

Anxiety and depression in patients with advanced macular degeneration: current perspectives

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Abstract: Age-related macular degeneration (AMD) – despite advances in prevention and medical treatment options – remains prevalent among older adults, often resulting in functional losses that negatively affect the mental health of older adults. In particular, the prevalence of both anxiety and depression in patients with AMD is high. Along with medical treatment options, low vision rehabilitation and AMD-specific behavioral and self-management programs have been developed and have demonstrated effectiveness in improving the mental health of AMD patients. This article reviews the prevalence of anxiety and depression in patients with advanced AMD, discusses potential mechanisms accounting for the development of depression and anxiety in AMD patients, presents the state-of-the-art of available interventions for addressing anxiety and depression in AMD patients, and delineates recommendations for eye care professionals regarding how to screen for these two prevalent mental health problems and how to facilitate appropriate treatment for patients with AMD.

Keywords: age-related macular degeneration, vision impairment, depression, anxiety, vision rehabilitation, behavioral and self-management interventions

Introduction

Age-related macular degeneration (AMD) is a common cause of vision impairment and blindness¹ affecting approximately 9% of the global population. It is most prevalent among individuals with European ancestry.² Approximately 0.4% of the general population has late or advanced AMD with the prevalence of advanced AMD rising to 8% among those 75 years of age and older.³ While the prevalence of all types of AMD has somewhat declined over the past decade, due to enhanced medical prevention and treatment options,⁴ the number of people with all types of AMD is expected to increase due to the rapid and consistent growth of the aging population. Recent projections estimate that worldwide the number of individuals with AMD will reach 196 million in 2020 and 288 million in 2040.²

There are two major types of AMD: one is the atrophic or non-exudative AMD, which progresses slowly and accounts for 80%–90% of AMD cases. The other type is the neovascular or exudative AMD which affects 10%–20% of patients but progresses rapidly, accounting for 80%–90% of cases with severe vision loss.^{5,6} Research has shown that a combination of antioxidant vitamins and mineral supplementation reduces the risk of developing advanced AMD in patients with intermediate atrophic AMD.⁷ Furthermore, anti-VEGF treatment was found to be effective in the clinical management of neovascular AMD.^{8,9}

The most common negative consequence of the vision impairment caused by AMD is increased functional disability,^{10–12} which puts AMD patients at increased risk for mental health problems such as high levels of clinical depression and anxiety.^{13–15} It was

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the hope that with the advent of effective treatment options for AMD that functional disability and the risk for mental health problems could be reduced. However, while most patients with neovascular AMD can achieve positive treatment outcomes from anti-VEGF injections, there are approximately 10% whose treatment outcomes are non-optimal and fall below their expectations and are, therefore, still at increased risk for depression.¹³ Hence, current advances in treatment options cannot eliminate the risk for mental health problems in individuals with advanced AMD.

Therefore, this article provides an overview of the prevalence of anxiety and depression in patients with advanced AMD, discusses potential mechanisms that account for the development of depression and anxiety in patients with AMD, presents the state-of-the-art of available interventions for addressing anxiety and depression in patients with AMD, and proposes recommendations for eye care professionals regarding how to screen for these two prevalent mental health problems and how to facilitate appropriate treatment for patients with AMD.

Prevalence of depression and anxiety in patients with AMD

Depression and anxiety are common in older adults,¹⁶ and even more common in older adults with visual impairment. Clinically significant subthreshold symptoms of depression have been found in approximately one-third of visually impaired older adults, which is approximately twice as high as the lifetime prevalence rates in the normally sighted general older population,^{13,15,17} where depressive symptoms affect roughly 15%.^{18,19} The prevalence of major depressive disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria in visually impaired samples aged ≥ 60 years ranges from approximately 5% to 7%,^{15,17} while in community studies prevalence rates of just under 2% are reported.^{18,19}

Among older adults with visual impairment, those with AMD seem to be particularly at risk for depression compared to those with other eye diseases.^{10,20} Popescu et al²¹ compared rates of depression in older adults with AMD, glaucoma, and Fuchs corneal dystrophy and found the highest rate of 39% in the AMD group. When treatment outcomes fall below expectations, rates of depression are high even among those AMD patients who received VEGF treatment.¹⁰

Reports on anxiety are more variable. A recent study of 615 visually impaired individuals aged 60 years and over (55.3% with AMD) showed that 15.6% had subthreshold symptoms of anxiety, compared to 11% in normally sighted peers.¹⁷ Over 7% (7.5%) of visually impaired persons were

diagnosed with an anxiety disorder according to the *DSM-IV*, compared to 3.2% in the normally sighted. Agoraphobia (4.2%) and social phobia (2.4%) were particularly prevalent among those with visual impairment. Thus, as the authors conclude, visually impaired older adults are more prone to develop anxiety disorders related to specific places or social situations such as being on a bus or eating at a restaurant.

Among patients with AMD, prevalence estimates range between 9.6% and 30% for anxiety.²² However, case-control studies found that people with AMD were not more likely to experience symptoms of anxiety compared to those without AMD.²² Likewise, in a community-based sample of 662 individuals aged over 70 years, anxiety was significantly associated with self-reported cataract, but not with AMD.²⁰ Taken together, significant numbers of older adults with AMD experience depression and anxiety; thus, both constitute major public health problems in this population. However, symptoms of depression seem to be more prevalent than symptoms of anxiety and appear to be more prevalent among older adults with visual impairments compared to other adult populations. Nevertheless, there is evidence that specific anxiety disorders are particularly prevalent in visually impaired older adults, requiring specific interventions.

Potential mechanisms for the development of depression and anxiety in AMD

Four potential mechanisms for the development of depression and anxiety among patients with vision loss have been suggested. First, a strong relationship exists between loss of functional capacity and depression symptoms.^{13–15} Initial responses to the loss of functioning and valued activities may primarily consist of distress and frustration, and in some cases, a diagnosable adjustment disorder. A vicious cycle develops for the patient when the distress around these losses precipitates depression symptoms. The decreased motivation associated with these depressive symptoms leads to less engagement with valued activities, which, in turn further exacerbates the symptoms, and may exacerbate subthreshold or minor depression to major depressive disorder.

The second mechanism is a basic deficit in problem solving skills. Most AMD patients are 60 years and older, and have developed a well-tested repertoire of skills to approach common problems in life. Vision loss, however, is a novel problem for which such skills have not been developed and existing skills may not be sufficient to address this problem. Thus, approaches that emphasize actively approaching, developing, and applying problem solving skills have been found successful in reducing existing depression symptoms

for a variety of populations,²³ including older, primary care patients with depression²⁴ and depressed patients with comorbid executive functioning.²⁵ In addition, problem solving treatment (PST) approaches can be effective in preventing depression symptoms among older patients with vision loss.²⁶ These studies rely on teaching participants a systematic problem solving technique with which to remove barriers to activity engagement and increase pleasurable activities. Third, based on the life-span theory of control,²⁷ some authors suggest that different control strategies may need to be enacted at different stages of AMD.^{12,23} This theory proposes that it is of evolutionary advantage for individuals to use a variety of strategies to maximize control over their life and environment. These “control strategies” may be classified as primary – aimed at actively changing the external environment – or secondary – adapting one’s attitudes to better match losses in active control (eg, goal adjustment). The theory further suggests that both primary and secondary control can be either selective or compensatory. Thus, selective primary control, means that the older adult invests his or her energy, time, and effort in selected high priority goals (such as putting in additional effort to being able to read), whereas selective secondary control describes when motivational resources, such as goal commitment are used selectively (such as giving up one’s preference for reading for a less preferred, but feasible option: books on tape). Compensatory primary control describes a strategy in which the individual bolsters behavioral and emotional resources by external means (obtaining visual aids to help with reading), whereas compensatory secondary control involves “disengaging from the unattainable goal through self-protective strategies”,²⁸ such as reducing the importance of reading for one’s well-being and seeking other sources of information. In the context of vision loss, primary control strategies that involve putting in more effort to harness internal resources and using low vision devices to maintain functioning are most useful early in the disease process. With declining vision and loss of everyday functioning it may be more useful to refocus one’s energy on realistic rather than futile goal pursuits (eg, finding non-visual sources of information). This helps preserve a sense of self and contributes to the preservation of psychological health, because it reduces the frustration of feeling inadequate. In contrast, when inappropriate control strategies are used, the risk for distress is elevated.

Finally, recent work suggests that AMD is particularly difficult for individuals to cope with because it involves a poor future outlook: either sudden, unpredictable losses in visual field or visual acuity (for exudative AMD), or gradual

and untreatable vision loss over decades (for dry AMD).^{5,6} Dreading these future changes contributes to anxiety and feelings of hopelessness. Although the specific type and level of vision loss is difficult to predict in AMD, a gradual loss of certain abilities can be anticipated both as a result of AMD and aging in general. Many older adults, for example, must make decisions about whether to remain living at home or move into a more supportive environment. Sörensen et al have proposed an approach to preventing these psychological sequelae to vision loss by adapting problem solving therapy to include preparing for potential future needs and making plans for future loss of function.²⁹ This preventive problem solving training combines vision loss group education with in-home training. The education addresses AMD characteristics, etiology, and progression in lay terms, presents potential in-home adaptations to low vision, explains orientation and mobility training concepts, and probes potential emotional reactions to vision loss. The in-home training starts with traditional problem solving approaches and then applies these techniques to “areas of future concern”. Participants generate and/or are shown a list of potential future problems and work through how they can prepare for these. Preliminary results (not yet published or peer reviewed) in a randomized clinical trial suggest that depression symptoms are reduced post-preventive problem solving training for women in the treatment vs control group and for men at 6-month follow-up.³⁰

Interventions designed to address depression and anxiety in AMD patients

Although research has consistently demonstrated that there is a high prevalence of depression in older people with impaired vision^{31–36} and that depression is most likely to develop in those who experience activity limitations (such as reduced participation in social activities and leisure pursuits),^{37,38} depression in visually impaired persons, is under-diagnosed and treated.^{33,36,39,40} This is concerning because AMD is associated with diminished quality of life, accelerated functional decline, and costly sequelae such as falls and nursing home placement.⁴¹ Depression may exacerbate these risks. Until we develop standardized and effective protocols for detecting and managing depression in this high risk population, a large proportion of patients with AMD will be at risk of potentially preventable consequences.⁴¹

Low vision rehabilitation approaches

Current treatment for AMD consists of medical treatment (for neovascular AMD), vitamin therapy, and low

vision rehabilitation. For many patients, however, medical treatment is either not indicated (eg, anti-VEGF treatment is not effective for dry AMD), or when it is, many patients continue to experience psychological distress.¹³ Low vision rehabilitation aims to reduce vision-related disability by maximizing residual vision through training in the use of optical and assistive devices, orientation and mobility skills, and general compensatory strategies. But is low vision rehabilitation a reasonable treatment for depression? To the extent that depression in AMD results from activity restrictions, and that low vision rehabilitation fosters activity re-engagement, low vision rehabilitation might have an “antidepressant” effect. It may even ward off feelings of anxiety. From a cost perspective, it is worth considering whether existing treatment modalities, such as low vision rehabilitation, ameliorate mental health problems. In the case of depression, some studies show improvement in depression following standard low vision treatment,^{42,43} while others do not.^{40,44} Rees et al⁴⁵ and Roets-Merken et al⁴⁶ provide comprehensive reviews of the topic. To our knowledge, there are no studies investigating the effects of low vision rehabilitation in reducing anxiety in AMD patients. However, we do know that fewer than 25% of low vision rehabilitation service providers in the US offer any psychological treatment.⁴⁷

Mixed findings notwithstanding, it must be noted that patients with depression may be less likely to utilize low vision services,^{40,48} and thus research that evaluates the efficacy of rehabilitation to reduce depression may be hindered by selection bias. From a clinical standpoint, the association between depression and underutilization of low vision rehabilitation suggests that service uptake may be impeded in patients who have severe depression, because of the motivational symptoms associated with the disorder. Furthermore, patient characteristics (eg, personality traits) and treatment barriers (eg, transportation issues, financial limitations) may drive inconsistent study results, and perhaps suggest that a “one size fits all” approach to rehabilitation is not ideal.

Behavioral and self-management programs

To better address the psychological health of low vision patients, AMD-specific behavioral and self-management programs have been developed and tested in randomized controlled trials, but are not currently part of standard care.^{49–58} A core element of many of these interventions is teaching problem solving skills to help patients manage limitations brought on by vision loss. Holloway et al synthesized the results of eight studies that examined the efficacy

of problem solving based interventions to improve vision function, emotional distress, and depression. Overall, these types of intervention were found to be mildly successful in improving emotional distress, but there was no significant impact on depression. This finding should be interpreted cautiously because only half of the studies included in this review assessed depression as an outcome, the number of included studies was small, and many of the studies included participants who were not depressed. Treatment effects, however, were strongest in patients who were depressed at the start of treatment.⁵⁹

Highlights of problem solving based studies are as follows. The “Preventing Depression in AMD” trial tested the efficacy of PST to prevent depression in patients with newly diagnosed AMD.⁴⁹ PST taught patients problem solving skills to compensate for activity limitations during six home-based treatment sessions. Participants were randomized to PST or a usual care control group. At 2 months, 12% of PST participants were depressed compared to 23% of controls ($P<0.05$) indicating that PST-treated participants had half the rate of depression 2 months post-treatment. PST participants were less likely to relinquish valued activities than control participants (23% vs 37%, respectively; $P=0.04$). A meditational analysis showed that PST prevented depression to the extent that activity relinquishment was minimized. These effects, however, were not sustained, as rates of depression were similar in both groups at 6 months (21% of PST participants vs 27% of controls). This trial demonstrated that a problem solving skill-based intervention can prevent depression in the short term but that beneficial effects decay over time.

Rees et al⁴⁵ developed and tested a self-management program that was grounded in problem solving theory to address patients’ functional and emotional needs. Compared to controls, participants in the active treatment group did not show improved quality of life, emotional well-being, self-efficacy, or improved adaptation to vision loss at 6 months. Results of this study, however, have limited applicability because the sample contained a mix of ophthalmologic diagnoses, and overall, was psychologically healthy at baseline. Brody et al^{51,60} designed a self-management program that included basic information about AMD, education on rehabilitative strategies, and problem solving skills training. Compared to controls, treatment participants had significant improvements in mood and function at 6 weeks, and these effects were strongest for participants who were depressed at baseline. Intervention effects were sustained at 6 months. Birk et al⁶¹ pilot tested a group-level self-management intervention that included progressive muscle relaxation,

sharing of experiences, techniques for coping with negative thoughts and feelings, information regarding resources, and problem solving. Participants in the active treatment group had decreased depressive symptoms, and increased function scores, feelings of autonomy, and active coping. Although neither group demonstrated an increase in positive affect, the control group had increased negative affect. Wahl et al⁶² compared two self-management interventions (emotion-focused and problem-focused) in a pilot study of 54 participants. The emotion-focused intervention was based on Birk et al's program.⁶¹ It was hypothesized that the emotion-focused intervention would lead to improved depressive symptoms and that the problem-focused intervention would result in better adaptation to vision loss. Results showed that those in the emotion-focused intervention had a greater decline in depression immediately after the intervention. As expected, participants in the problem-focused intervention demonstrated greater improvement in problem solving-orientation and adaptation to vision loss. None of the beneficial effects of either intervention were sustained 2 months post-intervention, suggesting that longer term interventions, or perhaps maintenance doses, may be needed. Overall, studies that tested problem based interventions were successful in treating depressed participants, however, effects tend to decay over time.

Depression treatment in combination with low vision rehabilitation

Another strategy for treating and/or preventing depression is to bundle depression treatment with low vision rehabilitation. Girdler et al⁵⁰ compared low vision rehabilitation enhanced with a self-management group to usual care in 77 older persons attending a low vision clinic (most had AMD). The enhanced intervention was an 8-week group program led by a social worker and an occupational therapist in which participants were taught strategies for managing vision loss. Participants in the enhanced intervention group had higher levels of activity engagement and lower rates of depression (17% vs 51%; $P < 0.001$). They also reported greater improvements in activity participation, self-efficacy, and adjustment to vision loss. This study shows that an integrated low vision rehabilitation program that addresses psychosocial functioning may prevent and treat depression.

Rovner et al²⁶ conducted a randomized trial to test the efficacy of a depression focused low vision rehabilitation intervention to prevent depression in patients with AMD and subclinical depressive symptoms. All participants were evaluated by a low vision optometrist, prescribed appropriate

low vision devices, and were randomized to six in-home occupational therapy sessions or six in-home placebo sessions that involved supportive therapy (ie, non-goal directed empathic listening). Participants in the occupational therapy group, in addition to being taught compensatory strategies, were administered a behavioral treatment for depression. The rate of depression at 4 months was halved in the actively treated group compared to the placebo group (12.6% vs 23.4% respectively, $P = 0.04$). Active treatment participants became more socially activated.

Conclusions on intervention approaches

While there are no published studies evaluating the effectiveness of interventions designed to treat anxiety symptoms in AMD patients, many of the above reviewed studies show that behavioral interventions can treat or prevent depression in AMD. At this time, researchers and practitioners have a better understanding of the mechanisms linking vision impairment to depression. Also, researchers have identified therapeutic "ingredients" of successful interventions (for example, teaching problem solving skills, facilitating social engagement) to treat depression in AMD. Wahl⁶³ and Schilling et al⁶⁴ suggest that a life-span approach to adaptation to vision loss may enhance existing treatment. The life-span theory of control suggests that early on in the disease process, it is in patients' best interests to enact primary control strategies such as harnessing internal resources (eg, effort) and utilizing external strategies (eg, use low vision devices) to maintain function. As vision declines and functional deficits increase, secondary strategies can enable patients to divest resources from futile goal pursuits in order to preserve sense of self (eg, devalue unobtainable goals and divert energy to realistic goals). This shift in control strategy may be vital to preserving psychological health.

Implications for future research

The next challenge is to develop an evidence-based intervention that can be implemented within existing care models, meets a broad range of treatment needs (eg, rehabilitative, psychological, social), and is streamlined, cost effective, and reimbursable. For instance, Margrain et al⁶⁵ are currently investigating an integrated approach in which low vision patients will be screened for depression. Patients who have significant depressive symptoms will be randomized to a PST arm, a depression referral group, or a wait list control group. Participants in the PST group will receive a collaborative PST in which a trained interventionist will provide depression treatment and will integrate the low vision treatment plans into the patients' care.

Reimbursement policies will likely have to be modified to accommodate the treatment of psychiatric symptoms. The current system covers low vision rehabilitation only if there is potential to improve performance of activities of daily living, including self-care and home management skills. Maintenance therapy, which research suggests may be necessary to maintain benefits, are not covered.

Recommendations for eye care professionals

In the absence of available practice models that specifically address depression and anxiety, traditional low vision rehabilitation (which includes care provided by low vision optometrists, occupational therapists, low vision specialists, and other professionals with training in low vision rehabilitation) presents the best current treatment option to address these mental health problems in a rehabilitation context. We suggest that to improve the status quo, practitioners should incorporate depression and anxiety screenings into rehabilitation programs, so that patients whose depression and/or anxiety is not responding to rehabilitation can be identified and referred to targeted mental health care. Moreover, better outreach models may be needed to attract, in particular, depressed patients and facilitate their participation in low vision rehabilitation.

How can eye care professionals best address depression and anxiety in patients with AMD?

At the most accessible level, depression screenings, in particular, should be done in the ophthalmology clinic. Indeed, the preferred practice guidelines from the American Academy of Ophthalmology advise that:

The ophthalmologist may inquire about symptoms of clinical depression and, when appropriate, suggest that the patient seek professional advice, as depression may exacerbate the effects of AMD.⁶⁶

Ophthalmologists and other eye care professionals are uniquely positioned to identify vision-related deficits and related psychiatric symptoms. Discussing depression, for example, with patients can be awkward, uncomfortable, and time consuming, and few eye care professionals have specific training in this area. Most patients, however, do not feel embarrassed or uncomfortable when discussing depression.⁶⁷ Such conversations can be initiated by asking patients what their vision loss is preventing them from doing, how their independence is hindered by AMD, what they fear most about

the loss of vision, and whether they are able to participate in enjoyable activities such as hobbies and social interaction. This line of questioning can be followed by the administration of a brief, standardized depression screen. The Depression module from the Patient Health Questionnaire-9 (PHQ-9; http://www.phqscreeners.com/pdfs/02_PHQ-9/English.pdf) is a useful tool for assessing whether depression symptoms or tendencies are present.⁶⁸ For increased efficiency, some clinicians ask the first two items of the PHQ-9 as an initial depression screen. If the patient endorses either of these items, the clinician follows up with the remaining seven. This can be a time-saving way to screen large groups of patients to improve detection of undiagnosed depression.⁶⁹

The same screening procedure could be used for anxiety. However, whereas efficient screening tools for depression are available to eye care professionals, anxiety screens are more difficult to identify, especially because anxieties among patients with AMD are often situation-specific. The most likely candidate, the Generalized Anxiety Disorder 7-item scale (GAD-7; http://www.phqscreeners.com/pdfs/03_GAD-7/English.pdf),⁷⁰ does not take into account the situational nature of AMD-related anxiety. Nevertheless, if there is reason to suspect a more generalized anxious response to either the diagnosis of AMD or related loss of vision, this scale is widely used and has been validated with a variety of populations. Given our limited understanding of anxiety in the context of AMD, our subsequent discussion will focus on depression.

For patients who screen positive for significant depressive symptoms, eye care professionals can destigmatize depression, emphasize that depression is a common and understandable reaction to vision loss, and explain that suffering due to depression can be alleviated by treatments such as medication, psychotherapy/counseling, or perhaps low vision rehabilitation. A brief note to the patient's primary care physician to alert them to the patient's depression may lead to indicated mental health treatment and result in symptom reduction. For example, low vision patients who were referred to their primary care physicians, and were subsequently treated for depression, experienced significant reduction in symptoms.⁷¹ Other research demonstrates that when "watchful waiting" procedures are implemented for older low vision patients, approximately one-third of those with subclinical depression recovered. On the other hand, 18% developed worsening, clinically significant depressive or anxiety disorders.⁷²

Who should be screened for depression?

Research shows that the severity of vision loss is not related to depression among older adults with vision impairments.

Perceptions of vision impairment, rather than objective measures such as visual acuity, are more strongly correlated with depression.⁷³ In fact, patients who report functional vision problems (eg, difficulty navigating steps or seeing objects in peripheral vision) are 90% more likely to be depressed than patients who do not report such problems, independent of visual acuity.⁷³ It is therefore suggested that all patients with AMD be screened for psychiatric symptoms, regardless of AMD stage.

Integrating routine depression screening into ophthalmology care will necessitate efficient training programs. Rees et al⁷⁴ researched and subsequently responded to the need for depression training among eye care professionals. They interviewed 94 eye care staff (including 20 ophthalmologists) regarding their attitudes toward and knowledge about depression. On average, the respondents estimated that slightly more than half of all ophthalmology patients may be depressed, and most correctly identified the characteristic symptoms of depression. Yet, at the same time, many failed to recognize the physical symptoms of depression (eg, bodily pain), and incorrectly believed that depression could be treated with sleep medications or alcohol. Respondents' confidence discussing depression and its treatment was moderate at best. The investigators⁷⁵ then pilot tested a depression training program. It was delivered over the course of three 90-minute sessions, and covered topics such as education about depression, screening, and implementation strategies. Post-training interviews showed increased confidence discussing and screening for depression. As a result, 44% of participants have initiated plans to institute depression screening into their practices.

Conclusion

In conclusion, AMD is a prevalent eye condition among older adults which can have profound consequences for both functional and psychological well-being. There is mounting and consistent evidence that depression is common within this population, with approximately one-third reporting clinically significant depressive symptomatology. The prevalence of depression among older adults with AMD is also higher than among both general populations of older adults and those with other common age-related medical conditions. While there has been less research regarding the prevalence and consequences of anxiety, some preliminary evidence indicates that older adults with AMD are also at greater risk for anxiety disorders than their age-peers without AMD. Also, it is important to remember that depression and anxiety often co-exist. The results of several clinical trials testing

mental health interventions to treat depression among older adults with AMD have shown promising short-term results, especially those incorporating problem solving techniques and behavioral activation. Unfortunately, treatment effects do not appear to be maintained over time and additional studies are needed to determine optimal dosage and/or "booster" sessions needed to achieve long-term remission of depressive symptoms. It is clear, however, that eye care clinicians can no longer ignore the importance of addressing depression and anxiety among their patients with AMD. At the very least, screening for depression and anxiety needs to be incorporated in regular practice, especially given the availability of relatively simple tools with established validity.^{68,70} Integrated models of care, meshing both low vision rehabilitation and mental health services, seem the most promising, and continued research is needed to demonstrate the effectiveness and efficacy of such models in improving both functional and mental health among older adults with advanced AMD.

Disclosure

The authors report no conflicts of interest in this work.

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