DEPRESSIVE symptoms include “feeling sad, demoralized, lonely, helpless, or worthless, wishing you were dead, having trouble sleeping, crying, feeling everything is an effort, and not being able to get going” (1). Although these symptoms are common in the general population, they are more frequent in older adults (2,3), especially in those with health and functional limitations (4,5). Furthermore, it has been shown that older adults with clinically relevant levels of depressive symptoms have an increased risk of becoming frail (5–7) and developing incident chronic diseases such as cancer (8), diabetes (9), heart disease (10), and stroke (11). Older adults with clinically relevant levels of depressive symptoms are also at greater risk for adverse outcomes for existing comorbid conditions (12), have lower health-related quality of life [HRQoL (13)], and have greater mortality risk (14).

Accordingly, much interest has focused on the recognition and treatment of clinically relevant levels of depressive symptoms and depression among older adults (15–18). In this brief report, we evaluate the effects of the National Institutes of Health–funded, multisite randomized controlled trial (RCT) known as Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) (19). ACTIVE evaluated the effectiveness and durability of three distinct cognitive interventions—memory, reasoning, and speed-of-processing—on a variety of proximal, primary, and secondary outcomes. Previous reports have shown significant effects of the cognitive interventions, especially speed-of-processing, on both proximal and primary outcomes (20,21), as well as on secondary outcomes such as HRQoL (22,23). Here, we extend the focus on secondary outcomes by evaluating the effects of speed-of-processing on clinically relevant changes in the level of depressive symptoms at 1- and 5-years posttraining.

We focus on the speed-of-processing intervention because its etiologic mechanism operates through sensory motor elaboration and repetition; it is known that procedural tasks like this have a broader pattern of regional brain activation than explicit memory or reasoning tasks (24). The resulting improvements in brain activation and/or structure are hypothesized...
to delay the onset and/or to reduce the risk of cognitive slowing, which is the most significant contributor to overall cognitive decline (25). Thus, we expected that because cognitive slowing is prevented by the speed-of-processing intervention, we should also see a protective effect of that intervention against clinically relevant increases in depressive symptoms. We did not expect to find significant protective effects for the memory or reasoning treatment arms.

METHODS

Design

ACTIVE is a multisite RCT with three treatment arms and a no-contact control group, and it has been described in detail elsewhere (19–23). Each of the three treatment arms (memory, reasoning, and speed-of-processing) involved 10 standardized, equal length intervention sessions. Outcome assessors were blinded to treatment group assignment and obtained baseline outcome assessments prior to treatments, with reassessments conducted at 1-, 2-, 3-, and 5-years postbaseline.

Sample

All study participants were community dwelling (ie, able to live independent of formal care) and older than 65 years. Recruitment strategies varied across the six sites, with 4,970 potential participants identified from March 1998 through October 1999 (15). Potential participants (n = 905, 18%) were excluded due to cognitive impairment (26), poor corrected vision, hygiene or dressing dependencies, Alzheimer’s disease, a stroke during the past year, limited life expectancy due to cancer or active chemotherapy or radiation treatment, difficulty communicating, intentions to move out of the area soon, anticipated scheduling conflicts, or prior cognitive training; 1,263 (25%) other potential participants refused to participate. The 2,802 remaining potential participants were screened, enrolled, and randomized. Of these, 2,014 (72%) had complete data available at 1 year and 1,516 (54%) had complete data available at 5 years.

Interventions

The first five intervention sessions focused on strategy instruction and practice exercises, and the remainder provided additional practice. The content consisted of laboratory-type and everyday activities that were well specified in trainer manuals (19). Reasoning training focused on inductive reasoning, especially the ability to solve problems that followed a serial pattern and were manifest in executive functioning. Memory training focused on verbal episodic memory, especially using mnemonic strategies for remembering lists, sequences of items, text material, and main ideas and story details. Speed training focused on visual search and the ability to identify and locate visual information quickly in a divided-attention format.

Depressive Symptoms

We used a 12-item version of the reliable and well-validated Center for Epidemiological Studies–Depression scale (CES-D) to measure depressive symptoms (1,27). The response set had four levels: rarely or none of the time (0), some of the time (1), much of the time (2), and most or all of the time (3). Thus, the CES-D-12 scores ranged from 0 (no depressive symptoms acknowledged) to 36 (all 12 depressive symptoms acknowledged to occur most or all of the time). Clinically relevant increases in depressive symptoms were defined using two thresholds—≥0.5 and ≥1.0 SD increases in the CES-D-12 scores between baseline and 1 and 5 years—which are consistent with traditional criteria for medium and large effect sizes, respectively (22,23,28,29).

Attrition Bias

Because only 72% and 54% of the original participants had complete data available to examine clinically relevant increases in depressive symptoms between baseline and 1 and 5 years, respectively, the potential for attrition bias existed. Therefore, to maintain an intention-to-treat approach, we used separate propensity score models to adjust for potential attrition bias at 1 and 5 years (30–33). For each follow-up period, we estimated a multivariable logistic regression model of whether complete data were available, and computed the predicted probabilities of inclusion in the analytic samples (34). These models included treatment group assignment; demographic, socioeconomic, and cognitive; health; and functional status measures at baseline (complete lists available on request). Both models fit the data well [C statistics = 0.80 and 0.78; Hosmer–Lemeshow statistic p values = .21 and .73 (34,35)]. Within each propensity score (predicted probability) quintile, we determined the average participation rate (ie, inclusion in the analytic samples, or P) and used the inverse (1/P) to weight the data. This gives greater influence to participants in the analytic samples most like those not included. Finally, the propensity score weights were adjusted so that the final weighted N was equal to the actual number of participants in the analytic samples (ie, 2,014 and 1,516).

Analytic Method

After weighting the data to adjust for potential selection bias, we used multivariable logistic regression to model the effects of the three treatment groups on the two thresholds (ie, ≥0.5 and ≥1.0 SD) of clinically relevant increases in depressive symptoms at 1- and 5-years postbaseline (34). Each intention-to-treat analysis had three steps, with the first including only three dummy variables contrasting each treatment group with the no-contact control group, the second adding the baseline level of depressive symptoms to ensure that the results were not sensitive to start values, and the third adding the baseline levels on the Mini-Mental State Examination (MMSE) (36) and the eight Short Form 36-Item (SF-36) scale scores (26) to determine whether or not...
the treatment effects were mediated by cognitive and functional status.

RESULTS

Descriptive

Among 2,036 participants in the 1-year analytic sample, there were 508 in the memory group, 498 in the reasoning group, 518 in the speed-of-processing group, and 512 in the no-contact control group. The mean age at baseline was 73.4, 24% were men, 24% were Black, and the average educational attainment was 13.6 years. The mean MMSE score was 27.5, the average number of Activities of Daily Living (ADLs) with difficulty was 0.3 (out of three tasks), the average number of Instrumental ADLs (IADLs) performed with any level of assistance or supervision was 1.3 (out of seven tasks), the mean number of chronic conditions was 2.2, and 14% reported being in fair or poor (vs excellent, very good, or good) health. The overall mean CES-D-12 score at baseline was 5.1 (it was 4.9, 5.6, 5.2, and 5.0 in the memory, reasoning, speed-of-processing, and no-contact control groups, respectively; p = .235), with 18% having no symptoms, and an interquartile range of 1–8. Based on the ≥0.5 SD threshold for clinically relevant increases in CES-D-12 scores (ie, a score gain ≥2.53), 25% (n = 510) had clinically relevant increases at 1 year and 27% (n = 420) at 5 years. Based on the ≥1.0 SD threshold for clinically relevant increases in CES-D-12 scores (ie, a score gain ≥5.05), 12% (n = 236) had clinically relevant increases at 1 year and 12% (n = 187) at 5 years.

Multiple Logistic Regression

Table 1 contains the results obtained from the intention-to-treat, multivariable logistic regression analyses at both 1 and 5 years for both the ≥0.5 and ≥1.0 SD thresholds for clinically relevant levels of increased depressive symptoms. Relative to the no-contact control group, only the speed-of-processing intervention had a statistically significant, protective effect against clinically relevant increases in depressive symptoms, lowering that risk by 30% at both time points for the ≥0.5 SD threshold (adjusted odds ratios [AORs] = 0.700 and 0.698 at 1 and 5 years, p values = .012 and .013). Similar results (AOR = 0.669 with p = .013 at 1 year; AOR = 0.651 with p = .059 at 5 years) were obtained for the ≥1.0 SD threshold for baseline CES-D-12, MMSE, and eight SF-36 scale scores (Panel A) and at 1-year postbaseline (Panel B). No differences were observed among the control, memory, or reasoning groups at either time point or at either threshold. For both the ≥0.5 and the ≥1.0 SD thresholds and at both 1- and 5-year postbaseline, adjusting for baseline depressive symptom levels, MMSE scores, and the eight SF-36 scale scores did not alter the magnitude of the protective effects of the speed-of-processing intervention.

DISCUSSION

We have shown significant differences by treatment intervention group in the onset of clinically important increases in depressive symptoms at both 1- and 5-years postbaseline for both the ≥0.5 and the ≥1.0 SD thresholds. These differences were attributable to the protective effect among participants in the speed-of-processing treatment group. When compared with the no-contact control group, these differences amounted to 30% less risk of developing clinically relevant increases in depressive symptoms. Based on the no-contact control group, prevalence of such symptom increases at 1 and 5 years (ie, 28% and 31%, respectively, using the ≥0.5 SD threshold and 13% using the ≥1.0 SD threshold), this translates into substantial attributable

Table 1. AORs Obtained From Multiple Logistic Regression Models of Two Threshold Definitions of Clinically Relevant Increases in CES-D-12 Depressive Symptoms (ie, ≥0.5 SD [Panel A] and ≥1.0 SD [Panel B]) at 1-Year (N = 2,014) and 5-Year (N = 1,516) Postbaseline

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>1 y AOR Adjusted for Baseline CES-D-12 Scores</th>
<th>1 y AOR Adjusted for Baseline MMSE, and Eight SF-36 Scale Scores</th>
<th>5 y AOR Adjusted for Baseline CES-D-12 Scores</th>
<th>5 y AOR Adjusted for Baseline MMSE, and Eight SF-36 Scale Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>0.809</td>
<td>0.798</td>
<td>.827</td>
<td>0.782</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.857</td>
<td>0.881</td>
<td>.875</td>
<td>1.034</td>
</tr>
<tr>
<td>Speed-of-processing</td>
<td>0.700 (p = .012)</td>
<td>0.703 (p = .013)</td>
<td>.697 (p = .013)</td>
<td>0.698 (p = .023)</td>
</tr>
</tbody>
</table>

Note: AORs = adjusted odds ratios; CES-D-12 = Center for Epidemiological Studies–Depression scale, 12-Item Version; MMSE = Mini-Mental State Examination; SF-36 = Short Form 36-Item Health-Related Quality of Life (and includes the physical functioning [10 items], role limitations due to physical functioning [four items], bodily pain [two items], general health perceptions [five items], vitality [four items], social functioning [two items], role limitations due to emotional problems [three items], and mental health [five items] scales).
(ie, absolute) risk reductions of 8.4% and 9.3%, respectively, for the ≥0.5 SD threshold and 3.9% for the ≥1.0 SD threshold. Moreover, these protective effects were not altered by adjusting for baseline depressive symptom levels, MMSE scores, or the eight SF-36 scale scores, suggesting that these factors did not mediate the association between the intervention and the changes in depressive symptoms.

This raises the question of how the speed-of-processing intervention protected against clinically relevant increases in depressive symptoms. There are two main classes of potential mechanisms by which the speed-of-processing intervention may protect against a clinically relevant increase in the number of depressive symptoms. The first includes indirect mechanisms where the protection is mediated by a behavior or function that is directly improved by speed-of-processing training. Candidate mediators include HRQoL (22,23), driving behaviors (37), and timed IADLs (38,39). The second class includes direct mechanisms where the effect of speed-of-processing training affects brain functions related to mood. Candidate mechanisms include the enhancement of neuromodulatory system function through intensive activation of attentional and reward systems during procedural learning (40,41), and a broad enhancement of brain function driven by the regional brain activation resulting from procedural learning (24). Given the importance of depressive symptoms and the risks of polypharmacy in older adults, nonpharmacological approaches (like the speed-of-processing intervention) for protecting against clinically relevant worsening in depressive symptoms have considerable promise in gerontology and geriatrics.

Our results are especially important for five reasons. First, ACTIVE is the largest community-based, multisite RCT ever conducted that focused on improving or maintaining cognitive performance among older adults (19). This substantially increases both the internal and the external validity of our findings (42). Second, the 12-item CES-D is a widely used, highly reliable, and well-validated measure of depressive symptoms (1,27), which substantially increases the construct validity of our findings (42). Third, we used propensity score methods (30–33) to adjust for potential attrition bias in a multiple logistic regression intention-to-treat analysis (34), which substantially increases the statistical conclusion validity of our findings (42). Fourth, we used both medium and large effect size thresholds [≥0.5 and ≥1.0 SD; (29)] for defining clinically relevant increases in depressive symptoms, and our results were robust across definitions and time periods, which further increases both the internal and the construct validity of our findings (42). Fifth, the speed-of-processing intervention is computer based, designed to be self-administered, and allows an individual to proceed at his or her own pace, thus increasing the likelihood that maximal effective dosing could be delivered.

Based on the RCT findings presented here and elsewhere several important cognitive, functional, and psychosocial outcomes, we believe that a more widespread implementation and evaluation of the speed-of-processing intervention within the context of a representative setting is a reasonable next step. A version of the speed-of-processing intervention is now available, which simplifies distribution and delivery, allows individual dosing, and can automatically generate progress reports over the Internet or a standard modem connection to a secure, centralized server. These features could enhance the efficacy of the intervention and should be explored in future clinical research.

Funding

The ACTIVE cognitive training trial was supported by grants from the National Institutes of Health to six field sites and the coordinating center, including the following: Hebrew Senior-Life, Boston (NR04507), the Indiana University School of Medicine (NR04508), the Johns Hopkins University (AG14260), the New England Research Institutes (AG14282), the Pennsylvania State University (AG14263), the University of Alabama at Birmingham (AG14289), and the University of Florida (AG014276). Dr F.D.W. is Co-Center PI of and Drs M.W.V.W. and R.M. are investigators at the Center for Research in the Implementation of Innovative Strategies in Practice at the Iowa City VAMC, which is funded through the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service (HFP 04-149).

Conflicts of interest

The opinions expressed here are those of the authors and do not necessarily reflect those of the funding agencies; academic, research, and governmental institutions; or corporations involved.

Correspondence

Address correspondence to Fredric D. Wolinsky, PhD, Department of Health Management and Policy, College of Public Health, University of Iowa, 200 Hawkins Drive, E205 General Hospital, Iowa City, IA 52242. Email: fredric-wolinsky@uiowa.edu

References


