Neuropsychiatric Function in Chronic Lung Disease: the Role of Pulmonary Rehabilitation

Charles F Emery PhD, Marquisha R Green MA, and Sooyeon Suh MA

Chronic lung disease is associated with increased psychological distress (especially anxiety and depression) and neuropsychological impairments (primarily in flexible problem-solving and information-sequencing), which decrease quality of life, disease management, and survival. This review summarizes current data regarding the prevalence of neuropsychiatric disorders, the assessment tools commonly used to measure and monitor neuropsychiatric symptoms, the effect of pulmonary rehabilitation on neuropsychiatric symptoms, the mechanisms by which exercise rehabilitation may influence neuropsychiatric functioning, and the clinical implications of the data. *Key words: pulmonary rehabilitation, exercise, chronic lung disease, chronic obstructive pulmonary disease, COPD, anxiety, depression, psychological, problem-solving, information-sequencing, quality of life, neuropsychiatric.* [Respir Care 2008;53(9):1208–1216. © 2008 Daedalus Enterprises]

Introduction

Neuropsychiatric symptoms associated with chronic lung disease include elevated psychiatric distress as well as impairments in neuropsychological functioning. The most prevalent psychiatric disorders in patients with chronic lung disease are depression and anxiety. Neuropsychological dysfunction is generally evident in problem-solving deficits and difficulty with abstract thinking and sequencing tasks. This review summarizes current data regarding

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the prevalence and common symptoms of psychiatric disorders in patients with chronic lung disease, and frequently used assessment tools for measuring and monitoring neuropsychiatric symptoms. We will highlight effects of pulmonary rehabilitation on neuropsychiatric symptoms in patients with chronic lung disease, the mechanisms by which pulmonary rehabilitation may influence neuropsychiatric functioning, and the clinical implications of the extant data. Most of the research has been with patients with chronic obstructive pulmonary disease (COPD); therefore, we will focus primarily on that patient group.

Patients with COPD are more likely than age-matched peers to report symptoms of distress, especially depression and anxiety. In addition, psychological distress in patients with COPD is associated with impaired quality of life and restricted activities of daily living.[1] Furthermore, functional capacity of patients with COPD is more strongly associated with emotional/psychosocial factors (eg, depression, anxiety, somatization, low self-esteem, attitudes toward treatment, social support) than with traditional physiological indicators.[2] Although psychological factors are associated with functional performance, the influence of psychological factors on disease progression and mortality in patients with COPD is still unknown.

Neuropsychological functioning is important to address in patients with COPD, because cognitive deficits may contribute to difficulty monitoring the intensity of their symptoms,[3] reduced adherence to their medications,[4,5] and poor quality of life, as reflected in reduced functional abilities.[6]

Psychiatric Symptoms

Depression

Six percent to 42% of patients with COPD have substantial symptoms of depression or clinical depression.[7-9] Depression in patients with COPD is often marked by feelings of hopelessness and pessimism, reduced sleep, decreased appetite, increased lethargy, concentration difficulty, and social withdrawal (Fig. 1).[10] Depression is associated with impairment in functional abilities and performing activities of daily living,[2,11-13] poorer self-reported health,[14] impaired self-management of disease exacerbations, and poor health behaviors.[15-17] The correlation between depressed mood and disease severity is modest,[18] but depression symptoms are important correlates of perceived functioning, and subclinical depression symptoms are associated with greater self-reported physical disability and poorer quality of life.[19]

Anxiety

Recent estimates indicate a prevalence of anxiety disorders ranging from 2% to over 50% in patients with COPD.[7,9,11,16] Anxiety is associated with reduced functional ability and rehospitalization in patients with chronic lung disease.[11,20] Symptoms of anxiety are manifested in a variety of ways, including physiological signs of arousal, such as tachycardia, sweating, and dyspnea.[21] Symptoms of anxiety may overlap with symptoms of depression (see Fig. 1). A substantial proportion (up to 41%) of patients with COPD may experience panic attacks, characterized by bouts of intense anxiety, physiological arousal, temporary cognitive impairment, and a strong desire to flee the situation.[16,22] Interestingly, although patients with panic report more catastrophic misinterpretations of bodily symptoms, they do not differ from patients without panic on measures of physical functioning, disease severity, shortness of breath, or psychological distress. Thus, it has been suggested that panic symptoms may reflect a cognitive interpretation of pulmonary symptoms rather than objective pulmonary status.[22]

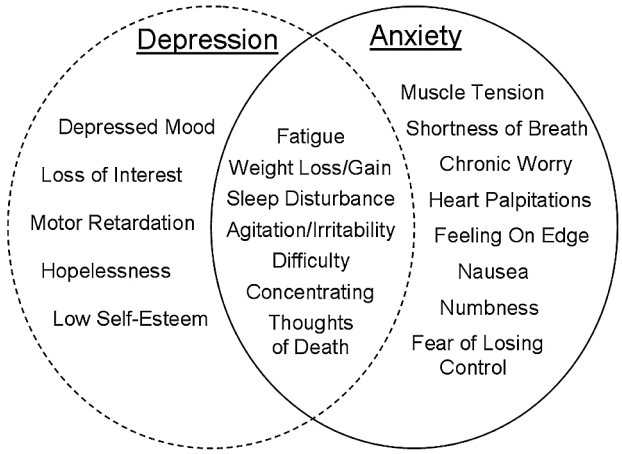

Fig. 1. Common symptoms of depression (dashed circle) and anxiety (solid circle) in patients with chronic obstructive pulmonary disease.

Fluctuation of pulmonary symptoms associated with daily stressors does not appear to be influenced by anxiety symptoms per se.[23] However, symptoms of panic disorder may distract patients from self-management of disease exacerbations.[16] The small number of published studies on this subject is confounded by differences in the measurement of anxiety.

Neuropsychological Functioning

In patients with COPD, mild neuropsychological deficits have been observed that cannot be explained by normal aging.[24] Cognitive impairment, in turn, is associated with mortality and may compromise medical and surgical management in patients with COPD (Fig. 2).[4,25] However, there is debate regarding the nature of the deficits and the

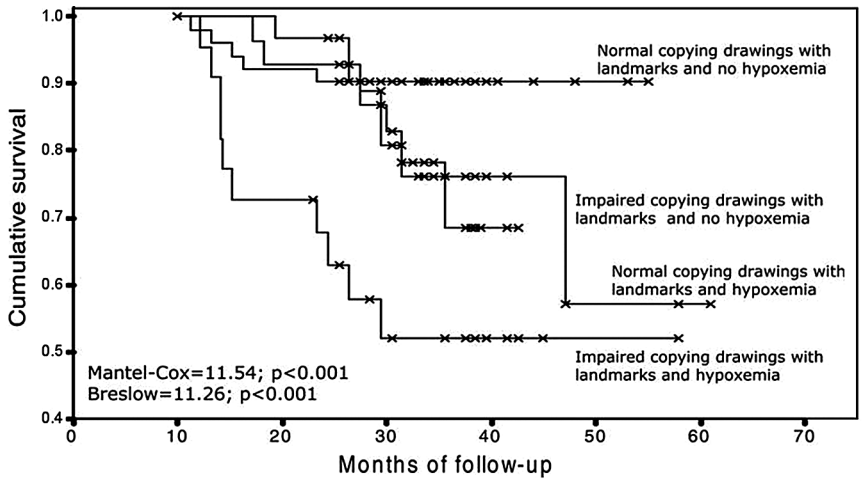

Fig. 2. Cumulative survival in patients grouped according to the absence or presence of a combined abnormal score on the copying-a-drawing-with-landmarks test (of neuropsychological functioning) and hypoxemia. (Adapted from Reference 25, with permission.)

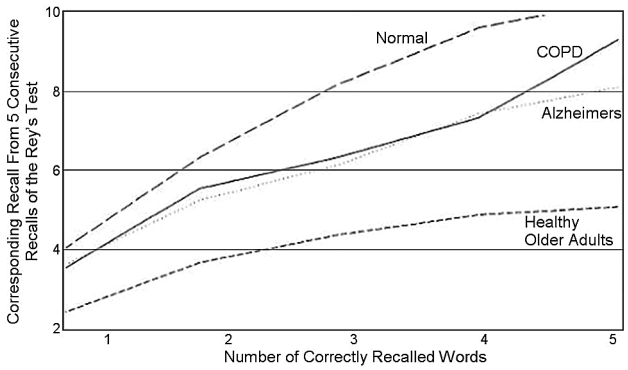

Fig. 3. Learning curves of normal subjects, patients with chronic obstructive pulmonary disease (COPD), patients with Alzheimer's disease, and healthy older adults. The curves are obtained by plotting the number of correctly recalled words against the corresponding recall from 5 consecutive recalls of the Rey's test. (Adapted from Reference 28.)

extent to which they are related to hypoxemia. Impairments have been documented in verbal processing, attention, deductive thinking, drawing skills, passive recognition, active recall, abstract reasoning, memory, language, and speed of performance,[25-29] but verbal intelligence does not appear to be affected.[30] Studies confirm that the cognitive performance of patients with COPD reflects isolated deficits that do not resemble cognitive deficits in patients with dementia.[31,32] Learning in patients with COPD is slower than normal, but significantly better than in patients with Alzheimer's disease (Fig. 3). Hypoxemia is associated with greater impairment in cognitive performance, but cognitive performance of severely hypoxemic subjects is generally better than that of demented patients.

Frequently cited data from the combined Nocturnal Oxygen Therapy Trial and the Intermittent Positive Pressure Breathing Trial document a positive correlation between neuropsychological impairment and hypoxemia.[30] Control subjects performed better than mildly hypoxemic patients, who performed better than moderately or severely hypoxemic patients. Hypoxemic patients demonstrate deficits in verbal memory, mental flexibility, delayed recall, attention, and drawing ability.[25,33,34] However, those studies and others indicate that neuropsychological functioning is not associated with standard pulmonary function variables (eg, forced expiratory volume in the first second) and appears to be only moderately associated with hypoxemia.[35] Age and education typically have accounted for the largest share of differences in neuropsychological performance.[30] Because sleep disorders also are associated with hypoxemia and neuropsychological dysfunction,[36] it has been suggested that sleep-disordered breathing and sleep apnea may be additional risk factors for neuropsychological impairment in patients with COPD.[37] In addition, depressive symptoms may exacerbate cognitive deficits, but cognitive impairment in these patients is not strongly associated with depression.[26]

Shim and colleagues described biological correlates of these neuropsychological deficits; they found diminished cerebral metabolism in the parietal white matter of the brain in COPD patients.[38] Patients with COPD have deterioration in cerebral perfusion in the brain, and hypoxemic patients exhibit greater decreases in perfusion than do nonhypoxemic patients.[33] Hypoxemic patients with COPD also exhibit abnormalities in cerebral membrane phospholipids.[39]

Assessment Strategies

Despite the relatively high prevalence of depression and anxiety in patients with COPD, depression and anxiety often are not assessed or treated in this population.[11,40,41]

Depression and Anxiety

Common measures of depression include the Beck Depression Inventory,[42] and the Center for Epidemiological Studies Depression Inventory.[43] The Beck Depression Inventory is a widely-used, 21-item measure of depressive symptoms, and it has excellent psychometric properties.[44] The score range is 0 to 63, and a score $>$ 20 indicates moderate depression. The Center for Epidemiological Studies Depression Inventory is a 20-item measure of depression; it has been validated in community-residing older adults. The score range is 0 to 60. A score $>$ 16 indicates depression that may be clinically important. Both of these measures provide useful indicators of change in depressive symptoms. The Beck Depression Inventory is frequently used in therapeutic settings to document week-to-week change in depressive symptoms.[45] The Patient Health Questionnaire Depression Scale[46] is a 9-item self-report measure to screen and diagnose depressive disorders in patients in primary care. It has good reliability ($\alpha = 0.89$) and adequate validity,[47] and provides a useful measure of change in depressive symptoms.

Anxiety measures include the Beck Anxiety Inventory[48] and the State-Trait Anxiety Inventory.[49] The Beck Anxiety Inventory is a 21-item measure of symptoms of anxiety; it has excellent internal consistency and good test-retest reliability (1-week interval) of 0.75.[50] The score range is 0 to 60. A score $>$ 20 indicates moderate anxiety. The State-Trait Anxiety Inventory is a 40-item measure; 20 items assess transient (state) anxiety, and 20 items assess long-standing (trait) symptoms of anxiety. Both the Beck Anxiety Inventory and the State-Trait Anxiety Inventory are useful for evaluating changes in symptoms of anxiety.

A measure designed to evaluate both depression and anxiety in physically ill patients is the Hospital Anxiety and Depression Scale,[51] which is a self-administered questionnaire with 14 items (7 on anxiety and 7 on depression). None of the 14 items focus on somatic symptoms of depression or anxiety; this minimizes the potential of confounding by physical symptoms of illness, which often overlap with symptoms of distress. Thus, it may be a particularly useful measure for patients with COPD.

Neuropsychological Function

Cognitive function has long been conceptualized in the 2 broad domains of fluid and crystallized intelligence.[52] Crystallized intelligence refers to accumulated knowledge from experience and training, and it generally tends to remain intact well into old age. Fluid intelligence refers to reasoning and problem-solving ability, and is measured by tasks that involve rapid and flexible manipulation of ideas and symbols. Fluid intelligence declines with age,[53,54] and decreases are most evident in working memory, processing speed, organization, flexible problem-solving, and attentional control. The fluid component of intelligence is of greatest relevance for studies of patients with COPD, because deficits have been observed primarily in those components of neuropsychological functioning.

The most common instrument used in neuropsychological assessment batteries is the Wechsler Adult Intelligence Scale III, which measures overall intellectual ability and has index scores that reflect verbal and performance domains of functioning.[55] The performance domain score reflects fluid intelligence; therefore, the subtests that compose the performance score (eg, digit symbol, digit span) are used most frequently to evaluate deficits associated with COPD. Additional neuropsychological measures commonly used to evaluate patients with COPD include:

- Trail Making Test: Measures sequencing ability and visual motor tracking[56]
- Stroop Interference Test: Measures ability to shift perceptual set and meet changing demands of a task[57]
- Wisconsin Card Sort: Measures abstract conceptual skills, cognitive flexibility, and ability to test hypotheses and utilize error feedback[58]
- Selective Reminding Task: Measures verbal learning and memory[59]
- Controlled Oral Word Association Test: Measures capacity for organized processing of verbal information[60,61]
- Wechsler Memory Scale III: Measures attention, concentration, visual memory, and verbal memory[55]

The Mini Mental Status Examination is a global assessment tool used widely in clinical settings and in research.[62] Although patients with COPD are significantly more likely to exhibit deficits on the Mini Mental Status Examination,[26] it provides only a gross indicator of cognitive function and is not useful for identifying specific areas of cognitive dysfunction in patients with COPD.[63]

Studies have examined self-perceptions of cognitive performance, but have not evaluated the extent to which self-perceptions reflect objective cognitive performance. Mood and other indicators of psychiatric functioning may be confounding variables in the self-assessment of cognitive functioning, because depression and anxiety are associated with perceptions of poorer cognitive performance, regardless of objective cognitive performance.

Pulmonary Rehabilitation

Exercise rehabilitation of patients with COPD, in programs ranging from 3 weeks to 1 year, is associated with enhanced psychological functioning, including reduced depression and anxiety.[35,64-67] Although not all studies have

indicated enhanced psychological well-being following exercise rehabilitation,[68] the preponderance of recent evidence supports the utility of exercise rehabilitation for reducing depression and anxiety. The conflicting results from the various studies may reflect differences in the degree to which patients with COPD experience symptoms of distress, and differences in the measurement of psychological outcomes.

Studies of exercise and cognitive function in patients with COPD indicate that exercise is associated with enhanced cognitive performance.[35,64,69] In particular, there is evidence of an association between exercise and verbal fluency and other cognitive measures that reflect components of fluid intelligence (sequencing, problem-solving, abstract reasoning). One study found no overall improvement in cognitive performance following a 3-week intervention, but the patients who were more impaired at baseline had significant improvement in cognitive function.[65] Overall, these data are consistent with results of recent studies with healthy older adults, which indicated a positive effect of exercise on cognitive tasks that reflect executive function (eg, purposive behavior, self-control, ability to shift attention).[70,71] However, to date the experimental evidence is still limited regarding the influence of exercise interventions on cognitive performance in patients with COPD.

Two relatively recent studies examined the effect of long-term exercise on cognitive functioning in patients with COPD. One study found that an 18-month training program of aerobic and strength-training exercises was associated with improved cognitive performance, as measured with the Culture Fair Intelligence Test, which measures fluid intelligence.[69] A second study found that exercise nonadherence was associated with a decline in cognitive performance during a 12-month follow-up.[72] The latter provided follow-up data from an exercise intervention in patients with COPD, in whom verbal fluency improved.[35] Although performance on the verbal fluency task was maintained regardless of exercise during follow-up, participants who were nonadherent during the follow-up period had a significant decline in performance on a task that reflected alertness and psychomotor speed (digit symbol subtest of the Wechsler Adult Intelligence Scale) and in exercise endurance (as measured by maximum oxygen consumption), but there was no association between decline in maximum oxygen consumption and decline in cognitive performance. The 18-month longitudinal study found an association between improved exercise capacity and improved cognitive performance,[69] but neither of these long-term follow-up studies evaluated additional mechanisms (mediators or moderators) in the relationship between exercise and cognitive performance.

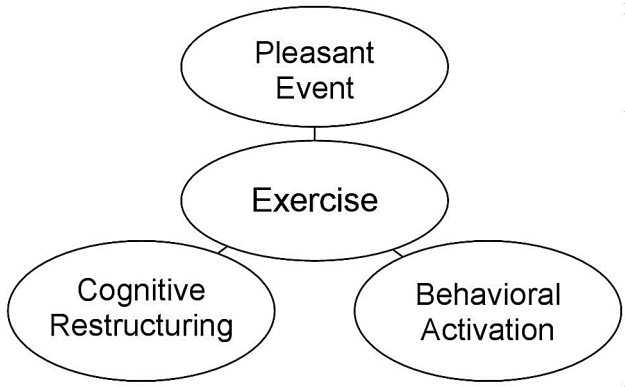

Fig. 4. Hypothesized cognitive and behavioral mechanisms by which exercise affects depression.

Mechanisms

Several mechanisms have been hypothesized to explain the effect of exercise rehabilitation on psychiatric symptoms and on cognitive/neuropsychological performance.

Depression

Reduction in depression following exercise may result from both biological and behavioral influences. Increases in endogenous opiates (eg, endorphins, enkephalins) following exercise are associated with reduced depression.[73-76] A second proposed biological exercise mechanism is increased availability of brain neurotransmitters such as serotonin, dopamine, and norepinepherine, all of which are typically low in depressed individuals. Several animal studies have documented increased brain levels of serotonin and norepinephrine following exercise.[77-81] Exercise also appears to be associated with reduction in pro-inflammatory cytokines (eg, interleukin 6), which are associated with depressed mood and general psychiatric distress.[82,83]

Behavioral mechanisms also have been hypothesized (Fig. 4). Exercise may provide a distraction from worrying or engaging in thought patterns that are more susceptible to depression, such as rumination. Active distraction significantly remediates depressed mood.[84,85] In addition, depressed individuals often have low self-efficacy for obtaining desirable goals and coping with their depression. Exercise may increase self-efficacy by providing individuals with a meaningful mastery experience.[86,87] Exercise engages participants in regular, pleasurable activity, thereby providing daily pleasant events that reduce depression.[88] Group exercise also provides regular social contact and social support that may reduce depression in socially-isolated individuals. Exercise in healthy older adults increases social support and social functioning.[89]

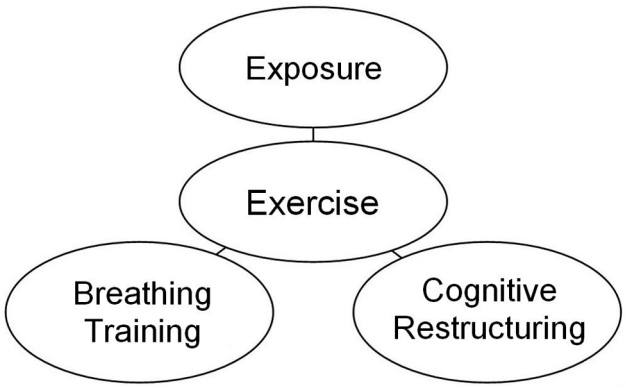

Fig. 5. Hypothesized cognitive and behavioral mechanisms by which exercise affects anxiety.

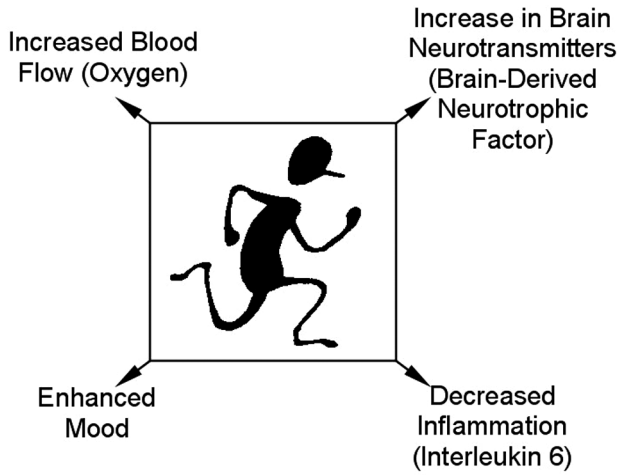

Fig. 6. Hypothesized mechanisms by which exercise affects neuropsychological function.

Anxiety

Anxiety reductions are likely to occur via the biological and behavioral mechanisms listed above and shown in Figure 5. In addition, because anxiety symptoms (eg, dyspnea, hyperventilation) may mimic symptoms of respiratory disease, exercise rehabilitation allows participants to experience their symptoms safely and become desensitized to the symptoms by learning to distinguish between physical and emotional symptoms. Dyspnea causes fear of suffocation and death, which is a source of substantial anxiety.[10] Individuals who are anxious may misinterpret or catastrophize about the experience of dyspnea.[90] The emotional arousal of anxiety increases ventilatory demand on the body, which may lead to hypoxia or hypercapnia. Increased physiological arousal, in turn, exacerbates anxiety symptoms, which then produce greater physiological insufficiency, resulting in a circular pattern that is difficult to break.[10]

A thermogenic effect of exercise also has been postulated. Increased temperature in specific brain regions, such as the brain stem, may lead to an overall feeling of relaxation and decrease in tension.[73,91]

Neuropsychological

There are several proposed mechanisms by which exercise rehabilitation may improve neuropsychological status in patients with COPD (Fig. 6). First, exercise may increase blood flow to the brain and increase the transport and utilization of oxygen in the cerebral environment and therefore enhance cerebral metabolic activities.[91-94] Exercise also may affect cognitive function by stimulating brain neurotransmitters such as brain-derived neurotrophic factor, which is associated with regulation of neuronal proliferation and differentiation. In rodents, exercise increases hippocampal brain-derived neurotrophic factor and enhances brain plasticity.[95,96] Human studies found that acute exercise increases brain-derived neurotrophic factor,[97,98] with corresponding increase in cognitive performance.[99] It has also been suggested that increased oxygen transport to the brain following exercise may enhance metabolism of several neurotransmitters such as acetylcholine, dopamine, norepinephrine, and serotonin.[100,101]

Biobehavioral mechanisms may also operate to link exercise and cognitive function by reducing distress. Clinical depression is associated with impaired cognitive functioning and specific deficits in executive functioning, psychomotor speed, visuospatial tasks, and attention.[102,103] Khatri and colleagues[70] found that 4 months of exercise in depressed middle-age and older adults was associated with greater improvement in memory and executive functioning than was 4 months of anti-depressant medication. Thus, it appears that exercise-related processes contribute to cognitive change and that reduced depression alone is not sufficient to produce change in cognitive function.

Clinical Implications

There is good evidence of neuropsychiatric benefits from pulmonary rehabilitation, especially improved mood and cognitive performance. Randomized controlled studies in the past 10 years have found reduced depression and anxiety, and improved capacity for abstract thinking and sequencing, and these data resulted in a more enthusiastic endorsement of psychological/psychiatric benefits in recent guidelines for pulmonary rehabilitation.[104] This is encouraging news for clinical treatment of patients with COPD in pulmonary rehabilitation. However, these data also indicate a need for regular assessment of psychiatric symptoms and neuropsychological functioning in patients, because of the relatively high rates of distress and dysfunction,

as well as the need to document the severity of distress/dysfunction and the importance of documenting changes in neuropsychiatric outcomes during the course of pulmonary rehabilitation. Many of the measures of psychiatric distress identified above are self-report indicators that are relatively easy for patients to complete and for pulmonary rehabilitation staff to score. Thus, one important implication of this review is to encourage regular and widespread evaluation of neuropsychiatric functioning in patients entering pulmonary rehabilitation. For many patients, pulmonary rehabilitation will reduce distress. For patients with greater distress, additional behavioral or pharmacologic treatment may be an important adjunct to pulmonary rehabilitation. A second implication of the data summarized above is that patients need to maintain their physical activity regimen to sustain the gains in physical-fitness, mood, and cognitive performance following pulmonary rehabilitation. Thus, it is especially important to help patients identify sources of support (personal and/or institutional) to continue their exercise following participation in pulmonary rehabilitation.

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