Chapter 8

Respiratory Disorders: Effects on Neurocognitive and Brain Function

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Introduction

Diseases and/or disorders of the pulmonary system may affect brain behavior relationships due to impaired oxygen delivery (i.e., anoxia, hypoxia). Neurons are dependent on oxygen and without oxygen cellular function is disrupted and damage to cell structure leading to neuronal death may follow. A variety of respiratory disorders such as cardiac or respiratory arrest, carbon monoxide poisoning, obstructive sleep apnea, chronic obstructive pulmonary disease, and acute respiratory distress syndrome result in anoxia or hypoxia which can result in anoxic brain injury. The neuronal injury is manifest structurally by lesions and neuronal atrophy and functionally as neurocognitive and neuropsychiatric impairments.

The incidence of cardiac arrest with anoxia and cerebral ischemia occurs in more than 400,000 cases per year, of which more than 80% of these patients are likely to have poor neurological outcomes [1, 2]. Improvements in emergency and critical care medicine have resulted in approximately 200,000 cardiac resuscitations per year of which over 70,000 patients survive but constitute only 1% of those admitted to brain injury rehabilitation centers [3]. Other respiratory disorders associated with anoxia or hypoxia may also cause anoxic brain injury. The severity of anoxia/hypoxia does not appear to be related to development of neuropsychological impairments. However, the degree of neuropsychological impairment appears parallel to the degree of morphologic abnormalities as demonstrated by quantitative MRI image analysis [4, 5]. Neuropsychological deficits are common in respiratory disorders with concomitant hypoxia including impaired memory [6–8], executive function [9, 10], apperceptive agnosia [11], visual–spatial deficits [12], and generalized neurocognitive decline [6, 13, 14].

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Effects of Hypoxia

The human brain constitutes approximately 2% of the total body mass but utilizes 20% of the total oxygen consumption [15]. The brain requires oxygen to produce energy and uses aerobic glucose oxidation to produce 95% of the brain's adenosine triphosphate (ATP). ATP serves as a source of energy for many metabolic processes including neural function. ATP releases energy when it is broken down into ADP by hydrolysis during cell metabolism. Neocortical and subcortical functions depend upon continuous supply of oxygen, as neurons are not able to store oxygen and glucose for later use [16]. Hypoxia or anoxia damages multiple organ systems especially those with high oxygen utilization such as the central nervous system. Oxygen and glucose are required to maintain the function of the central nervous system (CNS) and reduction or depletion of oxygen and glucose results in neuronal injury. Slight decreases in oxygen delivery may cause permanent biochemical and morphological changes. Anoxia is defined as absence of oxygen in arterial blood or tissues, hypoxia as tissue oxygen

C.L. Armstrong (ed.), L. Morrow (Associate editor), *Handbook of Medical Neuropsychology*,
DOI 10.1007/978-1-4419-1364-7_8,

deprivation, and hypoxemia as reduced oxygenation of the blood [17, 18]. Hypoxia and anoxia are often used interchangeably as anoxia is severe hypoxia.

Regional brain oxygen utilization is not homogeneous with some brain regions more vulnerable to the effects of anoxia/hypoxia, particularly structures at the end of the vascular supply or with high metabolic rates [19]. Selective vulnerability of some brain regions has been attributed to vascular or hemodynamic specificity [19], increased regional metabolism of glucose [20], and/or proximity to structures with high levels of excitatory amino acids such as glutamate [21, 22]. Vulnerable brain regions include the neocortex, hippocampus, basal ganglia, cerebellar Purkinje cells, primary visual cortex, frontal regions, and thalamus [23–25].

Mechanisms of Brain Injury

Anoxia or ischemia causes a pathophysiological cascade that leads to neuronal damage and death (for reviews of the mechanisms see [17, 26]). Mechanisms of anoxic-induced neuronal injury include the following: (1) Decreased ATP production without decreasing ATP utilization, resulting in energy depletion, ionic pump failure, K^+ outflow, and inflow of Ca^{2+} [27]; (2) lactic acidosis due to anaerobic metabolism [28]; (3) excitotoxic damage due to excessive glutamate release leading to increased neuronal firing, calcium influx, and neuronal death [26]; (4) increased calcium influx and intracellular accumulation of calcium due to ionic pump failure [29]; (5) the formation of oxygen radicals during reperfusion or reoxygenation [17]; (6) nitric oxide synthase leading to impaired neurotransmission, protein synthesis, and membrane peroxidation [17]; and (7) anoxia or ischemia resulting in neuronal necrosis and/or apoptosis or programmed cell death [30, 31]. Controversy exists in the literature regarding whether hypoxia in the absence of ischemia can result in brain injury [32]. Neuropsychological sequelae following hypoxia without ischemia occurred in 22 patients with hypoxia without hypotension, all were comatose and recovery to the premorbid level of function occurred in only 50% of the patients [33]. In fact three patients with hypoxia (PO_2 less than 45 mmHg) without hypotension died of cardiac failure, indicating that factors other than ischemia contributed to poor outcome [34]. Further, neuropsychological impairments are common in patients with pulmonary disorders in which continuous or intermittent hypoxia or hypoxemia occur without ischemia. For example, patients with pulmonary disorders including chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) with concomitant hypoxia have neuropsychological deficits similar to patients with anoxia due to cardiac or respiratory arrest.

Neuroimaging Findings

As stated previously, some brain regions are more vulnerable to the effects of anoxia/ischemia, particularly structures at the end of the vascular supply, with high metabolic rates [19], and/or proximity to structures that contain excitatory amino acids such as glutamate [21, 22]. Anoxic brain injury results in focal and diffuse neuropathologic lesions and atrophy [7, 35–37] including lesions in the hippocampus [38, 39], basal ganglia, cerebellum [40], subcortical and periventricular white matter lesions [41], and atrophy of the corpus callosum [42]. Generalized brain volume loss leading to ventricular enlargement and sulcal widening [36] and hippocampal atrophy are also common [7, 43]. A review of anoxic brain injury ($N = 90$) found that 44% of individuals had cortical edema or atrophy, 33% had cerebellar lesions, 22% had basal ganglia lesions, 21% had hippocampal atrophy, and 3% had thalamic lesions [36]. Hippocampal damage, including lesions and atrophy [38, 39], has long been established as a common consequence of anoxia. Hippocampal atrophy can be identified on magnetic resonance scans as volume reduction. Previous research has suggested that the hippocampus may be more vulnerable to hypoxic injury than adjacent medial temporal lobe structures such as the parahippocampal gyrus or temporal lobes [44].

Neurological and Neuropsychological Sequelae

Poor neurological outcomes after brain injury include death, coma, vegetative state, severe neurologic

disability [45], neurocognitive sequelae, and development of new psychiatric disorders [35, 36]. Neuropsychological deficits following anoxia brain injury are heterogeneous and include agnosia [11], impaired memory [8, 39, 46], executive dysfunction [9, 10], impaired visual–spatial skills [12], generalized neurocognitive impairments [14], and motor disturbances [47]. Psychological and behavioral changes include euphoria, irritability, emotional volatility, depression, and anxiety [48, 49]. This chapter will review some common respiratory disorders and associated neurocognitive and neuropsychiatric sequelae.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) refers to a group of pulmonary diseases with airflow limitation that is not fully reversible including chronic bronchitis and emphysema, which occur without an asthmatic component. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs [50]. Both chronic bronchitis and emphysema are characterized by airway obstruction that may be partially reversible. COPD is the fourth leading cause of death in the United States and leads to serious, long-term disability [51]. The estimated prevalence of COPD in the United States in the adult population is 5–10% [52]. Chronic obstructive pulmonary disease (COPD) is a growing cause of morbidity and mortality worldwide and the prevalence of stage II (forced expiratory volume of 30 to <50% predicted) or higher COPD was 10.1% overall, 11.8% for men, and 8.5% for women [53]. More than 14 million people are currently diagnosed with COPD and an additional 12 million likely have COPD that has not been diagnosed [54]. COPD is a progressive, degenerative disease process that results in airflow obstruction, air trapping, hyperinflation of the lungs, and impaired gas exchange. The most important risk factor for development of COPD is cigarette smoking [55]. Other risk factors include family history of pulmonary disease, exposure to allergies and/or irritants, and pulmonary infection [56]. Symptoms include shortness of breath, dyspnea, cough, increased sputum production, and wheezing. As the disease process advances, the pulmonary changes lead to abnormal sleep structure, sleeplessness, poor physical and neurocognitive function, poor exercise tolerance, lack of appetite, weight change, fatigue, and dyspnea [57]. Dyspnea or air hunger, manifest as difficult or labored breathing [58], can lead to hypoxia/hypoxemia, which, as noted above, is linked to brain injury and development of neurocognitive impairments [59], depression, and anxiety [56].

Neurocognitive Morbidity

Neurocognitive impairments are common in patients with chronic obstructive pulmonary disease (COPD) [60]. The pattern, extent, and severity of neurocognitive impairments in COPD patients are variable, but are associated with hypoxemia [61, 62]. Patients with COPD have impaired memory, executive function [63], flexible thinking [61], attention, and slow mental processing speed [64]. In general, neurocognitive impairments correlate with the duration and severity of the hypoxia [62, 65]. However, even patients with mild hypoxemia have neurocognitive impairments in a variety of cognitive domains [61, 62]. The severity of the neurocognitive impairments is also associated with older age and duration of COPD [66]. Further, older age, poorer aerobic fitness, and reduced pulmonary function predict worse neurocognitive performance [67]. Frequently reported neurocognitive impairments include executive dysfunction; reduced perceptual motor speed, impaired memory, and attention; and reduced intellectual function [68]. Investigations to date find great inter-individual variability in neurocognitive impairments in COPD patients. Memory is one of the most commonly affected neurocognitive domains in COPD. For example, impaired verbal memory is associated with poor adherence to the patients' medication regimen [69].

As noted above, neurocognitive impairments in COPD patients correlate with hypoxia/hypoxemia [61, 62]. Moderate to severe hypoxemia deficits lead to poor motor skills, abstract reasoning, attention learning, and memory and language skills [70]. Prigatano et al. [60] found that COPD patients with mild hypoxemia had mild impairments in "higher cerebral problem-solving skills." Other studies find impaired memory, problems forming new concepts, problems with flexible thinking [61], impaired attention, and slow mental processing speed [64] correlate with the

severity of hypoxia [62, 65]. In fact COPD patients with mild hypoxia, the majority of who were treated with supplemental oxygen, had neurocognitive impairments [63]. Several studies suggest that long-term oxygen treatment improves cognitive functioning [62, 65]. Alternatively, acute oxygen treatment may not improve cognitive functioning in some COPD patients [71]. One study found that COPD patients had significantly worse intellectual function and attention than controls and the neurocognitive impairments did not correlate with disease severity (i.e., lung function, blood gas analysis, nocturnal oxygen saturation) [72]. Current data suggest the ability to predict neurocognitive impairments on the basis of the severity of the disease or hypoxemia is poor and the effectiveness of oxygen therapy for improving cognitive functioning of COPD patients is unclear.

Potential reasons for the lack of relationship between hypoxemia and neurocognitive impairments may due to non-compliance with oxygen therapy or other factors such as variable duration of illness and illness severity (such as variable duration and severity of hypoxemia), comorbid disorders, poor medication adherence, and reduced functional capacity and physiologic reserve to name a few [73]. For example, COPD patients that have impaired global cognitive performance and memory had poor adherence to medication regimes [69]. Physical exercise may improve cognitive function in healthy individuals through improved cerebral metabolism and oxygenation [74]. Pulmonary rehabilitation consisting of exercise, education, and psychosocial counseling improved psychomotor speed and mental flexibility [75]. However, memory and concentration did not improve [75], neurocognitive impairments that are associated with hypoxia/hypoxemia induced hippocampal damage rather than those associated with fatigue. Risk factors and mechanisms of neurocognitive impairments, as well as interventions that may lead to improved cognitive functioning in COPD patients, remain to be determined.

In addition to neurocognitive impairments COPD patients have impaired physical function, health status, and reduced quality of life. These patients often are impaired in their ability to perform activities of daily living (i.e., bathing, dressing, toileting, transfer, continence, and feeding) which are related to their pulmonary function, cough, wheezing, and dyspnea [76]. COPD patients report poor physical function that contributed to reduced quality of life compared to healthy control subjects [60]. Further, the degree of physical limitations paralleled the severity of the COPD. Decreased exercise tolerance and dyspnea are related to poor health status and functional abilities [77]. Even COPD patients with mild hypoxemia have significantly lower quality of life (measured using the Medical Outcome Survey short form-36; SF-36) compared to healthy controls [78]. Higher levels of depression and anxiety symptoms are also associated with reduced quality of life in COPD patients [79].

Neuropsychiatric Morbidity

Neuropsychiatric disorders, especially depression and anxiety, are common in patients with COPD. The prevalence of neuropsychiatric disorders is as high as 30–58% of COPD patients [80]. Other studies note the prevalence of depression is as high as 42% [81] and 37% of patients have anxiety disorder [82]. Depression increases with increased hypoxemia, carbon dioxide levels, or dyspnea [83]. Hypoxia may be a cause factor in the development of depression and anxiety in COPD due to brain injury (see section "Mechanism of Brain Injury") [84]; however, treatment with oxygen results in little or no improvement in the severity of the depression [85]. Even patients who undergo long-term oxygen therapy have severe depression [86]. It is unclear why oxygen treatment improves neurocognitive function but not neuropsychiatric function, but may be due to physical or psychological responses. Another possible cause of neuropsychiatric morbidity may be negative self-perception and restrictions in behavioral functioning due to reduced physical capacity [75]. Exercise rehabilitation in COPD patients improves depression and anxiety [75].

Anxiety is also common in patients with pulmonary disorders such as COPD. Vögele et al. found 55% of COPD had a diagnosis of an anxiety disorder compared to 30% of controls [87]. Vögele and colleagues found no associations between anxiety levels and respiratory function in the COPD group, but there was positive association between anxiety levels and physical symptoms, as well as negative cognition in COPD patients with anxiety disorders. The above findings confirm the high prevalence rate of neurocognitive and neuropsychiatric disorders in patients with COPD [87].

COPD Summary

COPD is a chronic obstructive pulmonary disorder associated with poor physical health, reduced physical function, neurocognitive impairments, and neuropsychiatric manifestations including depression and anxiety. Oxygen treatment may improve neurocognitive function in some patients. Studies using exercise rehabilitation show improvements in physical functioning, endurance, neurocognitive functioning, and improved neuropsychiatric well-being [70, 75].

Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a common cause of mortality and morbidity and affects 150,000 people per year [88] or more [89] in the United States. Patients are critically ill and survival has improved from less than 50% to approximately 70% [90–92] resulting in approximately 100,000 ARDS survivors per year. Acute respiratory distress syndrome is characterized by acute lung injury, hypoxemia, reduced total thoracic compliance, and diffuse bilateral infiltrates [93, 94]. Although the pathophysiology of ARDS is unclear it occurs in response to a variety of insults including sepsis, shock, trauma, pneumonia, massive transfusion, and other medical/surgical conditions. ARDS is frequently accompanied by organ dysfunction, which includes central nervous system dysfunction. Treatment of ARDS requires aggressive supportive care including positive pressure ventilation [92] and increased oxygen concentration with risks of barotrauma, oxygen toxicity, and nosocomial infection. Survivors of ARDS are often left with pulmonary function abnormalities, neuromuscular weakness, diminished health-related quality of life, neuropsychiatric and neurocognitive deficits [95–97].

Investigations of the neurologic dysfunction in ARDS survivors have been relatively neglected compared to other organ systems. A study that assessed CNS dysfunction using the Glasgow Coma Scale score found that greater severity of the initial neurologic dysfunction (lower Glasgow Coma Scale scores) and no change or worsening of the neurologic dysfunction were associated with higher 30-day mortality [98]. Neurologic complications of ARDS involve the central and peripheral nervous systems and contribute to significant mortality and morbidity. Brain imaging data in 15 ARDS patients suggest that neurologic morbidity includes neuropathologic changes including generalized brain atrophy and structural lesions [99]. The patients with ARDS and brain CT scans had a longer hospital and ICU length of stays, duration of mechanical ventilation, and lower FiO_2 compared to ARDS patients without brain imaging. The patients who underwent brain CT imaging had significantly larger ventricular volumes for the lateral ventricles, III ventricle, temporal horns of the lateral ventricles, total ventricular volume, and ventricle-to-brain ratio (a measure of diffuse atrophic change and a general index of white matter integrity; p values 0.02–0.008) compared to the normal control subjects [99]. Clinical radiological brain CT reports identified seven patients with atrophy that support the finding of ventricular enlargement and brain atrophy. Six of the 15 ARDS patients had mild to moderate cerebral atrophy or ventricular enlargement including hippocampal atrophy in one patient and one patient had increased temporal horn size [99]. The observed brain atrophy may be due to hypoxia during critical illness [96, 100]. The nonspecific brain injury manifested by reduced gyral volume, increased sulcal space, passive increase in ventricular volume, and increased cerebrospinal fluid is common following hypoxic brain injury [101]. While the sample size is small, the data suggest that longer ICU and hospital length of stays, longer duration of mechanical ventilation and lower FiO_2 may be risk factors for brain injury [99]. Both the patients with ARDS with and without CT scans had significant cognitive impairments including impaired memory, attention, mental processing speed, and executive function at hospital discharge and 1 year post-hospital discharge. These findings suggest that ARDS may result in neuropathologic injury and concomitant neuropsychological impairments.

Mechanisms of Injury

The mechanisms of ARDS-induced brain injury are just beginning to be elucidated, but hypoxemia is undoubtedly implicated [96, 100]. Hopkins et al. measured pulse oximetry in a prospective cohort of mechanically ventilated ARDS survivors and assessed the relationship between the duration and severity of

mean oxygen saturation below 90, with neurocognitive outcome [96] (pulse oximetry: SpO_2 level <90 is approximately a PaO_2 of 50% or severe hypoxia). The pulse oximetry was measured for a total of 31,665 h, excluding data without a good pulse waveform. Patients' mean saturations were below 90% for 122 ± 144 h per patient. The degree of hypoxemia correlated significantly with neurocognitive sequelae [96]. Supportive evidence for the role of hypoxia in brain injury includes CA1 neuronal in the hippocampus due to hypoxia and increased S-100B protein serum levels in pigs with acute lung injury [102]. Other mechanisms of brain injury following ARDS include hyperglycemia [103], delirium [104], hypotension [105], and the use of sedatives or analgesics [106]. The mechanisms of neurologic dysfunction are likely multi-factorial in nature. Thus, ARDS may result in significant long-term brain-related morbidity manifest by neurocognitive impairments, neuropsychiatric morbidity, and decreased quality of life.

Neurocognitive Morbidity

Neurocognitive impairments in ARDS patients are long lasting and are reported at 6 months [107], 1 year [96, 105, 108], 2 years [100], and 6 years following hospital discharge [109, 110]. Hopkins and colleagues found ARDS survivors had global neurocognitive decline and impaired memory, attention, concentration, mental processing speed, and global neurocognitive decline [96]. At 1-year follow-up, 30% of the 55 patients had lower intellectual function and 78% had impaired memory, attention, concentration, and/or mental processing speed. In other studies of ARDS survivors neurocognitive sequelae occurred in 73% (54 of 74) of survivors at hospital discharge, 46% (30 of 66) at 1 year, and 47% (29 of 62) at 2 years [100, 105]. Regarding global intellectual function, Hopkins et al. showed that ARDS patients' estimated premorbid IQ was significantly higher than their measured IQ at hospital discharge but improved to their premorbid level by 1-year follow-up [100]. The finding that patients recovered over time with regard to IQ does not necessarily suggest a comparable recovery in all cognitive domains, as data from traumatic and anoxic brain injury literature suggest that some cognitive abilities are more likely to improve.

The neurocognitive impairments appear to improve during the first 12 months post-hospital discharge [100]. For example, at hospital discharge 70% of ARDS survivors had neurocognitive impairments whereas only 45% had neurocognitive impairments at 1 and 2 years following hospital discharge [100]. While highly prevalent, cognitive impairment demonstrated by ICU survivors is also often quite severe. The aforementioned ARDS patients with cognitive sequelae all fell below the sixth percentile of the normal distribution of cognitive functioning, displaying marked neuropsychological deficits in memory, executive functioning, attention, and mental processing abilities. Impairment does not impact all domains equally – and deficits in some areas rebound relatively more completely than others. The duration of the neurocognitive impairments in at-risk ARDS survivors lasts years and may be permanent. Two studies found that 25–33% of ARDS survivors have neurocognitive impairments 6 years after ARDS [109, 110]. The observed neurocognitive impairments are similar to those reported in other ARDS survivors [108, 109, 111], medical ICU survivors [112], following carbon monoxide poisoning [113], and several years after elective coronary artery bypass surgery [114]. Risk factors for acute and chronic neurocognitive impairments following ARDS are unknown and should be the subject of future studies.

Neuropsychiatric Morbidity

Psychiatric or neurobehavioral morbidity following ARDS is common and includes depression, anxiety, and posttraumatic stress disorder (PTSD). It is unclear whether psychiatric disorders are a psychological reaction to extraordinary emotional and physiologic stress, sequelae of brain injury sustained due to ARDS and its treatment, or all of the above. The combination of medications (e.g., sedatives, narcotics, atypical antipsychotic medications, physiological changes, pain, altered sensory inputs, and an unfamiliar environment may contribute to emotional changes) [115–117]. The prevalence and severity of depression, anxiety, and PTSD in survivors of critical illness are variable [109, 117–119]. Depression occurs in a quarter [100] to over half of ARDS survivors [118]. For example, one study found 43% of ARDS patients had depression [120] and

another study reported that over 50% of ARDS survivors had depression 1 year after intensive care unit treatment [118]. A longitudinal study found that ARDS survivors have moderate to severe depression (16 and 23%) and anxiety (24 and 23%) at 1 and 2 years, respectively [100, 105]. While data are accumulating regarding depression following ARDS, less is known regarding anxiety. Anxiety occurs in as many as 41% of ARDS survivors [121, 122]. A longitudinal ARDS study found that anxiety occurred in 24% at 1 and 2 years [100, 105].

The most commonly reported anxiety disorder in ARDS populations is posttraumatic stress disorder (PTSD). Posttraumatic stress disorder is the development of characteristic symptoms that occur following a traumatic event(s) where triggers include a serious personal threat experienced with helplessness and intense fear [123]. Schelling and colleagues were the first to report PTSD following ARDS and intensive care unit treatment [124]. Almost a third of the ARDS survivors reported impaired memory, bad dreams, anxiety, and sleeping difficulties after ICU discharge, with a prevalence rate of PTSD of 28%. Others have reported high rates of PTSD in ARDS survivors [125]. The prevalence of PTSD is as high as 38% [126] and persists years after intensive care unit discharge [109]. For example, PTSD has been reported at hospital discharge and 8 years after discharge [124]. One treatment study found that ARDS patients treated with hydrocortisone had a significant reduction in the development of PTSD compared to patients without treatment (19 vs. 59%).

ARDS Summary

The significant and sometimes permanent effects of ARDS on neurocognitive and neuropsychiatric functioning are increasingly recognized in the intensive care community regarding the importance of this issue; however, it is less recognized in the psychological or neuropsychological communities. Since the presence of cognitive impairment among ARDS survivors was first systematically identified a decade or so ago, progress has been made to study and better characterize this phenomenon. Neurocognitive impairments following ARDS are prevalent, occur in wide-ranging cognitive domains, and are functionally disruptive. Key questions remain unanswered with regard to determining mechanisms, risk factors, and the degree to which brain injuries associated with ARDS are amenable to rehabilitation.

Carbon Monoxide Poisoning

Carbon monoxide is a colorless, odorless gas produced as a by-product of combustion. Common sources of CO are internal combustion engines and faulty furnaces [127]. Carbon monoxide is the leading cause of poisoning injury and death worldwide [128] and the most common cause of accidental and intentional poisoning in the United States. Carbon monoxide results in approximately 40,000 emergency department visits [129] and 800 deaths per year in the United States [130]. The acute symptoms of CO poisoning are nonspecific and are similar to those associated with flu-like illness, which can make diagnosis of CO poisoning difficult. The brain and heart are particularly vulnerable to the pathological effects of CO [128].

Carbon monoxide poisoning results in focal and generalized neuroanatomical abnormalities observed on magnetic resonance (MR) and computed tomography (CT) imaging. Brain lesions following CO poisoning occur in the cortex [131], cerebellum [132], thalamus [133], and substantia nigra [134]. Lesions also occur in subcortical structures including white matter [135] and basal ganglia including the globus pallidus [136], caudate, and putamen [137, 138]. White matter hyperintensities occur in the periventricular and centrum semiovale or deep white matter regions [41]. In addition to neural lesions, carbon monoxide poisoning may cause neuronal cell loss and concomitant structural atrophy. Atrophy occurs in the fornix [139], hippocampus [37], and corpus callosum [42]. Generalized atrophy is also reported with brain volume reduction manifested by reduced gyral volume, increased sulcal space, and passive ventricular enlargement [37]. One study found CO-poisoned patients had atrophy in the putamen, caudate, and globus pallidus [140].

Neurocognitive Morbidity

Neurocognitive impairments commonly occur following CO poisoning in previously healthy individuals

[113]. It is estimated that between 15 and 49% of individuals diagnosed with acute CO poisoning will develop neurocognitive sequelae [141]. A recent review of 18 group studies ($N = 979$) and 16 case studies ($N = 35$) found that 94% of the case studies and 33.9% of patients in the group studies had cognitive impairments [142]. Neurocognitive sequelae of CO poisoning are heterogeneous regarding onset, severity, neurocognitive domain affected, and the pattern of neurocognitive deficits is variable [37]. Carbon monoxide-related neurocognitive impairments include impaired memory [143], executive function [144], slow mental processing speed, decreased intellectual function [37], apraxia, aphasia, and agnosia [145]. Neurocognitive sequelae lasting 1 month [146, 147], or more [113, 148], occur in 25–50% of patients with loss of consciousness or COHb levels greater than 25% [147, 149].

Weaver and colleagues studied individuals with acute carbon monoxide poisoning who were compared for neurocognitive outcome following either hyperbaric oxygen or normobaric oxygen treatment in a randomized double blind clinical trial. The neurocognitive impairments were significantly more frequent in the normobaric oxygen group (14.5%) as compared with the hyperbaric oxygen group (3.9%; $p = 0.03$) [113]. Hyperbaric oxygen therapy reduced neurocognitive impairments by 46% at 6-week outcome. Both groups improved with time, but the difference in neurocognitive impairments between the groups was maintained at 12 months [113]. Thus, treatments such as hyperbaric oxygen may potentially prevent or reduce the neurocognitive impairments that occur following CO poisoning. Risk factors for development of neurocognitive sequelae following acute CO poisoning were assessed using multivariable logistic regression in 163 CO-poisoned patients not treated with hyperbaric oxygen [150]. Of the 163 patients, 68 (42%) manifested neurocognitive sequelae [150]. The risk factors for development of neurocognitive sequelae were aged ≥36 years (odds ratio 2.6; $p = 0.005$) and CO exposure intervals ≥24 h (odds ratio 2.4; $p = 0.019$).

Neuropsychiatric Morbidity

Neuropsychiatric morbidity following CO poisoning are common and include depression, anxiety [151], obsessive and compulsive behavior, hallucinations [152], violent outbursts [145], elated mood [146], irritability, and decreased frustration tolerance [153]. The prevalence of CO-related neuropsychiatric morbidity ranges from 33 to 100% [37, 146, 154]. For example, a study by Jasper et al. found significant depression and anxiety in CO-poisoned patients: 45% at 6 weeks, 44% at 6 months, and 43% at 12 months [151]. Accidentally CO-poisoned patients are as likely as individuals with intentional CO poisoning to have depression and anxiety at 6 and 12 months. Patients with neurocognitive sequelae had a higher rate of depression and anxiety at 6 weeks compared to those with no neurocognitive sequelae, but not at 12 months. Patients with intentional CO poisoning have a higher rate of depression and anxiety at 6 weeks compared to accidental CO-poisoned patients, but not at 6 and 12 months. Although there was some subgroup improvement in depression and anxiety over time, the overall prevalence did not change. Hyperbaric oxygen therapy did not reduce the rate of depression and anxiety, but did reduce neurocognitive sequelae [151]. Consistent findings across CO studies to date are the high rate of depression and anxiety following CO poisoning. Similar prevalence rates of depression and anxiety occur in patients with traumatic brain injury and stroke [155], chronic obstructive pulmonary disease [156], acute respiratory distress syndrome [118], and acute myocardial infarction [157].

Accurately predicting outcomes in CO poisoning is difficult as markers of poisoning severity do not appear to predict outcomes. The severity of CO poisoning (measured by COHb level ≤15% without loss of consciousness) did not result in lower rates of neurocognitive sequelae in less severe CO-poisoned patients compared to patients with more severe poisoning (COHb >15% or loss of consciousness) [158]. Other studies have similarly found COHb levels are not related to neurocognitive deficits [139, 148, 159]. Furthermore, COHb levels and loss of consciousness are neither associated with nor predict clinical outcome [148, 160]. Neither symptoms of poisoning, neurocognitive impairment [37, 148], white matter hyperintensities [41], fornix atrophy [139] nor corpus callosum atrophy [42] is related to CO poisoning severity (e.g., loss of consciousness or COHb level).

CO Summary

Carbon monoxide poisoning may result in significant neurocognitive and neuropsychiatric sequelae which persist 12 months or more post-CO poisoning. Patients with neurocognitive sequelae have a higher rate of depression and anxiety at 6 weeks compared to those with no neurocognitive sequelae, but not at 12 months. Patients with intentional CO poisoning have a higher rate of depression and anxiety at 6 weeks compared to accidental CO-poisoned patients, but not at 6 and 12 months for those with intentional vs. accidental CO poisoning. Hyperbaric oxygen therapy did not reduce the rate of depression and anxiety, but does reduce neurocognitive sequelae. Clinicians need to be aware of neurocognitive and neuropsychiatric morbidity following CO poisoning and remain vigilant about CO prevention.

Obstructive Sleep Apnea

As many as 18 million Americans suffer from obstructive sleep apnea (OSA). Obstructive sleep apnea is more common among men and individuals who snore, are overweight, have high blood pressure, or have physical abnormalities in their upper airways [161, 162]. The incidence of obstructive sleep apnea in this patient population is greater than 70% and increases in incidence as the body mass index increases [163]. Obstructive sleep apnea is a sleep disorder that results in the absence (apnea) or reduction (hypopnea) of airflow lasting at least 10 s despite normal respiratory efforts [164, 165]. Apnea and hypopnea result in hypoxemia and disrupt or fragment the sleep cycle. OSA affects an estimated 2–4% of the middle-aged population and the prevalence increases with age [166, 167]. Common symptoms include excessive daytime sleepiness (EDS), snoring, gasping or choking during sleep, headaches (especially upon waking), irritability, mood disturbance, personality change, motor restlessness, and neurocognitive complaints [168, 169]. OSA is associated with development of pulmonary hypertension, cardiovascular and cerebrovascular disease, hypertension, arrhythmias, and hormonal abnormalities in adults [170–172]. Although OSA is associated with medical morbidity such as cardiovascular disease, its most functionally disruptive effects in adults appear to be neurocognitive and neuropsychiatric in nature [173].

Neurocognitive Morbidity

Patients with OSA may exhibit impairments in vigilance, attention, memory, general intellectual functioning, problem solving [174], executive dysfunction, visuospatial abilities [175], and psychomotor speed [174, 176]. Impairments in memory and attention are the most commonly reported [174]. The neurocognitive and neuropsychiatric morbidities associated with OSA are associated with both intermittent hypoxia and sleep fragmentation [176–178]. Further, neurocognitive impairments appear to be exacerbated by the severity and duration of hypoxemia [176, 179], higher apnea hypopnea index scores [180], and sleep arousals [180]. There is continued discussion regarding which of the above aspects of OSA are associated with neurocognitive impairments. Previous research has reported both improvement [181] and no change in cognitive function following nCPAP [182].

A study comparing neuroimaging and neuropsychological findings in 14 patients with OSA and 20 CO-poisoned patients found hippocampal and generalized atrophy and neuropsychological impairments in CO poisoning and OSA [144]. Hippocampal atrophy occurred in both groups; however, increased VBR due to generalized cerebral atrophy (i.e., whole brain volume loss) was greater in the CO group [144]. The groups may differ due to moderation of tissue damage from intermittent hypoxia observed on OSA instead of a single episode of longer duration as occurs in CO poisoning. Therefore, the duration of hypoxia may account for the more severe generalized brain atrophy observed in the CO patients. Alternatively, the long-term effects of chronic intermittent hypoxia, such as occurs in OSA, may result in cerebral vascular problems, neurodegeneration, and neurocognitive deficits due to the cumulative effects of the hypoxia [183]. The CO group consistently performed worse on most neurocognitive measures while the OSA group had more selective neurocognitive impairments (predominately executive dysfunction and impaired

memory). Improvement in neurocognitive function in OSA patients following 6 months of nasal continuous positive airway pressure (nCPAP) treatment was limited to executive function. Differences in test performance between the CO and OSA groups were more pronounced after the OSA group had received 6 months of nCPAP treatment [144]. Previous research has suggested that the hippocampus is more vulnerable to hypoxic injury than adjacent structures such as the parahippocampal gyrus or temporal lobes [44]. Alternatively, injury to the prefrontal cortex, rather than medial temporal lobe structures may be responsible for the neurocognitive and neuropsychiatric morbidity associated with OSA [173].

Neuropsychiatric Morbidity

Neuropsychiatric morbidity including depression and anxiety are common in patients with OSA [177, 164]. The prevalence of depression is 24% [184] to as high as 45% of individual with OSA [185]. Depression is associated with fatigue, feeling tired, sleepiness, and reduced motivation in OSA patients [186]. A study that assessed the prevalence of neuropsychiatric disorders in 171 patients with sleep disorders (83% with OSA) found that 11% of patients had major depression, 7% minor depression, 3% panic disorder, and 12% anxiety [187]. The rate of depression and anxiety in OSA is higher than population norms [188]. Gender differences in neuropsychiatric disorders appear to be more common in women than men with OSA, similar to that observed in the general population. While the prevalence of OSA is higher in men, McCall et al. [189] found women with OSA had more common and more severe symptoms of depression and milder hypoxemia was associated with worse depression [189]. Nasal CPAP does not appear to improve depression or anxiety [190]. However, one study noted some improvement after long-term nCPAP therapy (approximately 1 year) [191]. In addition uvulopalatal flap surgery improved depression and anxiety in OSA patients [188].

OSA Summary

The neurocognitive and neuropsychiatric impairments are common in individuals with OSA with intermittent hypoxia. The neurocognitive and neuropsychiatric sequelae are similar to those observed in CO poisoning and other pulmonary disorders and are associated with acute hypoxia. Research is needed to determine mechanisms, risk factors, and treatment for OSA-associated neuropsychiatric morbidity.

Rehabilitation Outcomes Following Anoxia

Outcome following severe anoxia is variable, however, the majority of patients have poor outcome [3]. Information regarding the effects of rehabilitation on neurocognitive outcome following anoxic brain injury is limited. Survival rates following post-anoxic coma range from 9 to 40% [192, 193]. Patients who survived anoxic coma regain mobility and ability to perform activities of daily living but not neurocognitive [194]. Outcome following anoxic coma was not predicted by age, sex, site of resuscitation, cause of anoxia, nor presence of post-anoxic seizures [193]. A single case suggested that "relatively" good neurocognitive function 1 month post-anoxic coma suggesting some recovery and benefit of rehabilitation [194]; however, this finding is not generally reported.

Groswasser et al. [195] followed a group of 31 comatose patients following anoxic brain injury, 13 were independent in activities of daily living, 2 regained premorbid neurocognitive functioning, and 4 returned to work, but only 1 to the same job. Patients who were younger with shorter coma had "relatively better outcomes". The differences in recovery may be due to the interaction of the diffuse damage and delayed cell death, but not the etiology of the anoxic brain injury. Armengol [195] reported eight individuals with severe anoxia who were treated in a long-term neurobehavioral rehabilitation program. Six of the eight individuals had poor outcome with significant impairments in attention, executive function, memory, reasoning, language, visuospatial, and motor skills, while two patients exhibited mild neurocognitive impairments. In-patient rehabilitation appears to improve functional status, with individuals who had higher Functional Independence Measure scores on admission had the best outcome; however, few resumed their previous jobs and level of function [196].

Little is known regarding rehabilitation outcomes in many hypoxic disorders. Further, it is unknown if the severity of hypoxia/hypoxemia is related to rehabilitation outcomes. For example, there are no studies that assess rehabilitation after ARDS. A few studies assess rehabilitation following COPD and OSA. As noted above, pulmonary rehabilitation consisting of exercise, education, and psychosocial counseling improved psychomotor speed and mental flexibility but not memory and concentration in COPD patients [75]. One study found lung volume reduction surgery plus pulmonary rehabilitation (exercise and education) compared to pulmonary rehabilitation alone and found improved neurocognitive and neuropsychiatric function in the lung volume reduction group [197]. It remains to be determined if rehabilitation on neurocognitive and neuropsychiatric morbidity in patients with hypoxia/hypoxemic disorders is effective.

Conclusions

Patients with respiratory disorders and concomitant brain injury exhibit both diffuse and focal brain injury and concomitant neurocognitive and neuropsychiatric sequelae. Respiratory disorders are heterogeneous and include cardiac or respiratory arrest, COPD, CO poisoning, OSA, and ARDS. The associated hypoxic or anoxic brain injury results in focal and diffuse neuropathologic lesions and atrophy including hippocampal, basal ganglia, cerebellar, and white matter abnormalities. Neuropsychological impairments include generalized intellectual decline, memory deficits, decreased attention, visuo-perceptual, problem solving, executive dysfunction, and decreased mental processing speed. Further, these individual may experience a high rate of neurobehavioral disorders including euphoria, irritability, hostility, depression, and anxiety and personality changes. Thus, respiratory disorders and their associated hypoxia and ischemia result in significant neurological structural and functional abnormalities, and neuropsychological impairments.

Questions remain regarding risk factors for development of neurocognitive and neuropsychiatric sequelae, precise mechanisms of brain injury, and whether there are treatments that will prevent or ameliorate these sequelae. Further, physicians and other health-care providers often are unaware and do not assess for the presence of neurocognitive impairments. A recent study found 42% of ARDS survivors underwent rehabilitation therapy, but most were not evaluated for neurocognitive impairments, with only 12% identified as having neurocognitive impairments by the clinical rehabilitation team [100]. Neurocognitive impairments appear to be under recognized by both intensivists and rehabilitation providers. Studies suggest that in non-critical care clinical settings many physicians fail to recognize (or assess) neurocognitive impairment in 35–90% of patients [198]. Increased identification of neurocognitive impairments patients with respiratory disorders may benefit patients by raising physician awareness potentially leading to increased referrals to rehabilitation specialists, neuropsychologists, speech and language therapists, and other health-care providers who can provide interventions such as cognitive remediation. It should be noted that there is a paucity of data regarding interventions for neurocognitive impairments or the potential benefit of such interventions in critically ill patients.

Today, it is recognized that neurocognitive sequelae are common in patients with respiratory disorders, especially those with concomitant hypoxia. The neurocognitive impairments are long lasting, and may be permanent, although substantial research needs to be done to fully understand the prevalence, nature, risk factors, etiology, and nuances of the neurocognitive and neuropsychiatric impairments in this population. Referrals to colleagues in rehabilitation medicine, psychiatric, neurology, or psychology would facilitate evaluation of potential areas of concern. Attention to proximal determinants and possible interventions to prevent neurocognitive morbidity are warranted and should be an emphasis in outcomes research. Such research will likely yield valuable insights into identification, the natural history, prognosis, and potential mechanisms of the neurocognitive deficits and guide the development, implementation, and fine-tuning of intervention programs.

References

1. Geocadin RG, Buitrago MM, Torbey MT, et al. Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. Neurology. 2006;67:105–08.

2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation. 2001;104:2158–63.
3. Bachman D, Katz DI. Anoxic-hypotensive brain injury and encephalitis. In: Mills VM, Cassidy JW, Katz DI, editors. Neurologic rehabilitation: a guide to diagnosis, prognosis, and treatment planning. Malden, MA: Blackwell Science Ltd; 1997. pp. 145–76.
4. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. J Int Neuropsychol Soc. 1995;1:501–09.
5. Johnson SC, Bigler ED, Burr RB, Blatter DD. White matter atrophy, ventricular dilation, and intellectual functioning following traumatic brain injury. Neuropsychology. 1994;8:307–15.
6. Bigler ED, Alfano M. Anoxic encephalopathy: neuroradiological and neuropsychological findings. Arch Clini Neuropsychol. 1988;3:383–96.
7. Hopkins RO, Kesner RP, Goldstein M. Item and order recognition memory in subjects with hypoxic brain injury. Brain Cogn. 1995;27:180–201.
8. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 1986;6:2950–67.
9. Lezak MD. Neuropsychological assessment. 3rd ed. New York, NY: Oxford University Press; 1995.
10. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. J Int Neuropsychol Soc. 1995;1:501–09.
11. Farah M. Visual agnosia. Cambridge, MA: MIT Press; 1990.
12. Barat M, Blanchard J, Carriet D. Les troubles neuropsychologiques des anozies cerebrales prolongees. Ann Readapt Med Phys. 1989;32:657–68.
13. Parkin AJ, Miller J, Vincent R. Multiple neuropsychological deficits due to anoxic encephalopathy: a case study. Cortex. 1987;23:655–65.
14. Wilson BA. Cognitive functioning of adult survivors of cerebral hypoxia. Brain Inj. 1996;10:863–74.
15. Ganong WF. Review of medical physiology. 10th ed. Los Altos, CA: Lange Medical Publications; 1981.
16. Hicks SP. Vascular pathophysiology and acute and chronic oxygen deprivation. In: Minckler J, editor. Pathology of the nervous system, vol 1. New York, NY: McGraw-Hill; 1968. pp. 341–50.
17. Biagas K. Hypoxic-ischemic brain injury: advancements in the understanding of mechanisms and potential avenues for therapy. Curr Opin Pediatr. 1999;11:223–8.
18. Kuroiwa T, Okeda R. Neuropathology of cerebral ischemia and hypoxia: recent advances in experimental studies on its pathogenesis. Pathol Int. 1994;44: 171–81.
19. Brierley JB, Graham DI. Cerebral complications of hypotensive anaesthesia in a healthy adult. J Neurol Neurosurg Psychiatr. 1984;25:24–30.
20. Blennow M, Ingvar M, Lagercrantz H, et al. Early [18F] FDG positron emission tomography in infants with hypoxic-ischaemic encephalopathy shows hypermetabolism during the postasphyctic period. Acta Paediatr. 1995;84:1289–95.
21. Martin RL, Lloyd HG, Cowan AI. The early events of oxygen and glucose deprivation: setting the scene for neuronal death? Trends Neurosci. 1994;17:251–7.
22. Siesjo BK, Bengtsson F, Grampp W, Theander S. Calcium, excitotoxins, and neuronal death in the brain. Ann N Y Acad Sci. 1989;568:234–51.
23. Chalela JA, Wolf RL, Maldjian JA, Kasner SE. MRI identification of early white matter injury in anoxic-ischemic encephalopathy. Neurology. 2001;56:481–5.
24. Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience. 1991;40:599–636.
25. Schurr A, Rigor BM. The mechanism of cerebral hypoxic-ischemic damage. Hippocampus. 1992;2:221–8.
26. Johnston MV, Nakajima W, Hagberg H. Mechanisms of hypoxic neurodegeneration in the developing brain. Neuroscientist. 2002;8:212–20.
27. Lutz PL, Nilsson GE. The brain without oxygen causes of failure and mechanisms for survival. Austin, TX: R.G. Landes Company; 1994.
28. Siesjo BK. Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab. 1981;1:155–85.
29. Schurr A, Lipton P, West CA, Rigor BM. The role of energy in metabolism and divalent cations in the neurotoxicity of excitatory amino acids in vitro. In: Krieglstein J, editor. Pharmacology of cerebral ischemia. Boca Raton, FL: CRC Press; 1990. pp. 217–26.
30. Steller H. Mechanisms and genes of cellular suicide. Science. 1995;267:1445–9.
31. Beilharz EJ, Williams CE, Dragunow M, et al. Mechanisms of delayed cell death following hypoxic-ischemic injury in the immature rat: evidence for apoptosis during selective neuronal loss. Brain Res Mol Brain Res. 1995;29:1–14.
32. Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia, and brain necrosis. Neurology. 2000;54:362–71.
33. Gray FD Jr., Horner GJ. Survival following extreme hypoxemia. J Am Med Assoc. 1970;211:1815–17.
34. Rie MA, Bernad PG. Prolonged hypoxia in man without circulatory compromise fail to demonstrate cerebral pathology. Neurology. 1980;30:433.
35. Bachevalier J, Meunier M. Cerebral ischemia: are the memory deficits associated with hippocampal cell loss? Hippocampus. 1996;6:553–60.
36. Caine D, Watson JD. Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J Int Neuropsychol Soc. 2000;6:86–99.
37. Gale SD, Hopkins RO, Weaver LK, et al. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj. 1999;13:229–43.
38. Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. Neuron. 2003;38:127–33.
39. Manns JR, Hopkins RO, Reed JM, et al. Recognition memory and the human hippocampus. Neuron. 2003;37:171–80.
40. Mascalchi M, Petruzzi P, Zampa V. MRI of cerebellar white matter damage due to carbon monoxide poisoning: case report. Neuroradiology. 1996;38:S.

41. Parkinson RB, Hopkins RO, Cleavinger HB, et al. White matter hyperintensities and neuropsychological outcome following carbon monoxide poisoning. Neurology. 2002;58:1525–32.
42. Porter SS, Hopkins RO, Weaver LK, et al. Corpus callosum atrophy and neuropsychological outcome following carbon monoxide poisoning. Arch Clin Neuropsychol. 2002;17:195–204.
43. Press GA, Amaral DG, Squire LR. Hippocampal abnormalities in amnesic patients revealed by high-resolution magnetic resonance imaging. Nature. 1989;341: 54–7.
44. Hopkins RO, Tate DF, Bigler ED. Anoxic versus traumatic brain injury: amount of tissue loss, not etiology, alters cognitive and emotional function. Neuropsychology. 2005;19:233–42.
45. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1:480–4.
46. Hopkins RO, Myers CE, Shohamy D, et al. Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. Neuropsychologia. 2004;42: 524–35.
47. Lishman WA. Organic psychiatry: the psychological consequences of cerebral disorder. 3rd ed. Oxford: Blackwell Science Ltd.; 1998.
48. Bahrke MS, Schukitt-Hale B. Effects of altitude on mood, behaviour, and cognitive functioning. A review. J Sports Med. 1993;16:97–125.
49. Li XY, Wu XY, Fu C, et al. Effects of acute mild and moderate hypoxia on human mood state. Space Med Med Eng (Beijing). 2000;13:1–5.
50. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2007;4:502–06.
51. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970–2002. J Am Med Assoc. 2005;294:1255–9.
52. Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? Chest. 2003;123:1684–92.
53. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370:741–50.
54. Tirimanna PR, van Schayck CP, den Otter JJ, et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract. 1996;46:277–81.
55. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest. 2002;121:121S–6S.
56. Leidy NK. Functional performance in people with chronic obstructive pulmonary disease. Image J Nurs Sch. 1995;27:23–34.
57. Hodgkin JE, Petty TL. Chronic obstructive pulmonary disease: current concepts. Philadelphia, PA: W.B. Saunders Company; 1987.
58. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85:751–8.
59. Prigatano GP, Parsons O, Wright E, et al. Neuropsychological test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease. J Consult Clin Psychol. 1983;51:108–16.
60. Prigatano GP, Wright EC, Levin D. Quality of life and its predictors in patients with mild hypoxemia and chronic obstructive pulmonary disease. Arch Intern Med. 1984;144:1613–19.
61. Grant I, Heaton R, McSweeny A, et al. Neuropsychological findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1982;142:1470–6.
62. Heaton RK, Grant I, McSweeny AJ, et al. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1983;143:1941–47.
63. Kozora E, Filley CM, Julian LJ, Cullum CM. 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. 1999;12:178–83.
64. Fix AJ, Golden CJ, Daughton D, et al. Neuropsychological deficits among patients with chronic obstructive pulmonary disease. Int J Neurosci. 1982;16:99–105.
65. Krop HD, Block AJ, Cohen E. Neuropsychologic effects of continuous oxygen therapy in chronic obstructive pulmonary disease. Chest. 1973;64:317–22.
66. Incalzi RA, Gemma A, Marra C, et al. Chronic obstructive pulmonary disease. An original model of cognitive decline. Am Rev Respir Dis. 1993;148:418–24.
67. Etnier J, Johnston R, Dagenbach D, et al. The relationships among pulmonary function, aerobic fitness, and cognitive functioning in older COPD patients. Chest. 1999;116:953–60.
68. Grant I, Prigatano GP, Heaton RK, et al. Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. Arch Gen Psychiatry. 1987;44:999–1006.
69. Incalzi RA, Gemma A, Marra C, et al. Verbal memory impairment in COPD: its mechanisms and clinical relevance. Chest. 1997;112:1506–13.
70. Kozora E, Emery C, Kaplan RM, et al. Cognitive and psychological issues in emphysema. Proc Am Thorac Soc. 2008;5:556–60.
71. Wilson DK, Kaplan RM, Timms RM, Dawson A. Acute effects of oxygen treatment upon information processing in hypoxemic COPD patients. Chest. 1985;88:239–43.
72. Orth M, Kotterba S, Duchna K, et al. [Cognitive deficits in patients with chronic obstructive pulmonary disease (COPD)]. Pneumologie. 2006;60:593–9.
73. Carter R, Nicotra B, Clark L, et al. Exercise conditioning in the rehabilitation of patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 1988;69:118–22.
74. Dustman RE, Ruhling RO, Russell EM, et al. Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiol Aging. 1984;5:35–42.
75. Emery CF, Leatherman NE, Burker EJ, MacIntyre NR. Psychological outcomes of a pulmonary rehabilitation program. Chest. 1991;100:613–7.

76. Kaptein AA, Brand PL, Dekker FW, et al. Quality-of-life in a long-term multicentre trial in chronic nonspecific lung disease: assessment at baseline. The Dutch CNSLD Study Group. Eur Respir J. 1993;6:1479–84.
77. Graydon J, Ross E. Patients with chronic respiratory disease: what influences level of functioning? Proceedings of the 12th work group meeting and international nursing research conference. Frankfurt, Germany: WENR; 1989. pp. 276–80.
78. Salik Y, Ozalevli S, Cimrin AH. Cognitive function and its effects on the quality of life status in the patients with chronic obstructive pulmonary disease (COPD). Arch Gerontol Geriatr. 2007;45:273–80.
79. Cully JA, Graham DP, Stanley MA, et al. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. Psychosomatics. 2006;47:312–9.
80. Hynninen KM, Breitve MH, Wiborg AB, et al. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. J Psychosom Res. 2005;59:429–43.
81. Gift AG, McCrone SH. Depression in patients with COPD. Heart Lung. 1993;22:289–97.
82. Porzelius J, Vest M, Nochomovitz M. Respiratory function, cognitions, and panic in chronic obstructive pulmonary patients. Behav Res Ther. 1992;30:75–7.
83. Gift AG, Cahill CA. Psychophysiologic aspects of dyspnea in chronic obstructive pulmonary disease: a pilot study. Heart Lung. 1990;19:252–7.
84. McSweeney AJ, Heaton RK, Grant I, et al. Chronic obstructive pulmonary disease; socioemotional adjustment and life quality. Chest. 1980;77:309–11.
85. Lahdensuo A, Ojanen M, Ahonen A, et al. Psychosocial effects of continuous oxygen therapy in hypoxaemic chronic obstructive pulmonary disease patients. Eur Respir J. 1989;2:977–80.
86. Borak J, Sliwinski P, Piasecki Z, Zielinski J. Psychological status of COPD patients on long term oxygen therapy. Eur Respir J. 1991;4:59–62.
87. Vögele C, von Leupoldt A. Mental disorders in chronic obstructive pulmonary disease (COPD). Respir Med. 2008;102:764–73.
88. Rubenfeld GD, Doyle RL, Matthay MA. Evaluation of definitions of ARDS. Am J Respir Crit Care Med. 1995;151:1270–1.
89. Rubenfeld GD. Epidemiology of acute lung injury. Crit Care Med. 2003;31:S276–84.
90. Abel SJ, Finney SJ, Brett SJ, et al. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). Thorax. 1998;53:292–4.
91. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS):1983–1993. J Am Med Assoc. 1995;273:306–09.
92. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–08.
93. Petty TL, Ashbaugh DG. The adult respiratory distress syndrome: clinical features and factors influencing prognosis and principles of management. Chest. 1971;60:233–9.
94. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. J Crit Care. 1994;9:72–81.
95. Davidson TA, Caldwell ES, Curtis JR, et al. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. J Am Med Assoc. 1999;281:354–60.
96. Hopkins RO, Weaver LK, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160: 50–6.
97. Weinert CR, Gross CR, Kangas JR, et al. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med. 1997;156:1120–8.
98. Russell JA, Singer J, Bernard GR, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. Crit Care Med. 2000;28:3405–11.
99. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. Brain Inj. 2006;20:263–71.
100. Hopkins RO, Weaver LK, Collingridge D, et al. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171:340–7.
101. Graham DI, Gennarelli TA, McIntosh TK. Trauma. In: Graham DI, Lantos PI, editors. Greenfield's neuropathology, vol 2. 7th ed. London: Edward Arnold; Hodder Headline Group; 2002. pp. 823–82.
102. Fries M, Dembinski R, Bickenbach J, et al. Brain damage in a porcine model of acute lung injury. Am J Respir Crit Care Med. 2004;169:A350.
103. Hopkins RO, Suchyta MR, Jephson A, et al. Hyperglycemia and neurocognitive outcome in ARDS survivors. Proc Am Thorac Soc. 2005;Abstracts 2:A36.
104. Jackson JC, Gordon SM, Hart RP, et al. The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol Rev. 2004;14:87–98.
105. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. J Int Neuropsychol Soc. 2004;10:1005–17.
106. Starr JL, Whalley LJ. Drug induced dementia. Drug Saf. 1994;11:310–17.
107. Hopkins RO, Jackson JC, Wallace CJ. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation. International Neuropsychological Society, 33rd Annual Meeting Program and Abstract Book. St. Louis, MO, 2005:61.
108. Al-Saidi F, McAndrews MP, Cheung AM, et al. Neuropsychological sequelae in ARDS survivors. Am J Respir Crit Care Med. 2003;167:A737.
109. Rothenhäusler HB, Ehrentraut S, Stoll C, et al. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen Hosp Psychiatry. 2001;23:90–6.

110. Suchyta MR, Hopkins RO, White J, et al. The incidence of cognitive dysfunction after ARDS. Am J Respir Crit Care Med. 2004;169:A18.
111. Marquis K, Curtis J, Caldwell E, et al. Neuropsychological sequelae in survivors of ARDS compared with critically ill control patients. Am J Respir Crit Care Med. 2000;161:A383.
112. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31:1226–34.
113. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002;347:1057–67.
114. Newman M, Kirchner J, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001; 344:395–402.
115. McCartney JR, Boland RJ. Anxiety and delirium in the intensive care unit. Crit Care Clin. 1994;10:673–80.
116. Skodol AE. Anxiety in the medically ill: nosology and principles of differential diagnosis. Semin Clin Neuropsychiatry. 1999;4:64–71.
117. Szokol JW, Vender JS. Anxiety, delirium, and pain in the intensive care unit. Crit Care Clin. 2001;17:821–42.
118. Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163:1389–94.
119. Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med. 2003;168:1457–61.
120. Weinert CR, Gross CR, Kangas JR, et al. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med. 1997;156:1120–8.
121. Granja C, Teixeira-Pinto A, Costa-Pereira A. Quality of life after intensive care – evaluation with EQ-5D questionnaire. Intensive Care Med. 2002;28:898–907.
122. Kapfhammer HP, Rothenhäusler HB, Krauseneck T, et al. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. Am J Psychiatry. 2004;161:45–52.
123. Gersons BP, Carlier IV. Post-traumatic stress disorder: the history of a recent concept. Br J Psychiatry. 1992;161:742–8.
124. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med. 1998;26:651–9.
125. Stoll C, Kapfhammer HP, Rothenhäusler HB, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose posttraumatic stress disorder in ARDS patients after intensive care treatment. Intensive Care Med. 1999;25: 697–704.
126. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001;29:573–80.
127. Weaver LK. Carbon monoxide poisoning. Crit Care Clin. 1999;15:297–317.
128. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning – a public health perspective. Toxicology. 2000;145:1–14.
129. Hampson NB, editor. Hyperbaric oxygen therapy: 1999 committee report revised. Kensington, MD: Undersea and Hyperbaric Medical Society; 1999.
130. Piantadosi CA. Carbon monoxide poisoning. N Engl J Med. 2002;347:1054–5.
131. Uchino A, Hasuo K, Shida K, et al. MRI of the brain in chronic carbon monoxide poisoning. Neuroradiology. 1994;36:399–401.
132. Bruno A, Wagner W, Orrison WW. Clinical outcome and brain MRI four years after carbon monoxide intoxication. Acta Neurol Scand. 1993;87:205–09.
133. Chang KH, Han MH, Kim HS, et al. Delayed encephalopathy after acute carbon monoxide intoxication: MR imaging features and distribution of cerebral white matter lesions. Radiology. 1992;184:117–22.
134. Kawanami T, Kato T, Kurita K, Sasaki H. The pallidoreticular pattern of brain damage on MRI in a patient with carbon monoxide poisoning. J Neurol Neurosurg Psychiatr. 1998;64:282.
135. Watanabe N, Nohara S, Matsuda H, et al. Statistical parametric mapping in brain single photon computed emission tomography after carbon monoxide intoxication. Nucl Med Commun. 2002;23:355–66.
136. Mori E, Yamashita H, Takauchi S, Kondo K. Isolated athymhormia following hypoxic bilateral pallidal lesions. Behav Neurol. 1996;9:17–23.
137. Martinez Bermejo A, Arcas J, Roche MC, et al. [Bilateral hypodensity of the basal ganglia. Clinico-evolutionary correlation in children]. Rev Neurol. 2001;33: 101–11.
138. Hsiao CL, Kuo HC, Huang CC. Delayed encephalopathy after carbon monoxide intoxication – long-term prognosis and correlation of clinical manifestations and neuroimages. Acta Neurol Taiwan. 2004;13:64–70.
139. Kesler SR, Hopkins RO, Weaver LK, et al. Verbal memory deficits associated with fornix atrophy in carbon monoxide poisoning. J Int Neuropsychol Soc. 2001;7:640–6.
140. Pulsipher DT, Hopkins RO, Weaver LK. Basal ganglia volumes following carbon monoxide poisoning: a prospective longitudinal study. Undersea Hyperb Med. 2006;33:245–56.
141. Myers RA, DeFazio A, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol. 1998;54:555–67.
142. Hopkins RO, Woon FL. Neuroimaging, cognitive, and neurobehavioral outcomes following carbon monoxide poisoning. Behav Cogn Neurosci Rev. 2006;5: 141–55.
143. Hopkins RO, Weaver LK, Kesner RP. Long term memory impairments and hippocampal magnetic resonance imaging in carbon monoxide poisoned subjects. Undersea Hyperb Med. 1993;20:15.
144. Gale SD, Hopkins RO. Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. J Int Neuropsychol Soc. 2004;10:60–71.
145. Garland H, Pearce J. Neurological complications of carbon monoxide poisoning. Q J Med. 1967;36:445–55.

146. Min SK. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide intoxication. Acta Psychiatr Scand. 1986;73:80–6.
147. Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet. 1989;2:414–9.
148. Thom SR, Taber RL, Mendiguren II, et al. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann Emerg Med. 1995;25:474–80.
149. Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. Anaesth Intensive Care. 1992;20:311–6.
150. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med. 2007;176:491–7.
151. Jasper BW, Hopkins RO, Duker HV, Weaver LK. Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. Cogn Behav Neurol. 2005;18:127–34.
152. Lee MS, Marsden CD. Neurological sequelae following carbon monoxide poisoning clinical course and outcome according to the clinical types and brain computed tomography scan findings. Mov Disord. 1994;9:550–8.
153. Hopkins RO, Weaver LK, Bigler ED. Psychological/emotional changes following carbon monoxide poisoning. Undersea Hyperb Med. 1997;24:20.
154. Smith JS, Brandon S. Morbidity from acute carbon monoxide poisoning at three-year follow-up. Br Med J. 1973;1:318–21.
155. Fleminger S, Oliver DL, Williams WH, Evans J. The neuropsychiatry of depression after brain injury. Neuropsychol Rehabil. 2003;13:65–87.
156. Bornson S, Claypoole K, McDonald GJ. Depression and chronic obstructive pulmonary disease: treatment trials. Semin Clin Neuropsychiatry. 1998;3:115–30.
157. Schleifer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. Arch Intern Med. 1989;149:1785–89.
158. Chambers CA, Hopkins RO, Weaver LK, Key C. Cognitive and affective outcomes of more severe compared to less severe carbon monoxide poisoning. Brain Inj. 2008;22:387–95.
159. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomized controlled clinical trial. Med J Aust. 1999;170:203–10.
160. Camporesi EM. Hyperbaric oxygen therapy: a committee report. Bethesda, MD: Undersea and Hyperbaric Medical Society; 1996.
161. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165:1217–39.
162. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162:893–900.
163. Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation: more evidence for routine screening for obstructive sleep apnea before weight loss surgery. Am Surg. 2008;74:834–8.
164. Guilleminault C, Cummiskey J, Motta J, Lynne-Davies P. Respiratory and hemodynamic study during wakefulness and sleep in myotonic dystrophy. Sleep. 1978;1:19–31.
165. Kelly DA, Claypoole KH, Coppel DB. Sleep apnea syndrome: symptomatology, associated features, and neurocognitive correlates. Neuropsychol Rev. 1990;1:323–42.
166. Bliwise DL, King AC, Harris RB. Habitual sleep durations and health in a 50–65 year old population. J Clin Epidemiol. 1994;47:35–41.
167. Young S, Geelhoed GC, Stick SM, et al. The effect of age on oxygen desaturation during histamine inhalation challenge in normal infants. Pediatr Pulmonol. 1993;16:158–62.
168. Agency for Health Care Policy and Research. Systematic review of the literature regarding the diagnosis of sleep apnea. Summary, Evidence Report/Technology Assessment: Number 1. Rockville, MD, 1998
169. Guilleminault C, van den Hoed J, Mitler MM. Clinical overview of the sleep apnea syndromes. In: Guilleminault C, Dement WC, editors. Sleep apnea syndromes. New York, NY: Alan R. Liss; 1978. pp. 1–12.
170. Harding SM. Complications and consequences of obstructive sleep apnea. Curr Opin Pulm Med. 2000;6:485–9.
171. Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. 2002;165:677–82.
172. Doran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001;163:685–9.
173. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11:1–16.
174. Findley LJ, Barth JT, Powers DC, et al. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest. 1986;90:686–90.
175. Kales A, Caldwell A, Cadieux R, et al. Severe obstructive sleep apnea-II: associated psychopathology and psychosocial consequences. J Chronic Dis. 1985;38:427–34.
176. Bedard MA, Montplaisir J, Richer F, et al. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol. 1991;13:950–64.
177. Barth JT, Findley LJ, Zillmer EA, et al. Obstructive sleep apnea, hypoxemia, and personality functioning: implications for medical psychotherapy assessment. Adv Med Psychother. 1993;6:29–36.
178. Valencia-Flores M, Bliwise DL, Guilleminault C, et al. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. J Clin Exp Neuropsychol. 1996;18:197–210.
179. Naegele B, Thouvard V, Pepin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep. 1995;18:43–52.

180. Cheshire K, Engleman H, Deary I, et al. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med. 1992;152:538–41.
181. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax. 1997;52:114–9.
182. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. Ann Intern Med. 2001;134:1015–23.
183. Neubauer JA. Invited review: physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol. 2001;90:1593–9.
184. Guilleminault C, Eldridge FL, Tilkian A, et al. Sleep apnea syndrome due to upper airway obstruction: a review of 25 cases. Arch Intern Med. 1977;137:296–300.
185. Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. J Clin Psychiatry. 1989;50:348–51.
186. Schwartz DJ, Karatinos G. For individuals with obstructive sleep apnea, institution of CPAP therapy is associated with an amelioration of symptoms of depression which is sustained long term. J Clin Sleep Med. 2007;3:631–5.
187. DeZee KJ, Hatzigeorgiou C, Kristo D, Jackson JL. Prevalence of and screening for mental disorders in a sleep clinic. J Clin Sleep Med. 2005;1:136–42.
188. Li HY, Huang YS, Chen NH, et al. Mood improvement after surgery for obstructive sleep apnea. Laryngoscope. 2004;114:1098–102.
189. McCall WV, Harding D, O'Donovan C. Correlates of depressive symptoms in patients with obstructive sleep apnea. J Clin Sleep Med. 2006;2:424–6.
190. Borak J, Cieslicki JK, Koziej M, et al. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. J Sleep Res. 1996;5:123–7.
191. Ramos Platon MJ, Espinar Sierra J. Changes in psychopathological symptoms in sleep apnea patients after treatment with nasal continuous positive airway pressure. Int J Neurosci. 1992;62:173–95.
192. Bedell SE, Delbanco TL, Cook EF, Epstein FH. Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med. 1983;309:569–76.
193. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. J Am Med Assoc. 1985;253:1420–6.
194. Kaplan CP. Anoxic-hypotensive brain injury: neuropsychological performance at 1 month as an indicator of recovery. Brain Inj. 1999;13:305–10.
195. Groswasser Z, Cohen M, Costeff H. Rehabilitation outcome after anoxic brain damage. Arch Phys Med Rehabil. 1989;70:186–8.
196. Schmidt JG, Drew-Cates J, Dombovy ML. Anoxic encephalopathy: outcome after inpatient rehabilitation. Neurorehabil Neural Repair. 1997;11:189–95.
197. Kozora E, Emery CF, Ellison MC, et al. Improved neurobehavioral functioning in emphysema patients following lung volume reduction surgery compared with medical therapy. Chest. 2005;128:2653–63.
198. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. Ann Intern Med. 1995;122:422–9.