Various psychological and cognitive difficulties have been documented in patients with emphysema. The aim of this article is to review prior literature on the prevalence of these difficulties in emphysema, as well as to identify specific studies demonstrating improvement in these areas after therapy. Traditional therapies such as continuous and intermittent oxygen therapy and comprehensive pulmonary rehabilitation are reviewed. In general, these studies demonstrate reductions in symptoms of depression and anxiety as well as specific improvements in complex attention and verbal fluency. In a more recent study, patients with emphysema who underwent lung volume reduction surgery (LVRS) demonstrated improved psychomotor speed, verbal memory, and naming skills at 6 months compared with patients with emphysema who were in comprehensive rehabilitation only. The patients with emphysema who had LVRS also demonstrated greater decline in depressive symptoms compared with the rehabilitation patients at 6 months. There were no associations between improved neuropsychological tests and changes in depression, exercise tests, pulmonary function, oxygenation, or quality of life scores, and thus the mechanism of behavioral improvement identified in the patients who underwent LVRS remained unclear. Overall, studies suggest that psychological and cognitive improvements occur subsequent to a variety of medical and behavioral treatment therapeutic approaches, and that LVRS appears to have an advantage for some patients with emphysema.

Keywords: chronic obstructive pulmonary disease; lung volume reduction surgery; neurobehavioral

COGNITIVE DEFICITS AND PSYCHOLOGICAL DIFFICULTIES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Emphysema, a form of chronic obstructive pulmonary disease (COPD), is a chronic progressive pulmonary disease with significant physical, cognitive, and psychological sequelae. Empirical studies have identified neuropsychological (i.e., cognitive) deficits in patients with COPD (1–7).

The pattern and extent of cognitive dysfunction reported in COPD vary across patients, and appear to be associated with disease severity. In patients with COPD with moderate to severe hypoxemia, deficits have been reported in simple motor movement and overall strength, perceptual–motor integration, abstract reasoning, attention to auditory stimuli, learning and memory, and language skills (2, 4–6, 8, 9). Mild hypoxemia may be associated with impairment in higher cerebral functioning, including abstract reasoning, auditory and visual attention, verbal and nonverbal learning and recall, and reasoning and motor skills (2, 4).

Psychological and behavioral changes have also been noted in patients with COPD. In a comprehensive review of 81 studies, Hyninnen and coworkers (10) reported that the prevalence of psychiatric disorders ranged from 30 to 58%. Depression and anxiety appear to be the most commonly observed psychological problems in COPD (10–14). The prevalence of depression has been estimated as between 10 and 79.1% (10, 15–17). Some of the discrepancies in estimations may relate to the method of assessing depression. For example, prior studies with higher levels of depression have tended to use self-report questionnaires rather than a clinically derived diagnosis of major depression (11). Eisner and colleagues (19) screened a large group of patients with moderate to severe COPD, using screening questionnaires followed by a psychiatric interview. They report prevalence rates of depression of 35% by questionnaire and 21% by clinical interview. This is consistent with another study that diagnosed depression in COPD on the basis of a structured psychiatric clinical interview and reported that 23% of the patients with COPD had major depression (20). The prevalence of depression in older adults in the general population has been estimated as between 8 and 20%; thus studies to date clearly indicate higher depression rates among patients with COPD (21). Multiple studies have also demonstrated poor quality of life among patients with COPD (22), and this was explored in greater detail by Kaplan and Ries (see pages 561–566 of this symposium [32]).

EFFECTS OF TREATMENT ON COGNITIVE AND PSYCHOLOGICAL FUNCTIONING IN COPD

Use of oxygen therapy (greater than 6 mo) improves cognitive performance in COPD, likely due to direct effects of improved oxygen delivery to the central nervous system (3, 23–26). Kropp and coworkers (3) found improvement in visual memory, verbal memory, and motor speed among subjects with COPD after 6 months of continuous oxygen therapy. Large multisite studies have also demonstrated the benefits of oxygen for cognitive function in COPD. For example, after 6 months of treatment in the Nocturnal Oxygen Therapy Trial, neuropsychological performance of patients receiving continuous oxygen was comparable to the performance of those receiving nocturnal oxygen. However, a subgroup of participants receiving continuous oxygen therapy evaluated again at 12 months experienced modest improvements in cognitive performance in comparison with patients receiving only nocturnal oxygen therapy (23).

There is also evidence suggesting that comprehensive multidisciplinary rehabilitation programs can improve cognitive functioning and psychological status in patients with emphysema (11, 27–29). Comprehensive rehabilitation programs for treatment of COPD are well established and typically include assessment, education, instruction on respiration, psychosocial support, and...
exercise training with the goal of restoring patients to the highest level of independent function (27). Emery and coworkers (28) reported improved complex attention in patients with COPD after a 30-day exercise rehabilitation program that included instructional/educational components, psychosocial counseling, and stress reduction. In a subsequent study, they reported improvement in verbal fluency and reduction in symptoms of anxiety and depression in a group participating in an exercise, stress reduction, and education program compared with a control group participating in stress reduction and education treatment only (30). This finding highlighted the utility of exercise for enhancing cognitive and psychological functions. Kozora and coworkers (29) found improvement in visual attention and semantic fluency among patients with COPD after a 3-week comprehensive rehabilitation program compared with untreated subjects with COPD and healthy control subjects similar in age, education, and sex. This program included exercise, educational, instructional, and psychosocial components. In addition to cognitive improvement, significant reduction in depressive symptoms was reported. Together, these studies indicate improved cognitive performance and psychological status after comprehensive rehabilitation with an exercise component.

EFFECTS OF LUNG VOLUME REDUCTION SURGERY ON COGNITIVE FUNCTIONING IN PATIENTS WITH EMPHYSEMA

In an ancillary study of the National Emphysema Treatment Trial (NETT), Kozora and coworkers (31) examined neuropsychological and psychological functioning of patients receiving lung volume reduction surgery (LVRS) compared with patients receiving only medical therapy (MT). Participants included 39 NETT patients (19 randomized to LVRS and 20 randomized to MT) and 39 healthy subjects matched by age, education, sex, and physical activity level (the control group). All MT and LVRS subjects were recruited at two sites participating in the NETT protocol. The 39 NETT subjects participated in a pulmonary rehabilitation program (exercise and education) for 6 to 10 weeks. As shown in Table 1, the groups included primarily older white men with a high school education. No demographic differences between the three groups were noted and there were no significant differences between the LVRS and MT groups in their overall duration of emphysema diagnosis, percent predicted FEV1, or maximum workload at baseline. Patients who underwent LVRS had a shorter six-minute-walk distance and higher PaCO2 than did patients receiving MT.

Neuropsychological, psychological, and quality of life measures were administered at baseline, after 6 to 10 weeks of comprehensive rehabilitation, and 6 months later. Neuropsychological measures were selected from tests found sensitive in prior COPD studies (29) and included four subtests from the Wechsler Adult Intelligence Scale—Revised to estimate IQ (33); the Logical Memory, Verbal Paired Associates, and Faces subtests from the Wechsler Memory Scales–Third Edition (34); the WAIS-R Digit Span and Arithmetic subtest (35); the Digit Vigilance Test (36); the Trail Making Test Forms A and B (37); the Complex Ideational Material subtest from the Boston Diagnostic Aphasia Examination (18); the Controlled Oral Word Association Test and Animal Naming Test (18, 38); a 15-item version of the Boston Naming Test (BNT-15) (18, 39); and clock drawing (18, 40). Psychological and quality of life measures included the Beck Depression Inventory (41), the State Trait Anxiety Inventory (42), and the Short Form (SF)-36 assessment of quality of life (43).

Statistical methods that control for practice effects across the three time points were used (based on data obtained from the control subjects at three time points). The LVRS group showed significant improvement (represented as a lower score) compared with the MT group at 6 months on a measure of psychomotor speed (Trail Making Test–Form A; \( P = 0.005 \)). Mean LVRS group scores for Trail Making Test–Form A were 42.2 seconds (SD \( = 12.4 \)) at baseline, 37.9 seconds (SD \( = 11.7 \)) at 6 months, whereas MT scores were 37.6 seconds (SD \( = 14.9 \)), 33.4 seconds (SD \( = 10.4 \)), and 37.0 seconds (SD \( = 15.3 \)) at the same testing times (Figure 1). Delayed recall for verbal information (Verbal Pairs II) also improved in patients undergoing LVRS compared with patients receiving MT (\( P = 0.025 \)). As indicated in Figure 2, scores over time were 5.2 (SD \( = 2.5 \)), 5.2 (SD \( = 2.6 \)), and 5.8 (SD \( = 2.2 \)) for patients undergoing LVRS compared with 6.1

%TABLE 1. SUBJECT DEMOGRAPHICS AND HEALTH CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>LVRS (n = 19)</th>
<th>MT (n = 20)</th>
<th>Control Subjects (n = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sex, %</td>
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<td>90</td>
<td>85</td>
<td>0.41</td>
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<tr>
<td>Female</td>
<td>26</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>Mean 64.8</td>
<td>64.3</td>
<td>64.0</td>
<td>0.88</td>
</tr>
<tr>
<td>SD</td>
<td>4.9</td>
<td>6.2</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Years of education</td>
<td>Mean 11.9</td>
<td>12.7</td>
<td>13.1</td>
<td>0.13</td>
</tr>
<tr>
<td>SD</td>
<td>1.4</td>
<td>2.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
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<td>95</td>
<td>97</td>
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<tr>
<td></td>
<td>Female 26</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Health Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean 1,048</td>
<td>1,261</td>
<td>1,301</td>
<td>0.021</td>
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<tr>
<td>Six-minute walk, ft</td>
<td>SD 344</td>
<td>188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>Mean 60.9</td>
<td>58.6</td>
<td>58.1</td>
<td>0.556</td>
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<tr>
<td>SD</td>
<td>12.4</td>
<td>11.7</td>
<td></td>
<td></td>
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<tr>
<td>PaCO2, mm Hg</td>
<td>Mean 45.2</td>
<td>41.0</td>
<td>41.3</td>
<td>0.043</td>
</tr>
<tr>
<td>SD</td>
<td>6.1</td>
<td>6.3</td>
<td></td>
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</tbody>
</table>

Definition of abbreviations: LVRS = lung volume reduction surgery; MT = medical therapy.
Trends toward improved performance for LVRS compared with MT were noted on sequential thinking and psychomotor speed (Trail Making Test–Form B; P = 0.053; Figure 3) and on a measure of naming to confrontation (BNT; P = 0.057; Figure 4). Examination of individual tests indicated overall improved cognitive performance within the LVRS group over time, with no change or decline from baseline cognitive performance in the MT group (see tables in original article [31]).

Post hoc analyses of the data indicate that there were no differences between the LVRS and MT groups on any of the neuropsychological measures at baseline. Controlling for physical differences at baseline (6-min walk, PaCO2, and workload), Trail Making Test–Form A remained significantly improved in LVRS compared with MT at 6 months (P = 0.02); and Verbal Pairs II remained marginally significant (P = 0.10).

Patients undergoing LVRS also experienced significant reductions in depression at 6 months, as reflected in total Beck Depression Inventory score and the Beck Depression Inventory Cognitive-Affective subscore, compared with patients receiving MT (P = 0.016 and P = 0.022, respectively). In addition, there was a trend toward reduced Beck Depression Inventory Somatic subscore in the LVRS group compared with the MT group at 6 months (P = 0.059). In the LVRS group, the mean for this subscore declined from 11.4 (SD = 7.1) at baseline to 6.9 (SD = 4.7) post-rehabilitation to 5.1 (SD = 3.6) at 6 months compared with 10.5 (SD = 6.2), 6.8 (SD = 3.3), and 8.9 (SD = 6.3) in the MT group at the same times (Figure 5). Interestingly, the self-reported depressive symptoms for the MT group appeared to increase at 6 months, returning toward the baseline level.

There was no difference between the LVRS and MT groups on the Acute or Chronic Anxiety subscores from the State Trait Anxiety Inventory. The SF-36 subscores were significantly improved in the LVRS group compared with the MT group in the following dimensions: Physical Functioning (P < 0.001), Role-Physical (P = 0.008), and Change in Health (P = 0.001). Trends were apparent for improved Role-Emotional (P = 0.055), Social Functioning (P = 0.055), and Vitality (P = 0.051). LVRS participants also experienced significant improvement compared with MT on all pulmonary measures (FEV1, PaO2, and PaCO2) and one measure of exercise workload.

Analyses were performed to examine potential mediators of cognitive improvement in the LVRS group between Time 2 (post-rehabilitation) and Time 3 (6 mo after randomization). Correlations between pulmonary, exercise, psychological, and neuropsychological measures were assessed. There were no associations between improved neuropsychological tests in the LVRS (Verbal Pairs II and Trail Making Test–Form B) and changes in depression (Beck Depression Inventory scores), exercise tests (6-min walk and cardiopulmonary exercise), pulmonary function, oxygenation, or quality-of-life scores.

Given the conservative nature of the control for practice effects in this analysis and the relatively poor health of the subjects before LVRS, these findings provide evidence of cognitive improvements post-LVRS. Only a subset of the cognitive measures showed significant improvement in LVRS compared with MT overtime. Of perhaps equal importance, none of the tests indicated poorer performance over time. Thus, for the patients undergoing LVRS, these data indicate no negative neuropsychological sequelae of the surgery. The results also reflect significantly less depression in patients undergoing LVRS compared with MT at 6 months. In contrast to our expectations, there was no direct evidence that improved cognition after LVRS was related to improved physical capacity (workload and 6-min walk) or pulmonary function. Indeed, improvement in the LVRS group on measures of verbal memory, visual–spatial function, and sequential ability cannot be accounted for by psychological changes, medications, or pulmonary/exercise measures. Subsequent re-
search is needed to further characterize and define the response of cognitive function to LVRS.

LESSONS LEARNED OR NOT: FUTURE DIRECTIONS

These data indicate that patients undergoing LVRS achieved improvements in neuropsychological and behavioral functioning over and above that explained by practice effects or MT. This finding adds to the growing list of clinical benefits of LVRS over MT for some patients. Analyses conducted to evaluate the mechanism of the effect were not fruitful. Increases in cognitive performance were not associated with changes in any of the other study outcomes. It is possible that sample size limited the statistical power available for these analyses of mechanisms. It is also possible that our outcome measures did not adequately assess activities of daily living that would be associated with improved cognitive performance. Although we observed significant improvements in cognitive function among the patients undergoing LVRS, we have no data indicating the duration of the improvements. Other studies suggest that increases in cognitive function associated with exercise are not sustained unless exercise is maintained (44). To the degree that patients undergoing LVRS are able to maintain an elevated activity level, cognitive improvement may be sustained. However, further research is needed to investigate longer term outcomes in patients who undergo LVRS, monitoring exercise behavior and other health behaviors during the follow-up period.

It is possible that our measures of cognitive performance were not sensitive to the full range of cognitive changes that patients may experience after LVRS. Further research examining performance on additional cognitive outcomes, such as reaction time, may be useful in documenting neurocognitive performance. In addition, further evaluation of behavioral change after LVRS would be important to help elucidate the relationship between behavioral and cognitive performance after surgery. We did not evaluate factors associated with significant reductions in depressive symptoms among the patients undergoing LVRS. Although it is possible that depressive symptoms were reduced as a result of patients experiencing fewer illness-related symptoms, we have no data available to evaluate this hypothesis.

Thus, there appear to be behavioral and cognitive benefits of LVRS for patients with emphysema compared with medical therapy. Further investigation is needed with larger sample sizes, additional measures of behavioral and cognitive outcomes, and a longer duration of follow-up to help identify mechanisms contributing to improvements in cognitive performance.

In summary, research to date suggests that a variety of therapeutic approaches used to treat patients with emphysema (including oxygen therapy, comprehensive rehabilitation programs, and surgical techniques) improve psychological and cognitive functioning. Continued studies of patient characteristics in relation to optimal treatment modality may be useful.

Conflict of Interest Statement: E.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.S.W. has current research grant support from New York University; his wife has current or recent research grant support from New York University. F.S.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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