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Low Vision Depression Prevention Trial in Age-Related Macular Degeneration: A Randomized Clinical Trial.

Barry W. Rovner
*Thomas Jefferson University*

Robin J Casten
*Jefferson Medical College*

Mark T Hegel
*Dartmouth Medical School*

Robert W Massof
*Wilmer Eye Institute, Johns Hopkins University School of Medicine*

Benjamin E Leiby
*Thomas Jefferson University Hospital*

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Running head: Low Vision Depression Prevention Trial

Barry W. Rovner, MD
Robin J. Casten, PhD
Mark T. Hegel, PhD
Robert W. Massof, PhD
Benjamin E. Leiby, PhD
Allen C. Ho, MD
William S. Tasman, MD

Departments of Psychiatry and Neurology, Jefferson Medical College  
Jefferson Hospital for Neuroscience  
900 Walnut Street  
Philadelphia, Pa 19107  
barry.rovner@jefferson.edu

Department of Psychiatry and Human Behavior, Jefferson Medical College  
Jefferson Hospital for Neuroscience  
900 Walnut Street  
Philadelphia, Pa 19107  
robin.casten@jefferson.edu

Departments Psychiatry and Community & Family Medicine  
Dartmouth Medical School  
Dartmouth Hitchcock Medical Center  
One Medical Center Drive  
Lebanon, NH 03756  
Mark.T.Hegel@Dartmouth.edu

Lions Vision Research and Rehabilitation Center  
Wilmer Eye Institute  
Johns Hopkins University School of Medicine  
6th Fl, 550 N Broadway, Baltimore, MD 21205  
rmassof@lions.med.jhu.edu

Division of Biostatistics  
Department of Pharmacology and Experimental Therapeutics, Jefferson Medical College  
1015 Chestnut St., Suite M100, Philadelphia, PA 19107  
bleiby@mail.jci.tju.edu

Wills Eye Institute  
Department of Ophthalmology; Jefferson Medical College
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Members of the Data and Safety Monitoring Committee and the Wills Eye Study Group are listed in Appendix 1.

Address for correspondence and reprints:
Barry W. Rovner, MD
Jefferson Hospital for Neuroscience
900 Walnut Street, 2nd Floor
Philadelphia, PA 19107
barry.rovner@jefferson.edu
TP: 215-503-1254
FAX: 215-503-1992
Abstract

**Purpose:** To compare the efficacy of Behavior Activation+ Low Vision Rehabilitation with Supportive Therapy+ Low Vision Rehabilitation to prevent depressive disorders in patients with Age-Related Macular Degeneration (AMD).

**Design:** Single-masked, attention controlled randomized clinical trial with outcome assessment at 4 months.

**Participants:** Patients with AMD and subsyndromal depressive symptoms attending retina practices (N = 188).

**Interventions:** Prior to randomization, all subjects had two outpatient low vision rehabilitation visits (LVR), and were then randomized to in-home Behavior Activation (BA+LVR) or Supportive Therapy (ST+LVR). Behavior Activation is a structured behavioral treatment that aims to increase adaptive behaviors and achieve valued goals. Supportive Therapy is a nondirective, psychological treatment that provides emotional support and controls for attention.

**Main Outcome Measures:** Diagnostic and Statistical Manual IV-defined depressive disorder based on the Patient Health Questionnaire-9 (primary outcome); Activities Inventory (AI); National Eye Institute Vision Function Questionnaire - 25 plus Supplement (NEI VFQ); and NEI VFQ Quality of Life (secondary outcomes).
**Results:** At 4 months, 11 (12.6%) BA+LVR subjects and 18 (23.4%) ST+LVR subjects developed a depressive disorder (Relative Risk (RR) 0.54; 95% Confidence Interval (CI) [0.27, 1.06]; p = 0.067). In planned adjusted analyses the RR was 0.51; (95% CI 0.27, 0.98; p = 0.04). A mediational analysis suggested that BA+LVR prevented depression to the extent that it enabled subjects to remain socially engaged. BA+LVR was also associated with greater improvements in functional vision than ST+LVR but there was no statistically significant between-group difference. There was no statistically significant change or between-group difference in quality of life.

**Conclusions:** An integrated mental health and low vision intervention halved the incidence of depressive disorders relative to standard outpatient low vision rehabilitation in patients with AMD. As the population ages, the number of persons with AMD and the adverse effects of comorbid depression will increase. Promoting interactions between ophthalmology, optometry, rehabilitation, psychiatry, and behavioral psychology may prevent depression in this population.
Age-related macular degeneration (AMD) is the leading cause of severe vision loss in older adults, with 6.5% having early signs of disease and 0.8% having late disease (i.e., neovascular AMD or geographic atrophy). By 2050, 17.8 million persons will have early AMD and 3.8 million will have late AMD. This will confront ophthalmologists, healthcare decision makers, insurers, and family members with the need to care for many visually disabled older persons. Although antiangiogenic treatments have greatly improved the prognosis of neovascular AMD, the majority of treated patients do not regain lost vision. No medical treatment is available for patients with geographic atrophy. Thus, many patients with AMD experience irreversible vision loss, impaired functional vision, and diminished quality of life. About 10%-30% of patients with AMD develop clinically significant depression, which is associated with higher levels of disability, medical costs, and mortality. Despite the substantial adverse effects of depression, many depressed persons receive no treatment because they perceive depression as a personal failure or an expected part of aging, they are uncertain how to access specialty mental health care, or their physicians lack the expertise or time to effectively diagnose and treat depression.

To investigate an integrated model of treatment, we conducted the Low Vision Depression Prevention Trial (VITAL). VITAL is a randomized controlled trial that compared the efficacy of Behavior Activation+ Low Vision Rehabilitation (BA+LVR) with Supportive Therapy+ Low Vision Rehabilitation (ST+LVR) to prevent progression to more severe depressive disorders in patients with bilateral AMD and early signs of depression. Prior to randomization, all subjects had two visits with low vision.
optometrists. Subjects were then randomized to in-home Behavior Activation or Supportive Therapy. In the former, occupational therapists delivered Behavior Activation to address depression and functional deficits due to vision loss. Behavior Activation is a structured behavioral treatment that aims to increase adaptive behaviors and achieve valued goals. In ST+LVR, master’s level therapists delivered in-home Supportive Therapy, which is a nondirective, psychological treatment that provides emotional support and controls for attention. The primary hypothesis of VITAL was that BA+LVR would be more effective than ST+LVR to prevent depressive disorders and improve functional vision and quality of life.
Methods:

Eligibility and Trial Design: Institutional Review Board (IRB)/Ethics Committee approval was obtained to conduct the Low Vision Depression Prevention Trial (clinical trials.gov NCT00769015). All subjects provided informed consent; study procedures were HIPAA-compliant and adhered to the tenets of the Declaration of Helsinki.

Subjects were recruited from a large private retina practice associated with the Wills Eye Hospital, Philadelphia, PA, who met the following inclusion criteria:

1) age over 65 years; 2) bilateral AMD (either neovascular disease or geographic atrophy); 3) best corrected visual acuity worse than 20/70 in the better-seeing eye; 4) more than 5 antiangiogenic injections if the better eye had neovascular disease, or no injections in the previous 3 months; 5) moderate difficulty performing a valued vision-dependent activity; and 6) subthreshold depressive symptoms, defined as a Patient Health Questionnaire-9 score greater than 5, or depressed mood or anhedonia several days per week. The exclusion criteria were: 1) on-going or anticipated antiangiogenic treatment; 2) current Diagnostic and Statistical Manual (DSM) IV-defined depressive disorder; 3) uncontrolled glaucoma, diabetic retinopathy, corneal dystrophy, or anticipated cataract surgery; and 4) cognitive impairment on an abbreviated version of the Mini-Mental Status Examination that omits vision-dependent items.

The study statistician randomized eligible subjects using a random-numbers table, sealed envelopes containing treatment assignments, and a fixed randomization scheme.
with a 1:1 allocation ratio to the 2 study groups, stratified by severity of vision loss (visual acuity of 20/70 to 20/100 vs. worse than 20/100 in the better eye).

**Treatment Interventions:**

**Low Vision Optometry:** One of five community-based low vision optometrists evaluated and treated all subjects prior to randomization. The two clinic visits included assessment of vision function (e.g., visual acuity, refraction), and prescribing devices and providing instruction on their use. The study provided $350 to all subjects to purchase a basic set of optical devices. Following these visits, subjects were randomized to Behavior Activation, which was delivered by one of five occupational therapists, or Supportive Therapy, which was delivered by one of three master’s level therapists (e.g., social workers).

**Behavior Activation (BA) + Low Vision Rehabilitation (LVR) [BA+LVR]:** The occupational therapists delivered 6 in-home, one hour Behavior Activation sessions over 8 weeks. Treatment emphasized the link between action, mood, and mastery, and promoted self-efficacy and social connection as ways to improve mood and function and counter self-defeating behaviors (e.g., social withdrawal). The occupational therapist suggested environmental modifications to improve function and, with the subject, developed Action Plans to accomplish valued personal and functional goals. The Action Plans drew on rehabilitation principles (e.g., breaking down tasks into manageable steps), were integrated into daily routines, and focused on increasing social activities.
and reducing vision-related task difficulty. The latter was accomplished by increasing magnification, improving lighting, highlighting objects with high-contrast tape, and simplifying routines.

**Supportive Therapy (ST) + Low Vision Rehabilitation (LVR) [ST+LVR]:** Supportive Therapy therapists delivered 6 in-home, one hour sessions over 8 weeks to facilitate discussion of illness, disability, and vision loss. Treatment facilitated personal expression about vision loss and disability and, in this trial, controlled for the nonspecific effects of attention.¹²

**Treatment Fidelity:** All sessions were audiotaped and an experienced psychotherapy researcher (MTH) and a certified low vision OT reviewed one-third of randomly selected tapes. On a scale from 1 to 5, with 5 representing better standing, the global treatment fidelity ratings of the occupational therapists and supportive therapists were above satisfactory (i.e., ≥ 3) at 3.5 (1.2) and 4.9 (.80), respectively.

**Study Measures:** Research assistants evaluated subjects in their homes masked to treatment assignment at baseline and 4 months to assess the following variables:

1. **Depression:** The primary outcome was a DSM IV diagnosis of major or minor depression based on the Patient Health Questionnaire-9 (PHQ-9).¹³ The PHQ-9 includes the 9 criteria that define DSM IV diagnoses of depression and is valid in low
vision patients.\textsuperscript{16} A scoring algorithm determines if the profile of symptoms meets
categorical diagnoses of depression.

\textbf{2. Self-Reported Functional Vision:} This was assessed using the Activities Inventory
and the National Eye Institute Vision Function Questionaire-25 (NEI VFQ) near and
distance activities subscales.\textsuperscript{17, 18} The Activities Inventory measures the ability to
achieve general vision-dependent activity goals, and perform specific vision-dependent
cognitive and motor tasks. An overall functional vision variable is estimated by Rasch
analysis.\textsuperscript{19} The NEI VFQ rates difficulty performing daily activities. Standardized scores
range from 0 to 100, with higher scores indicating better function.

\textbf{3. Vision-Related Quality of Life:} This was a latent variable comprised of the NEI
VFQ social functioning, mental health, role difficulties, and dependency subscales.
Standardized scores range from 0 to 100 with higher scores indicating better life quality.

\textbf{4. Vision Status:} This included standardized measurement of distance and near visual
acuity, contrast sensitivity, and the size and location of central scotomas.

\textbf{5. Physical Health Status:} This was assessed with the Chronic Disease Score and
the Medical Outcomes Study-6 (MOS-6). The Chronic Disease Score yields a weighted
score based on medication use that reflects severity of medical comorbidity.\textsuperscript{20} The
MOS-6 yields a global index of self-rated physical and mental health.\textsuperscript{21} Higher scores
on both scales reflect worse health status.
6. Personality: The Revised Neuroticism, Extroversion, Openness Five Factor Inventory (NEO-FFI) was used to assess the personality traits of neuroticism, conscientiousness, and openness to experience.\textsuperscript{22} Higher scores reflect higher standing on a given trait.

7. Behavioral Activation for Depression Scale: This scale measures engagement in social and occupational activities.\textsuperscript{23} Its four subscales tap: activation; avoidance/rumination; work/school impairment; and social impairment. Scores range from 0 to 42; higher scores reflect worse functioning.

8. Device Use: Subjects rated their frequency of use of various low vision aids (e.g., task lighting) and devices (e.g., magnifiers) to improve visual ability.

Statistical Methods

A sample of 144 subjects provided 90\% power to detect a 50\% reduction in depression incidence at 4 months. This calculation assumed equal numbers in the 2 visual acuity strata (with a 60\% incidence rate of depression in controls in the worse vision stratum, and 50\% in the better vision stratum) using a 2-sided continuity-corrected Mantel-Haenszel test of the hypothesis that the risk ratio equaled 1. Type I error rate was set at 5\%. We planned to recruit an additional 56 subjects to control for possible
improvements in visual acuity in subjects who might receive additional antiangiogenic treatments during the study and to account for a 10% attrition rate.

Continuous baseline demographic and clinical characteristics were summarized using means and standard deviations, and categorical variables using counts and percentages. For the primary efficacy analysis, we calculated stratum-specific relative risks and 95% confidence intervals for the incident depressive disorder at 4 months using Mantel-Haenszel methods. Poisson regression with robust standard errors was used to compute estimates of the intervention’s effect on depression incidence adjusted for important baseline variables. The stratification variable (visual acuity) and baseline depression score (PHQ-9) were included as adjustment covariates in all models. Other baseline covariates considered were related to the outcome at the bivariate level with p values < .10. Linear mixed effects models were used to analyze all available Activities Inventory, NEI VFQ, and Behavioral Activation for Depression Scale data at baseline and 4 months. We extended the mixed effects model to jointly analyze the four NEI-VFQ quality of life subscales at baseline and 4 months to account for correlation among the four subscales and allow for a multivariate test of group differences in change over time. Mediation analysis was performed using structural equation models.
Results

Figure 1 depicts the study flow chart. From July 2009 to February 2013 we reviewed the records of 2,324 potentially eligible patients. Of them, 1,158 (49.8%) declined participation, 706 (30.4%) were ineligible, and 272 (11.8%) could not be reached. There were no significant differences between enrolled subjects and eligible patients who declined participation in age, sex, or visual acuity (data not shown). Baseline assessments were conducted on 222 subjects. Of them, 23 subjects declined further participation and 11 were ineligible. Thus, 188 subjects were randomized to the two study interventions. Their average age was 84.0 years (standard deviation 6.94); 70.2% were women and 50.0% lived alone. As shown in Table 1, the demographic and clinical characteristics of subjects in the two treatment groups were similar except that BA+LVR subjects were somewhat older and married.

From baseline to 4 months, 19 (10.1%) subjects dropped from the trial (7 Behavior Activation; 12 Supportive Therapy). These subjects had higher baseline Chronic Disease Scores (i.e., worse medical status) and worse visual acuity than retained subjects but did not differ in PHQ-9 or MOS-6 scores (data not shown). After 4 months, there were no significant within-group or between-group changes in visual acuity, contrast sensitivity, scotoma size, Chronic Disease Score, or Behavioral Activation for Depression Scale scores (data not shown). The mean number of treatment sessions that BA+LVR and ST+LVR subjects received were 5.7 (1.1) and 5.0 (1.9), respectively.
Table 2 shows that 11 (12.6%) BA+LVR subjects and 18 (23.4%) ST+LVR subjects developed a depressive disorder by 4 months (Relative Risk (RR) 0.54; 95% Confidence Interval (CI) [0.27, 1.06]; p = 0.067). The treatment effect was more evident in subjects in the worse vision stratum (RR 0.37; 95% CI [0.14, 0.96]) than in subjects in the better vision stratum (RR 0.80; 95% CI [0.29, 2.18]). Overall, the absolute risk reduction was 11% and the number needed to treat (NNT), or number of patients who need to be treated to prevent one additional case of depression, was 9. For subjects with worse vision, the risk reduction was 20% and the NNT was 5. For subjects with better vision, the risk reduction was 3.4% and the NNT was 29. Baseline covariates that were associated with incident depression were higher MOS-6 score (i.e., worse self-rated health) and NEO-PPI neuroticism score (i.e., the trait tendency to experience negative affects).

Table 3 shows the results of an adjusted regression analysis that included treatment group, vision stratum, and baseline better eye scotoma size and PHQ-9, MOS-6, and neuroticism scores. The regression revealed that BA+LVR subjects were significantly less likely to develop a depressive disorder than ST+LVR subjects after adjustment for the covariates (RR 0.51; 95% CI [0.27, 0.98]; p = 0.04). Higher MOS-6 score remained an independent predictor of incident depression (RR 1.13 [95% CI [1.04, 1.21]) for each 1 point increase; p = 0.014).

To examine the potential impact of attrition, we conducted three separate sensitivity analyses. In the first analysis, all subjects with missing data who were alive at 4 months...
were considered as depressed. The stratum-adjusted RR was 0.56 (95% CI 0.34, 0.92); p=0.018. In the second analysis, all were considered not depressed. The stratum-adjusted RR was 0.58 (0.29, 1.16); p=0.12. In the third analysis, we used multiple imputation to create 100 data sets with imputed depression status for patients alive but without follow-up data. The imputation model included vision stratum, PHQ-9 score, and the other baseline covariates that were significantly related to depression incidence. The relative risk of incident depression was 0.56 (95% CI 0.29, 1.10); p=0.083. These analyses suggest that attrition did not impact the observed treatment effect to a substantial degree.

Table 4 shows change in Activities Inventory, NEI-VFQ functional vision and quality of life, and Behavioral Activation for Depression Scale subscale scores at 4 months by treatment group. Activities Inventory scores improved in both treatment groups. Although the effect was larger in BA+LVR (effect size = 0.72) than ST+LVR (effect size = 0.56), there was no statistically significant difference between groups. On the NEI VFQ, BA+LVR subjects had a statistically significant improvement in near activities (p=0.007) whereas ST+LVR subjects did not (p=0.20). In spite of this within-group difference, there was no statistically significant between-group difference (p=0.34). There were no significant within-group changes or between-group differences in distant activities or quality of life. BA+LVR subjects used a greater number of low vision devices than ST+LVR subjects [3.7 (1.5) vs. 2.9 (1.6); p = .003].
ST+LVR patients had significant declines in the Behavioral Activation for Depression Scale *Social Impairment* [mean change = -1.14 (-2.08, 0.21); p=0.02] while BA+LVR subjects had no decline. Figure 2 shows a significant effect of treatment on change in the *Social Impairment* (a), a significant association between change in *Social Impairment* and incidence of depression (b), and a nearly significant indirect effect of treatment on depression (a x b). These data suggest that change in *Social Impairment* at least partially mediated the relationship between treatment group and incident depression, such that BA+LVR prevented depression to the extent that it enabled treated subjects to remain socially engaged.
Discussion

We found that an integrated mental health and low vision intervention halved the incidence of depressive disorders (i.e., 12.6% versus 23.4%) relative to standard outpatient low vision rehabilitation in a high risk population of patients with AMD. Previous studies indicate that the incidence of depression in the absence of any rehabilitative treatment in patients with AMD ranges from 20%-28%. The preventive efficacy of BA+LVR was strong, with a NNT of 9 to prevent 1 case of depression. For subjects with worse vision, the NNT was 5, a remarkably good result. By comparison, the NNT is 38 for intensive glycemic control over 4 years to prevent one case of clinically important diabetic retinopathy. A mediation model suggested that social activation accounted for BA+LVR’s therapeutic effect.

BA+LVR was also associated with improved near functional vision. Although ST+LVR was associated with some but lesser improvement, the observed differences were not statistically significant. The low vision optometry treatment that all subjects received likely accounts for improvements in both groups. We found no significant changes in distance functional vision because BA+LVR focused on near activities. The quality-of-life measures failed to show a statistically or clinically significant change, likely reflecting the insensitivity of the measures to change. We also found that worse self-rated health was associated with incident depression independent of treatment. This finding indicates that patients with worse health perceptions require more intensive interventions.
VITAL is the first clinical trial to test a collaborative mental health care model that was integrated into an ophthalmologic setting. The strengths of this trial include systematic recruitment, successful randomization, low attrition, high subject adherence to protocol-driven treatments, maintenance of treatment fidelity, and control for attention. Generalizability and durability of treatment effects are uncertain, however, given the unique characteristics of the sample, the high refusal rate, and the relatively short follow-up period. A second limitation is reliance on the PHQ-9 for depression diagnosis rather than on a clinical interview. Despite these limitations, VITAL contributes to the growing literature on the benefits of LVR. The Low Vision Intervention Trial (LOVIT) demonstrated the efficacy of outpatient LVR to improve reading, mobility, information processing, and visual motor skills. Horowitz et al found that optical device use reduced functional disability and depressive symptoms in low vision patients. Brody et al found that a psychological self-management intervention improved well-being in patients with AMD, and we previously demonstrated the benefits of Problem Solving Therapy in patients with AMD. These studies indicate that LVR programs, especially those that emphasize social engagement, benefit patients with chronic vision loss.

Although depression is an understandable reaction to AMD, its high prevalence, persistence, associated disability, costs, and suicide risk make it a formidable problem. The 24% incidence rate of depression that we observed in controls substantiates this. Unfortunately, there are no established mechanisms to treat
depression in ophthalmologic settings. If depression were recognized, referral to primary care physicians alone would not meet patients’ vision rehabilitative needs. We developed a treatment alternative based on evidenced-based practice that screened for depression, increased linkages to LVR, and trained occupational therapists to deliver Behavior Activation. We standardized the intervention to facilitate its dissemination and drew on current Medicare reimbursement policies to support it, although Medicare does not reimburse for vision assistive equipment. In its current form, BA+LVR can serve as an initial treatment model to prevent depression in vision-impaired populations. Few occupational therapists, however, receive formal training in psychotherapies like BA to counter depression, and many ophthalmologists fail to refer patients to LVR. Thus, treatments like BA+LVR are not currently available. To become part of routine ophthalmologic care would require a commitment to comprehensive interdisciplinary care and financial investment to support standardized depression screening, psychiatric consultation, care coordination, and clinical and administrative staff training.

The cost savings of preventing depression are substantial because patients with depression have significantly higher total healthcare costs than nondepressed patients ($20,046 vs. $11,956). In this context, BA+LVR aligns with the intent of the Affordable Care Act, capitation-based contracts, and pay-for performance reimbursement strategies which support cost-lowering and quality-improving interprofessional interventions. As the population ages and the number of persons with AMD increases, the personal losses, disability, and costs of AMD will rise. This clinical trial suggests that increasing interactions between ophthalmology, optometry, rehabilitation, psychiatry,
and behavioral psychology can improve how we deliver care and achieve better outcomes for patients with AMD.
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* Deceased
References


