

Early Detection and Treatment of Neovascular Age-related Macular Degeneration

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Background: The neovascular form of age-related macular degeneration (AMD) can rapidly lead to severe loss of central vision and adversely affect the patient's quality of life. During the 1990s the only proven treatment for neovascular AMD was laser photocoagulation. Only a minority of patients are eligible to receive this treatment, however, and the treatment itself can cause acute retinal damage with immediate vision loss. Verteporfin therapy is a new treatment option involving photodynamic therapy that was recently shown to be relatively safe and effective in reducing the risk of vision loss in selected cases.

Methods: Recent literature was reviewed on management of choroidal neovascularization caused by AMD that proved beneficial in large-scale randomized clinical trials. These studies were selected through a MEDLINE search of files from 1982 to the present using the keywords "randomized clinical trials," "choroidal neovascularization," and "age-related macular degeneration," as well as through personal knowledge of recently completed trials.

Results and Conclusions: Primary care physicians can effect good treatment outcomes by detecting early signs of AMD and educating patients about the necessity of prompt referral to an ophthalmologist. Immediate referral is increasingly important because, compared with laser photocoagulation, current photodynamic therapy with verteporfin is applicable to more patients. Greater patient awareness of neovascular AMD and the importance of self-testing of vision can also be communicated to patients in primary care. (J Am Board Fam Pract 2002;15:142-52.)

Primary care physicians can play an important role in preventing loss of vision in patients with age-related macular degeneration (AMD). This condition is the most frequent cause of severe vision loss in persons older than 50 years in the Western world.¹ The prevalence of AMD increases with age and is likely to rise as the population of those older than 65 years increases. Worldwide estimates indicate that by 2020 as many as 8 million persons older than 65 years could suffer from AMD.²

To assist in the management of this common condition, primary care physicians should understand the natural history of AMD, know how to recognize those persons at risk of developing severe vision loss, and be able to interpret the earliest symptoms of the disease. They can also educate patients about AMD and refer appropriate patients promptly so that suitable treatment can be started, if indicated.³ An international survey found that only 2% of adults considered AMD to be the leading cause of blindness among those older than 50 years, and 82% of those surveyed were not familiar with AMD.⁴ To enhance the benefits that can be achieved with therapy for AMD, it is important to increase awareness among primary care physicians and their patients.

A new treatment for neovascular AMD, verteporfin combined with photodynamic therapy, has proved beneficial and has been approved by regulatory authorities in many countries, including the European Union and the United States. Previously, the only available treatment was laser photocoagu-

Submitted, revised, 15 June 2001.

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Supported in part by the Michael B. Panitch Stop AMD Research Fund. Dr. Bressler is also a consultant to QLT, Inc, and Novartis Ophthalmics. The terms of this agreement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

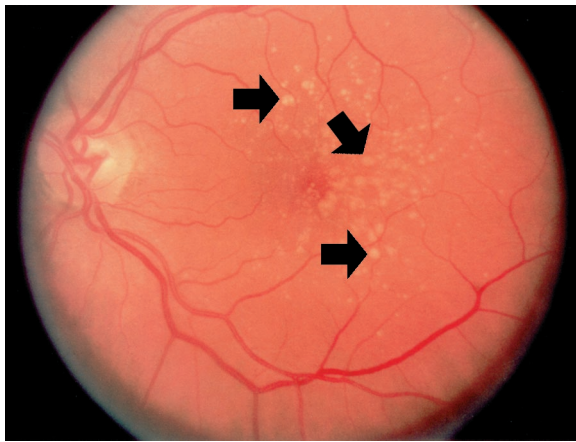


Figure 1. Fundus photograph showing numerous, large drusen (arrows) caused by abnormal thickening of the basement membrane of retinal pigment epithelium. Large drusen are larger than approximately one half of a retinal vein width as it passes over the optic nerve. (Reproduced with permission from the Wilmer Photograph Reading Center.)

lation. Because of this new treatment, the number of patients with AMD who can be treated has increased considerably.

Methods

A MEDLINE search of files from 1982 to the present used the keywords “randomized clinical trials,” “choroidal neovascularization,” and “age-related macular degeneration.” Selected recent reports of large-scale randomized clinical trials on management of choroidal neovascularization caused by AMD that proved beneficial were reviewed. A personal knowledge of recently completed trials also was incorporated into the literature.

Classification of Age-related Macular Degeneration

The macula is the region in the center of the retina that is responsible for central vision. The ability to perform such visual functions as reading, driving, and recognizing faces depends on the macula. The formation of drusen (yellow spots in the center of the macula, Figure 1) is an early sign of AMD (usually without significant vision loss), and they can be seen with an ophthalmoscope. There are two forms of AMD, neovascular and nonneovascular. Estimates indicate that only 10% to 20% of all patients with any sign of AMD have the neovascu-

lar form of the disease.^{5,6} Neovascular AMD, also known as exudative (or wet) AMD, accounts for approximately 90% of cases with severe vision loss, however.⁶ Considerable vision loss can also result from features associated with nonneovascular AMD, sometimes referred to as atrophic (or dry) AMD, but serious vision loss occurs much more rarely than with neovascular AMD.

Neovascular AMD is characterized by choroidal neovascular lesions. These lesions develop when abnormal blood vessels from the choroid grow and proliferate through breaks in the Bruch membrane (a layer between the retina and choroid) to beneath the retinal pigment epithelium (the outermost layer of the retina) (Figure 2). The abnormal leakage from these vessels can result in hemorrhage or detachment of the retinal pigment epithelium or the neurosensory retina (which overlies the retinal pigment epithelium). Accompanying scar formation can replace retinal tissue and result in permanent vision loss.

Risk Factors

A good understanding of the risk factors for AMD can help the physician be aware of those patients most at risk of developing the disease. Although increased age is the principal risk factor, epidemiologic studies have found several other risk factors associated with AMD, including cigarette smoking, elevated levels of serum cholesterol, hypertension, cardiovascular disease, race, and family history.⁷ A positive association between smoking and neovascular AMD has been suggested in both men⁸ and women,⁹ whereas an inverse association has also been found between dietary carotenoid intake and AMD.¹⁰ With the exception of age, however, none of these studies has indicated a definite causal relation between a specific risk factor and AMD.

Neovascular AMD in one eye is believed to predispose a person to developing neovascular AMD bilaterally. There is a high risk (>40%) of developing choroidal neovascularization in the second eye within 5 years of the development of choroidal neovascularization in the first eye.¹¹ Ocular and systemic risk factors for the development of choroidal neovascularization in the second eye include large drusen (greater than one half of the width of a retinal vein as it passes over the optic nerve), numerous drusen (at least five), focal hyperpigmentation of the retinal pigment epithelium, and systemic hypertension.⁷

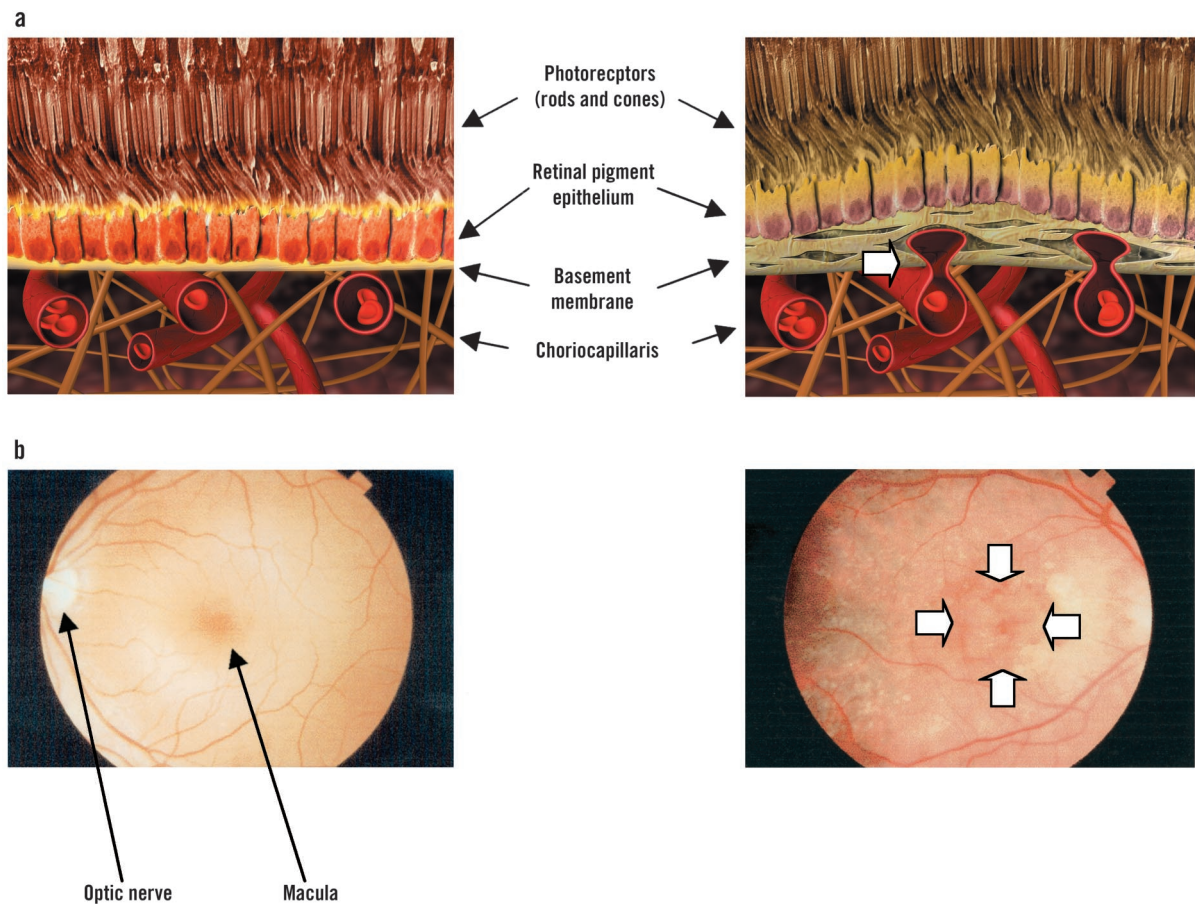


Figure 2. (a) Schematic diagrams showing histologic cross-section of the outer retina, and (b) fundus photographs of a normal eye (left panels) and one with penetration of basement membrane of the retinal pigment epithelium by new blood vessels from the choriocapillaris (right panels). The white arrows show an example of a choroidal neovascular lesion. (Schematic diagrams reproduced with permission from Novartis Ophthalmics AG. Fundus photograph [left panel] reproduced courtesy of the National Eye Institute, National Institutes of Health. Fundus photograph [right panel] reproduced with permission from the Wilmer Photograph Reading Center.)

Clinical Signs and Symptoms of Neovascular Age-related Macular Degeneration

Neovascular AMD has a wide spectrum of clinical manifestations, and symptoms can include loss of central vision with scotoma or distortion of central vision (metamorphopsia) (Figure 3), which patients often report as distortion of straight lines, such as door frames or posts or both. Light glare and loss of contrast sensitivity can also occur. Patients might notice that the size or color of objects appears different with each eye, and there might be showers of floaters or clouding of the entire visual field caused by vitreous hemorrhage. Photopsias (flickering or flashing lights) and formed hallucinations also can be associated with choroidal neovascularization.¹²

A major problem is that some patients might initially ignore symptoms of vision loss because they consider them to be a normal part of the aging process or incorrectly attribute them to the development of cataracts.¹³ This problem could be compounded if primary care physicians fail to inquire about sight problems in the patients at risk of developing AMD or do not warn patients how to recognize symptoms of AMD. Furthermore, symptoms can occur in only one eye. Because the brain can suppress awareness of the abnormal image when the other retina is healthy, the patient might be unaware that the first eye has been affected until the disease is at an advanced stage. Some with choroidal neovascularization can be asymptomatic, especially if the lesion is small or some distance



Figure 3. An example of how vision loss might be perceived in an eye of a patient with neovascular age-related macular degeneration if the observer looks at the center of the figure. (Reproduced with permission from Novartis Ophthalmics AG.)

from the fovea. Because of the rapid progression of the disease, the family physician should explain to patients who have drusen why they should see an ophthalmologist as quickly as possible, particularly if a patient experiences sudden deterioration of vision.¹⁴

Disease Impact

The visual prognosis for most patients with neovascular AMD is poor. Severe loss of central vision can be rapid. Visual acuity of a Snellen equivalent of 20/200 or less (which is classified as legal blindness when it occurs in the better-seeing eye) develops in many affected eyes within 2 years of diagnosis.¹⁵ The Macular Photocoagulation Study Group reported that approximately 12% of patients who had unilateral neovascular AMD and 50% of patients with bilateral neovascular AMD were legally blind within 5 years.¹⁶

Although neovascular AMD almost never causes total blindness, if it occurs in both eyes, patients' ability to perform normal daily tasks is greatly impaired and their quality of life is adversely affected.^{17,18} Those with neovascular AMD can experience difficulty with high-resolution tasks, such as reading, sewing, and telling the time; and some

might have trouble driving or distinguishing colors and facial expressions. Loss of vision leading to loss of independence and lowered self-esteem can be stressful for patients and their families. Visual impairment can decrease mobility, increase the risk of injury caused by falls,¹⁹ and result in emotional distress and depression.¹⁸

Diagnostic Tests for Neovascular Age-related Macular Degeneration

Diagnosis of neovascular AMD when it might be treatable is based mainly on an ophthalmoscopic examination using slit-lamp biomicroscopy and fluorescein angiography. Ophthalmoscopy is used to detect macular abnormalities that have characteristic features of neovascular AMD, including an elevation of the retinal pigment epithelium, subretinal or intraretinal fluid, lipid or hemorrhage, subretinal green-gray lesions, or subretinal fibrous tissue.²⁰ Fluorescein angiography is a special form of photographic imaging (not using x-rays) by which choroidal neovascularization can be visualized. Fluorescein dye is injected intravenously, and fundus photographs are taken at intervals up to 10 minutes after the dye injection.²¹ If choroidal neovascularization is suspected, imaging with fluorescein an-

giography can confirm its presence and determine whether treatment is indicated. The composition, size, and location of choroidal neovascularization on fluorescein angiography can influence the subsequent management and prognosis.

Patterns of fluorescence in these images can categorize choroidal neovascularization as classic or occult. Classic choroidal neovascularization appears as a bright area of well-demarcated choroidal fluorescence on the early phase of the angiogram, with leakage of fluorescein beyond the boundaries of this bright area appearing in the mid-phase frame (1 to 2 minutes after dye injection) and late-phase frame (5 to 10 minutes after dye injection). Occult choroidal neovascularization is indicated by an area of stippled or granular hyperfluorescence in the late-phase frames of the angiogram.

There are large variations in the natural course of AMD with respect to occult and classic choroidal neovascularization, depending on the composition of the neovascular lesion. In addition, the size and location of the lesion in relation to the central macula can strongly influence the course of the condition. Whereas most choroidal neovascular lesions in AMD include occult neovascularization and are subfoveal (under the center of the fovea),²² loss of visual acuity is most rapid in patients who have either classic choroidal neovascularization without occult neovascularization or predominantly classic choroidal neovascularization (the area of neovascularization is $\geq 50\%$ of the area of the entire lesion). The average loss of visual acuity is slower in patients who have occult choroidal neovascularization without classic neovascularization or who have minimal classic choroidal neovascularization (the area of neovascularization is $<50\%$ but $>0\%$ of the area of the entire lesion).

Treatment of Neovascular Age-related Macular Degeneration

The principal aim of treatment of neovascular AMD is to preserve visual acuity and to reduce the risk of additional severe vision loss for as long as possible. This goal can be accomplished by destroying the choroidal neovascularization without causing serious damage to the retina, thereby reducing the likelihood of progressive destructive scarring of the retina overlying and surrounding the choroidal neovascularization. There are currently two treatments for neovascular AMD that

have proved effective in large-scale randomized clinical trials: laser photocoagulation and photodynamic therapy with verteporfin.

Laser Photocoagulation

During the 1990s, most research into treatment focused on laser photocoagulation. The Macular Photocoagulation Study Group showed that laser photocoagulation was effective in the treatment of well-defined extrafoveal²³ or juxtafoveal²⁴ choroidal neovascularization secondary to AMD. In patients with subfoveal choroidal neovascularization, however, laser photocoagulation was not beneficial in eyes that had large lesions and moderate-to-good initial visual acuity. Furthermore, in the short term, eyes with small-to-medium subfoveal lesions and moderate-to-good visual acuity were more likely to have a worse outcome after laser photocoagulation until about 12 months after entry into the trials.²⁵ Only an estimated 13% to 26% of patients who have choroidal neovascularization meet the strict criteria used to select patients who would benefit from treatment.²⁶

The laser photocoagulation treatment itself causes thermal injury to the overlying retina and can cause a subsequent absolute scotoma. Consequently, most patients who have subfoveal lesions are not treated, because they might experience an immediate and permanent decline in central vision equivalent to the decline experienced in untreated patients. Unfortunately, most patients have a lesion that extends under the center of the retina. Moreover, even for patients receiving laser photocoagulation to lesions that do not extend under the foveal center, there is a high incidence (at least 50%) of recurrence of choroidal neovascularization through the foveal center within 1 to 3 years, which could result in further vision loss.^{27,28}

Verteporfin Therapy

Verteporfin therapy is a relatively new technique involving photodynamic therapy. Verteporfin (a benzoporphyrin derivative monoacid, BPD-MA; Visudyne, Novartis AG) is a light-activated drug that has proved effective in reducing the risk of vision loss in selected patients with subfoveal neovascular AMD.²⁹⁻³¹ The application of photodynamic therapy with verteporfin involves two main steps: intravenous infusion of the light-activated drug and activation of the drug by light at a specific wavelength (689 nm) with a low-power, nonther-

mal laser. The drug can be taken up by neovascu-
lature,²⁶ and light-activation induces a photochem-
ical reaction in the target area that causes
immunologic and cellular damage, including endo-
thelial damage of new vessels. Endothelial damage
and the resulting platelet adhesion, degranulation,
and subsequent thrombosis and occlusion of the
vasculature might be the predominant mechanism
by which light-activated drugs work. The therapy
includes retreatment as often as every 3 months if
leakage from choroidal neovascularization is de-
tected on follow-up fluorescein angiograms.

One of the principal aims of verteporfin therapy
for neovascular AMD is to damage choroidal neo-
vascularization selectively while preserving the ad-
jacent normal choriocapillaris, retinal pigment ep-
ithelium, and neurosensory retina. The goal is to
avoid the absolute scotoma caused by laser photo-
coagulation and permit the treatment of a broader
range of subfoveal choroidal neovascularizations
with respect to lesion size and initial visual acuity.

The safety and efficacy of verteporfin therapy
were shown in the phase III Treatment of AMD
with Photodynamic Therapy investigation, com-
prised of two 2-year, randomized, multicenter,
placebo-controlled, double-masked studies.^{29,30}
Verteporfin therapy resulted in a clinically relevant
benefit in patients with predominantly classic sub-
foveal choroidal neovascularization secondary to
AMD. In these patients, the risk of losing 15 or
more letters (equivalent to ≥ 3 lines of vision and
judged to be a noticeable and functionally impair-
ing deficit) on an eye chart was reduced from 61%
in the placebo-treated cases to 33% in the verte-
porfin-treated cases after 1 year. Two-year results
confirmed that these benefits were sustained, at
which time the risk of losing 15 or more letters was
reduced from 69% in the placebo-treated cases to
41% in the verteporfin-treated cases.³⁰ A subse-
quent trial showed that the therapy could reduce
the risk of moderate and severe vision loss in se-
lected patients with subfoveal lesions composed of
occult with no classic choroidal neovasculariza-
tions.³¹ These phase III studies suggested that as
the length of follow-up increases, the number of
cases requiring retreatment decreases, with fewer
retreatments needed in the second year of thera-
py.²⁹⁻³¹

The most frequently reported adverse events
with verteporfin therapy, occurring in approxi-
mately 10% to 20% of patients, were injection-site

reactions (including extravasation) and transient vi-
sual disturbances (including blurred vision, de-
creased visual acuity, and visual field defects). Less
than 5% of patients develop a severe decrease in
vision within the first week after treatment; despite
this possibility, the risk of severe loss of vision in 3
months is greater without treatment. Verteporfin
undergoes rapid clearance from the body,³² so sen-
sitive structures, such as the eyes and skin, are
photosensitive for only a short period. Patients
must be warned, however, that they will be sensi-
tive to direct sunlight or bright indoor lights for 24
to 48 hours after drug infusion and that they should
avoid direct sunlight for about 2 to 5 days after
treatment. It is most important for patients consid-
ering treatment to be aware that less than 5% of
treatments are associated with severe decrease in
vision within 1 week following treatment, only
some of which might be reversible.

The greatest benefits can be achieved if the
diagnosis is made early and patients receive verte-
porfin therapy before the lesions become too large
or cause too much destruction of the retina. Verte-
porfin therapy has now been approved by regula-
tory authorities in many countries, including the
European Union and the United States, and pro-
vides the means to treat neovascular AMD in many
patients whose condition was previously considered
untreatable. If these patients are to benefit from
treatment, it is vital that primary care physicians
educate patients and make prompt referrals to an
ophthalmologist, as needed.

Role of Primary Care Physicians in Neovascular Age-related Macular Degeneration

The development of effective treatments that re-
duce the risk of further vision loss (although they
rarely result in substantial vision improvement) and
prevent legal blindness makes it even more impor-
tant to detect neovascular AMD at an early stage so
that patients can be treated quickly. Many lesions
can become too large to treat with laser photoco-
agulation within a short time after diagnosis.³³ In
contrast, photodynamic therapy with verteporfin
can reduce the risk of vision loss in larger lesions
where early detection can allow treatment of cases
before serious loss of vision has occurred.

Regular screening and increased public aware-
ness of AMD can facilitate early detection. Im-

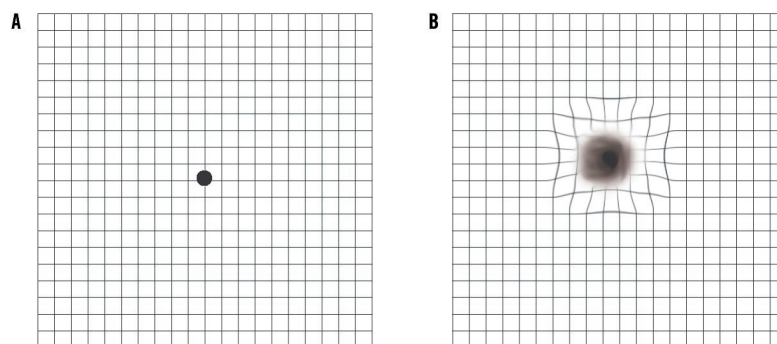


Figure 4. (a) A normal view of an Amsler grid and (b) the distortion of the straight lines (metamorphopsia) and black spot (scotoma), as might be seen by a patient with neovascular age-related macular degeneration.

proved education of primary care physicians is essential to increase recognition of the early signs and symptoms of neovascular AMD.³⁴ Studies have shown that training primary care physicians to recognize sight-threatening diabetic retinopathy can improve the rates of detection and referral to ophthalmologists of patients at high risk of vision loss³⁵; the same might be true for patients with AMD.

Screening

Primary care physicians play an important role in screening for AMD and referring patients to specialists.^{36–38} The rationale to screen patients for early-stage AMD has three key elements: (1) physicians can recognize the early signs of AMD (drusen), (2) they can instruct those patients in how to perform a self-examination that might detect choroidal neovascularization as soon as it develops or refer the patient to an eye care provider who can offer that education, (3) they can consider recommending an oral supplementation of a daily dose of antioxidants (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta carotene) and minerals (80 mg of zinc oxide and 2 mg of cupric oxide) to reduce the risk of vision loss from neovascular AMD or geographic atrophy,³⁹ and (4) they can provide prompt referral to an ophthalmologist who manages choroidal neovascularization as soon as it is suspected.

Although in the general population most patients recognize vision problems themselves, neovascular AMD can be asymptomatic at an early stage and remain undetected if self-examination is not performed daily, one eye at a time. The ability to detect neovascular AMD in one eye can be hin-

dered if the other eye has good vision, because with both eyes open the good eye compensates for the impaired vision in the affected eye. Thus, vision screening for persons older than 50 years might be valuable in managing AMD, especially if a person at risk of developing choroidal neovascularization is not performing a daily self-check. Screening tests should be simple, inexpensive, readily available, and quick to perform. Questionnaires, tests of visual acuity, and direct ophthalmoscopy can be included in the screening process.

An eye chart is useful to detect impairment of visual acuity.⁴⁰ Patients with AMD can have good acuity, however, and AMD can be missed if only visual acuity is tested.⁴¹ Most importantly, primary care physicians can perform direct ophthalmoscopy (after pupil dilation with 1–2 drops of 2.5% phenylephrine as a sympathomimetic to stimulate pupillary dilation and 0.5%–1.0% tropicamide as a parasympatholytic to inhibit pupillary constriction). Detection of any large drusen (Figure 1) should alert the physician to the early development of AMD. The physician can then inform the patient that he or she is at risk of developing neovascular AMD, consider oral supplementation of antioxidants and minerals as described above, and teach the patient how to monitor the condition, or the physician can refer the patient to an ophthalmologist.

Early diagnosis of neovascular AMD can be possible by using an Amsler grid or similar pattern of straight lines. A distortion of straight lines is a common early symptom of neovascular AMD (Figure 4). Patients are asked to cover one eye and, holding the grid at a comfortable reading distance (using any habitual reading glasses), focus on the

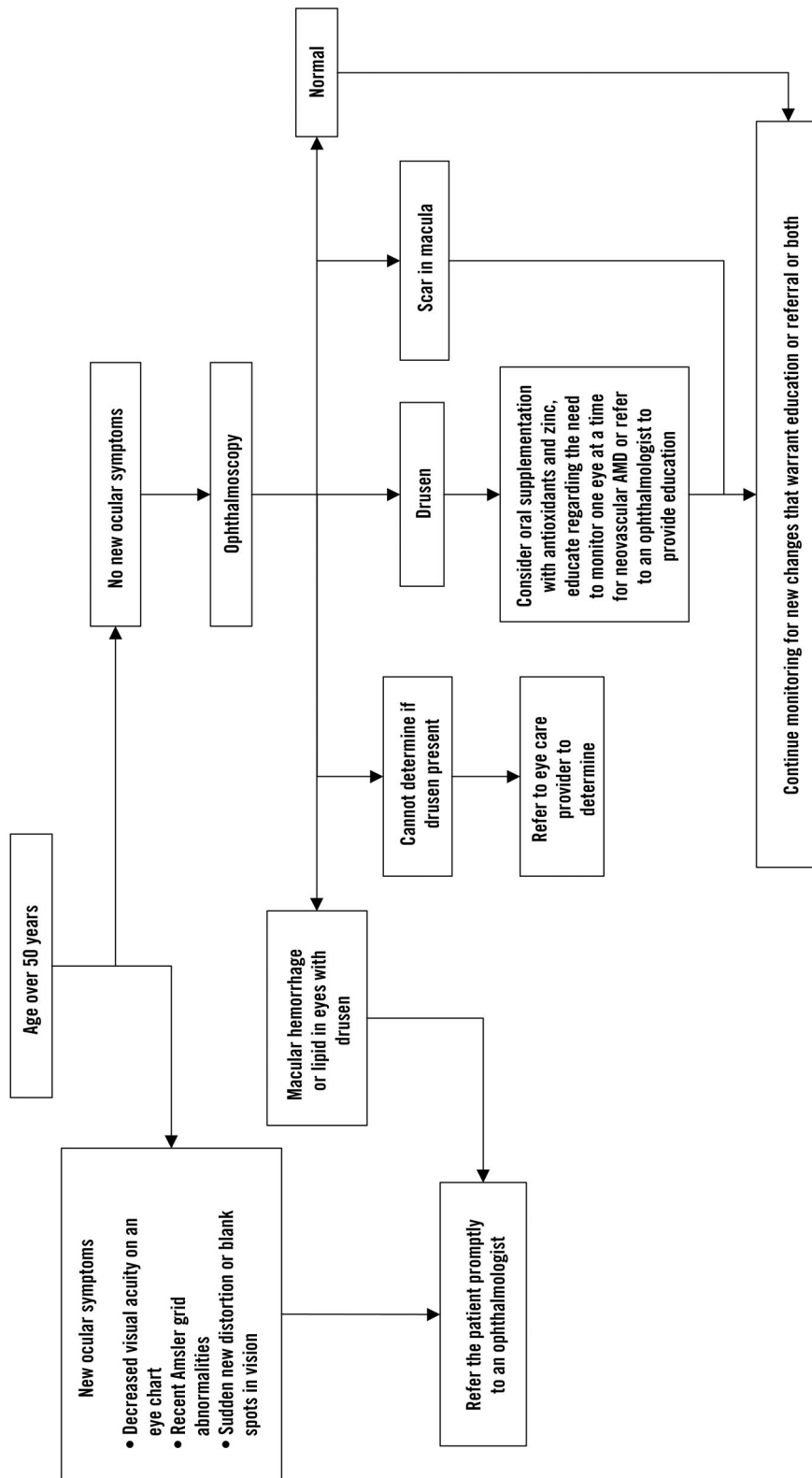


Figure 5. Proposed guidelines for primary care physicians for managing age-related macular degeneration.

center dot. They should then cover the other eye and repeat the procedure. Daily self-testing with an Amsler grid might be recommended to those at high risk of developing choroidal neovascularization (such as those who have large drusen) to detect early changes in central vision.⁴² Early detection of neovascular AMD would allow the patient to be evaluated promptly by an ophthalmologist, who can then confirm the diagnosis and determine whether laser photocoagulation or verteporfin therapy is indicated before the lesion becomes too large or causes serious vision loss. Because self-testing with an Amsler grid does not always detect neovascular AMD, regular assessment by an ophthalmologist is also advised.

Referral

Primary care physicians who suspect AMD should promptly refer their patients to an ophthalmologist. An algorithm for referral of patients with early signs of AMD (drusen) and suspected choroidal neovascularization is displayed in Figure 5. The risk factors that should prompt the physician to refer a patient include drusen (in the absence of symptoms), age older than 50 years, complaints of symptoms (difficulty reading or recognizing faces, flickering or flashing lights, showers of floaters, or straight lines appearing bent), and documentation of decreased visual acuity or previous distortion that has suddenly worsened. Signs that can be reliably detected only after dilation of the pupil include hemorrhage in the central macula of an eye with drusen.^{20,43} If the primary care physician is not comfortable in determining whether a patient has macular abnormalities (especially drusen) through a dilated pupil, the patient should be referred to an ophthalmologist to ascertain treatment.

Patient Education

Well-informed patients with visual symptoms are more likely to seek treatment before irreversible vision loss occurs.⁴⁴ Thus, it is important that physicians explain to patients with drusen the effects of neovascular AMD or refer their patients to an ophthalmologist who can provide this explanation.

Patients at high risk of developing neovascular AMD should be encouraged to check their central vision in each eye daily by looking at a straight object (such as a door frame or a telephone pole) or an Amsler grid.⁴³ It is important to emphasize the

need to respond promptly to any visual symptoms, so that treatment, if indicated, can be given before the condition progresses to an irreversible, untreatable stage.

The benefits and limitations of treatment should be explained to patients, emphasizing that it is not possible to reverse the deterioration, but that prompt treatment can preserve vision or reduce the risk of vision loss. Finally, all health care providers should give emotional support and reassurance, as well as referral to low-vision services, when appropriate. When vision loss is inevitable, patients should be helped to accept and adjust to a new lifestyle and taught to use low-vision aids. They should be assured that neovascular AMD almost never leads to total blindness.

Conclusions

Primary care physicians play a prominent role in the detection of neovascular AMD and in the facilitation of rapid referral of patients to ophthalmologists for detailed investigation and appropriate treatment. Patient education and teaching self-testing are also areas of increasing importance. Laser photocoagulation and photodynamic therapy with verteporfin each can reduce the risk of vision loss in selected patients with neovascular AMD. Oral supplementation with antioxidants and minerals can reduce the risk of vision loss in patients with drusen. Early detection and prompt referral are essential to ensure that patients gain optimal benefit from treatment.

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