeting depression, or lost functionality or chronic hypoxemia will decrease morbidity in that dimension, and potentially in the others as well. There is much research that remains to be done to delineate what the most effective interventions are, but they are progressing. As noted above, identification of direct genetic influences opens the door for early intervention in juvenile vulnerability to nicotine addiction. Research into improved rehabilitation efforts, and a clarification of the best use and format of oxygen supplementation is ongoing with an eye to both decreased physiologic morbidity and increased functionality. At the same time patients are learning self-advocacy and developing support groups to share information and increase their sense of community. Lastly, we continue to search for the best ways to manage depression in patients with COPD. The likely answer will be a combination of psychopharmacology and psychotherapy, but in view of the often refractory nature of the depression there is also a role for electroconvulsive therapy in this population. This developing armamentarium can then be customized to the unique constellation of contributing factors active for a given patient at a given time.

## Acknowledgments

The author's work is supported in part by grant #5103 from the Legacy Foundation.

## References

- Agle DP, Baum GL. 1977. Psychological aspects of chronic obstructive pulmonary disease. *Med Clin North Am*, 61:749–58.
- Alexopoulos GS, Meyers BS, Young RC, et al. 1997a. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*, 54:915–22.
- Alexopoulos GS, Meyers BS, Young RC, et al. 1997b. Clinically defined vascular depression. *American Journal of Psychiatry*, 154:562–5.
- Aloia MS, Arnedt JT, Davis JD, et al. 2004. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. *Journal of International Neuropsychological Society*, 10:772–85.
- Antonelli I, Marra C, Giordano A, et al. 2003. Cognitive impairment in chronic obstructive pulmonary disease – a neuropsychological and spect study. *Journal of Neurology*, 250:325–32.
- Ariyo AA, Haan M, Tangen CM, et al. 2000. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation*, 102:1773–9.
- Audrain-McGovern J, Lerman C, Wileyto EP, et al. 2004. Interacting effects of genetic predisposition and depression on adolescent smoking progression. *American Journal of Psychiatry*, 161:1224–30.
- Awad IA, Spetzler RF, Hodak JA, et al. 1986. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. *Stroke*, 17:1084–9.
- Aydin IO, Ulusahin A. 2001. Depression, anxiety comorbidity, and disability in tuberculosis and chronic obstructive pulmonary disease patients: applicability of GHQ-12. *Gen Hosp Psychiatry*, 23:77–83.
- Blann AD, McCollum CN. 1993. Adverse influence of cigarette smoking on the endothelium. *Thromb Haemost*, 70:707–11.
- Breslau N, Kilbey MM, Andreski P. 1993. Nicotine dependence and major depression. New evidence from a prospective investigation. *Arch Gen Psychiatry*, 50:31–5.
- Brown FW, Lewine RJ, Hudgins PA, et al. 1992. White matter hyperintensity signals in psychiatric and nonpsychiatric subjects. *Am J Psychiatry*, 149:620–5.
- Brown GW. 1986. *Psychological Medicine*, 6:238–47.
- Campbell JJ 3rd, Coffey CE. 2001. Neuropsychiatric significance of subcortical hyperintensity. *J Neuropsychiatry Clin Neurosci*, 13:261–88.
- Carney RM, Freedland KE, Sheline YI, et al. 1997. Depression and coronary heart disease: a review for cardiologists. *Clin Cardiol*, 20:196–200.
- Coffey CE, Figiel GS, Djang WT, et al. 1988. Leukoencephalopathy in elderly depressed patients referred for ECT. *Biol Psychiatry*, 24:143–61.
- Coffey CE, Wilkinson WE, Weiner RD, et al. 1993. Quantitative Cerebral Anatomy in Depression: A Controlled Magnetic Resonance Imaging Study. *Archives of General Psychiatry*, 50:7–16.
- Coffey CE, Wilkinson WE, Parashos LA, et al. 1992. Quantitative cerebral anatomy of the aging human brain: a cross-sectional study using magnetic resonance imaging. *Neurology*, 42:527–36.
- Covey LS. 1999. Tobacco cessation among patients with depression. *Prim Care*, 26:691–706.
- Covey LS, Glassman AH, Stetner F. 1997. Major depression following smoking cessation. *Am J Psychiatry*, 154:263–5.
- Covey LS, Glassman AH, Stetner F. 1998. Cigarette smoking and major depression. *J Addict Dis*, 17:35–46.
- Cruess DG, Evans LE, Repetto MJ, et al. 2003. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. *Biol Psychiatry*, 54:307–16.
- Davi G, Basili S, Vieri M, et al. 1997. Enhanced Thromboxane Biosynthesis in Patients with Chronic Obstructive Pulmonary Disease. *Am J of Respir and Crit Care Med*, 156:1794–9.
- Dunlop DD, Lyons JS, Manheim LM, et al. 2004. Arthritis and heart disease as risk factors for major depression: the role of functional limitation. *Med Care*, 42:502–11.
- Earnest MA. 2002. Explaining adherence to supplemental oxygen therapy: the patient's perspective. *J Gen Intern Med*, 17:749–55.
- El-Ad B, Lavie P. 2005. Effect of sleep apnea on cognition and mood. *International Review of Psychiatry*, 17:277–82.
- Elery TC, Liang H, Plomin R, et al. 2004. Parental familial vulnerability, family environment, and their interactions as predictors of depressive symptoms in adolescents. *Journal of the American Academy of Child and Adolescent psychiatry*, 43:298–306.

- Evans DL, Staab JP, Petitto JM, et al. 1999. Depression in the medical setting: biopsychological interactions and treatment considerations. *Journal of Clinical Psychiatry*, 60:40–55.
- Everson SA, Roberts RE, Goldberg DE, et al. 1998. Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Arch Intern Med*, 158:1133–8.
- Fergusson DM. 1996. Comorbidity between depressive disorders and nicotine dependence in a cohort of 16 year olds. *Arch Gen Psychiatry*, 53:1043–7.
- Figiel GS, Coffey CE, Weiner RD. 1989. Brain Magnetic Resonance Imaging in Elderly Depressed Patients Receiving Electroconvulsive Therapy. *Convuls Ther*, 5:26–34.
- Figiel GS, Krishnan KR, Breitner JC, et al. 1989. Radiologic correlates of antidepressant-induced delirium: the possible significance of basal-ganglia lesions. *J Neuropsychiatry Clin Neurosci*, 1:188–90.
- Figiel GS, Krishnan KR, Doraiswamy PM, et al. 1991. Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. *Neurobiol Aging*, 12:245–7.
- Forlenza MJ, Miller GE. 2006. Increased Serum Levels of 8-Hydroxy-2'-Deoxyguanosine in Clinical Depression. *Psychosomatic Medicine*, 68:1–7.
- Fujikawa T, Yamawaki S, Touhouda Y. 1994. Background factors and clinical symptoms of major depression with silent cerebral infarction. *Stroke*, 25:798–801.
- Fujikawa T, Yokota N, Muraoka M, et al. 1996. Response of patients with major depression and silent cerebral infarction to antidepressant drug therapy, with emphasis on central nervous system adverse reactions. *Stroke*, 27:2040–2.
- Grafton ST, Sumi SM, Stimac GK, et al. 1991. Comparison of postmortem magnetic resonance imaging and neuropathologic findings in the cerebral white matter. *Archives of Neurology*, 48:293–8.
- Guttmann CR, Jolesz FA, Kikinis R, et al. 1998. White matter changes with normal aging. *Neurology*, 50:972–8.
- Hall SM, Reus VI, Munoz RF, et al. 1998. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch Gen Psychiatry*, 55:683–90.
- Hickie I, Scott E, Mitchell P, et al. 1995. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry*, 37:151–60.
- Hitsman B, Pingitore R, Spring B, et al. 1999. Antidepressant pharmacotherapy helps some cigarette smokers more than others. *Journal of Consult Clin Psychol*, 67:547–54.
- Holahan CK, Holahan CJ. 1987. Self-efficacy, social support, and depression in aging: a longitudinal analysis. *Journal of Gerontology*, 42:65–8.
- Howard RJ, Beats B, Forstl H, et al. 1993. White matter changes in late onset depression: A magnetic resonance imaging study. *International Journal of Geriatric Psychiatry*, 8:183–5.
- Hurt RD, Sachs DP, Glover ED, et al. 1997. A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine*, 337:1195–202.
- Jonas BS, Mussolino ME. 2000. Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med*, 62:463–71.
- Kaplan HI, Sadock BJ. 1988. Synopsis of psychiatry. Baltimore: Lippincott, Williams and Wilkins. p 543.
- Kathol RG, Mutgi A, Williams J, et al. 1990. Diagnosis of major depression in Cancer patients according to four sets of criteria. *Am J Psychiatry*, 147:1021–4.
- Katon W, Sullivan MD. 1990. Depression and chronic medical illness. *J Clin Psychiatry*, 51:3–11; discussion 2–4.
- Kendler KS, Gatz M, Gardner CO, et al. 2006. A Swedish national twin study of lifetime major depression. *American Journal of Psychiatry*, 163:109–14.
- Khanzode SD, Dakhale GN, Khanzode SS, et al. 2003. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Report*, 8:365–70.
- Kohler CL, Fish L, Greene PG. 2002. The relationship of perceived self-efficacy to quality of life in chronic obstructive pulmonary disease. *Health Psychol*, 21:610–14.
- Kozora E, Filley CM, Julian LJ, et al. 1999. Cognitive functioning in patients with chronic obstructive pulmonary disease and mild hypoxemia compared with patients with mild Alzheimer disease and normal controls. *Neuropsychiatry Neuropsychol Behav Neurol*, 12:178–83.
- Krishnan KR, Goli V, Ellinwood EH, et al. 1988. Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry*, 23:519–22.
- Krishnan KR, Hays JC, Blazer DG. 1997. MRI-Defined Vascular Depression. *American Journal of Psychiatry*, 154:497–501.
- Krishnan KR, Hays JC, Tupler LA, et al. 1995. Clinical and phenomenological comparisons of late-onset and early-onset depression. *American Journal of Psychiatry*, 152:785–8.
- Krishnan KR, McDonald WM, Doraiswamy PM, et al. 1993. Neuroanatomical substrates of depression in the elderly. *Eur Arch Psychiatry Clin Neurosci*, 243:41–6.
- Kunik ME, Roundy K, Veazey C, et al. 2005. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*, 127:1205–11.
- Kurosawa H. 1983. The relationship between mental disorders and physical severities in patients with acute MI. *Jpn Circ J*, 47:723–5.
- Lerman C, Berrettini W. 2003. Elucidating the role of genetic factors in smoking behavior and nicotine dependence. *American Journal Medical Genetics Part B, Neuropsychiatric genetics*, 118:48–54.
- Lesser IM, Boone KB, Mehringer CM, et al. 1996. Cognition and white matter hyperintensities in older depressed patients. *Am J Psychiatry*, 153:1280–7.
- Light RW, Merrill EJ, Despars JA, et al. 1985. Prevalence of depression and anxiety in patients with COPD. Relationship to functional capacity. *Chest*, 87:35–8.
- Longstreth WT, Jr, Manolio TA, Arnold A, et al. 1996. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*, 27:1274–82.
- Markovitz JH, Shuster JL, Chitwood WS, et al. 2000. Platelet Activation in Depression and Effects of Sertraline Treatment: An Open-Label Study. *Am J Psychiatry*, 157:1006–8.
- McCarthy HC, Spence SH, Tate RL. 2002. Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. *Eur Respir J*, 19:47–53.
- Musselman DL, Tomer A, Manatunga AK, et al. 1996. Exaggerated Platelet Reactivity in Major Depression. *American Journal of Psychiatry*, 153:1313–17.
- Niaura R, Britt DM, Shadel WG, et al. 2001. Symptoms of depression and survival experience among three samples of smokers trying to quit. *Psychol Addict Behav*, 15:13–17.
- Ozge C, Ozge A, Unal O. 2006. Cognitive and functional deterioration in patients with severe COPD. *Behavioral Neurology*, 17:121–30.
- Patton GC, Hibbert M, Rosier MJ, et al. 1996. Is smoking associated with depression and anxiety in teenagers? *Am J Public Health*, 86:225–30.
- Penning MJ, Strain LA. 1994. Gender differences in disability, assistance, and subjective well-being in later life. *J Gerontol*, 49:S202–8.
- Penninx BWJH, van Tilburg T, Boeke AJP, et al. 1998. Effects of social support and personal coping resources on depressive symptoms: different for various chronic diseases? *Health Psychology*, 17:551–8.
- Ponizovsky AM, Barshtein G, Bergelson LD. 2003. Biochemical alterations of erythrocytes as an indicator of mental disorders: an overview. *Harv Rev Psychiatry*, 11:317–32.
- Rainer MK, Mucke HA, Zehetmayer S, et al. 2006. Data from the VITA Study do not support the concept of vascular depression. *Am J Geriatr Psychiatry*, 14:531–7.
- Salloway S, Malloy P, Kohn R, et al. 1996. MRI and neuropsychological differences in early- and late-life-onset geriatric depression. *Neurology*, 46:1567–74.

- Simonsick EM, Wallace RB, Blazer DG, et al. 1995. Depressive symptomatology and hypertension-associated morbidity and mortality in older adults. *Psychosom Med*, 57:427–35.
- Sullivan PF, Neale MC, Kendler S. 2000. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*, 157:1552–62.
- Taylor WD, Steffens DC, MacFall JR, et al. 2003. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*, 60:1090–6.
- van Dijk EJ, Vermeer SE, de Groot JC, et al. 2004. Arterial oxygen saturation, COPD, and cerebral small vessel disease. *J Neurol Neurosurg Psychiatry*, 75:733–6.
- van Ede L, Yzermans CJ, Brouwer HJ. 1999. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. *Thorax*, 54:688–92.
- van Manen JG, Bindels PJ, Dekker FW, et al. 2002. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax*, 57:412–16.
- Videbech P. 1997. MRI findings in patients with affective disorder: a meta-analysis. *Acta Psychiatr Scand*, 96:157–68.
- Wang L, Kittaka M, Sun N, et al. 1997. Chronic nicotine treatment enhances focal ischemic brain injury and depletes free pool of brain microvascular tissue plasminogen activator in rats. *Journal of Cerebral Blood Flow and Metabolism*, 17:136–46.
- Yohannes A. 2000. Mood disorders in elderly patients with COPD. *Reviews in Clinical Gerontology*, 10:193–202.
- Yudofsky SC, Hales RE. 1992. Textbook of neuropsychiatry. Washington, DC: American Psychiatric Press, Inc. p 166–9.
- Ziegelstein RC. 2001. Depression after myocardial infarction. *Cardiol Rev*, 9:45–51.

