Minireview

Repurposing medications for treatment of age-related macular degeneration: Insights from novel approaches to data mining

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Impact Statement

The prevalence of age-related macular degeneration (AMD) is expected to significantly grow in the coming decades, causing debilitating impacts on patients' quality of life while generating striking medical costs. Ophthalmologists are limited with the current therapeutic tools available to address this oncoming burden. Moreover, traditional methods of drug development are constrained and cannot guarantee to produce a new drug that is effective, affordable, and timely in nature. Drug repurposing, however, represents an efficient and cost-effective method to expand therapeutic tools for AMD using medications that are already approved and available. This review details several candidates that hold promise for repurposing, as shown through observational studies and advanced bioinformatics. It is the first review to detail all such candidates and may help spark prospective, clinical trials required to successfully repurpose medications for AMD.

Abstract

The economic and visual burdens associated with age-related macular degeneration (AMD) are expected to significantly increase in the coming years. As of now, interventions to delay or prevent AMD are limited. Hence, there is an urgent and unmet need to expand our therapeutic tools for AMD in a manner, that is, both efficient and cost-effective. In this review, we consider the idea of drug repurposing, in which existing medications with other indications can be re-imagined for treating AMD. We detail the results of several population-level studies that have shown associations between several candidates and decreased risk of AMD development or progression. Such candidates include the more extensively studied metformin and statins, in addition to recently identified candidates fluoxetine and L-DOPA (levodopa) that show promise. We then briefly explore results from an advanced bioinformatics study, which provides further evidence that existing medications are associated with AMD risk genes. Many of these candidates warrant further study in prospective, clinical trials, where their potential causal relationships with AMD can be thoroughly assessed.

Keywords: Age-related macular degeneration, drug repurposing, bioinformatics, big data, ophthalmology, retina

***Experimental Biology and Medicine* 2023; 248: 798–810. DOI: 10.1177/15353702231181188**

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in developed nations, with projections estimating that there will be 288 million global cases of AMD by the year 2040.[1] AMD's increasing prevalence will continue to significantly impact patients' quality of life,[2] while also generating economic costs measuring in the billions of dollars among the domains of direct medical care, indirect medical care, and productivity.[3] Clinically, AMD has been categorized into early, intermediate, and late stages. Drusen and retinal pigment epithelium (RPE) abnormalities are features of early or intermediate AMD, while late AMD is hallmarked by geographic atrophy and/or choroidal neovascularization.[4] The terms dry AMD and wet AMD are classically used to describe the absence or presence of neovascularization, respectively. Well-established risk factors for AMD include smoking,[5] obesity,[6] hypercholesterolemia,[7] female sex,[7] and advancing age.[8] Lifestyle alterations around these modifiable factors, namely smoking cessation and consumption of a low-fat diet, likely reduce risk but are also inadequate to prevent AMD development among all patients.

The visual burdens associated with AMD, combined with its increasing prevalence, pose a dire need for effective therapies targeting both dry and wet forms. Treatment for wet AMD relies primarily upon the use of intravitreal injection of agents that target vascular endothelial growth factor (anti-VEGF). Multiple anti-VEGF formulations have been shown to prevent vision loss and improve mean visual acuity in patients with wet AMD, showing corresponding decreases in retinal thickness and angiographic leakage.[9]

ISSN 1535-3702

Anti-VEGF agents now represent the gold-standard treatment for wet AMD, underscoring a transformation in the prognosis of this morbid stage of AMD. However, long-term studies of patients with AMD that underwent treatment with these antiangiogenic agents revealed that mean visual acuity decreased by 2.6–3 letters from baseline to five- to seven-year follow-up.[10,11] Furthermore, 18–20% of patients had a visual acuity of 20/200 or worse in these long-term studies.[10,11] Despite clear advances in managing wet AMD in recent years, there remains a large unmet need to further expand the therapeutic tools available for patients.

Treatment options for dry AMD are even more limited. The Age-Related Eye Disease Study (AREDS) investigated the effect of vitamin and mineral supplements on AMD prevention and progression. These supplements included beta-carotene, vitamin C, and vitamin E, all antioxidants, along with zinc.[12] These supplements are colloquially known as AREDS vitamins. While the dry form accounts for approximately 85% of AMD cases, current treatment with AREDS formulations mostly aims to prevent progression to advanced AMD in patients meeting specific high-risk criteria. AREDS formulations are associated with only a modest 28% risk reduction for progression to advanced AMD at five-year follow-up, with a 34% risk reduction at 10-year follow-up, and these reductions are primarily reserved for those patients with intermediate stages of AMD.[13,14] A further clinical trial found that the addition of lutein, zeaxanthin, and omega-3 fatty acids to the AREDS formulation did not further reduce the risk of progression to advanced AMD.[15] A variety of therapeutic options targeting different molecular pathways or protective mechanisms have been explored in clinical trials for intermediate and advanced dry AMD with geographic atrophy. While a variety of trials in earlier stages have demonstrated promising candidates for treating AMD, equally as many appear to have failed to meet their endpoints or have shown adverse events such as increasing the risk of converting to wet AMD that may accelerate vision decline and increased treatment burden.[16] Taken together, these findings suggest that there is an unmet therapeutic need for treating and potentially even curing dry AMD. Furthermore, our strategies driving drug development have failed us to this point. Newfound avenues of exploration that are both expeditious and financially reasonable are warranted.

Transitioning to novel models of drug development

Traditional models of drug development are limited by their drawn-out process, high failure rates, and exorbitant costs. From 2009 to 2018, the median research and development cost for new therapeutics and biologic agents in the United States of America was an estimated $985 million.[17] The average approval process for drugs with new molecular moieties stretched out close to a decade during the time spanning from 2010 to 2020.[18] Of the drugs that enter into clinical testing, fewer than one in eight are ultimately met with a stamp of approval.[19] These factors have forced clinicians and researchers to consider new methods of drug discovery, one of which includes drug repurposing. This approach leverages clinical, pharmacological, and biological data to identify already-approved medications that show reasonable promise outside of their original indication. Furthermore, these medications have well-established safety profiles, allowing them to bypass stages of preclinical testing, resulting in a shorter amount of time spent in development and development costs that are more economically reasonable.[20] Recently, drug repurposing has surged in popularity, with studies estimating that repurposing accounts for 30–35% of all approved drugs on an annual basis.[21,22]

The approach of repurposing existing therapeutics may hold particular promise for AMD, considering that dysregulation of complement, angiogenic, inflammatory, and lipid pathways have all been proposed in its pathogenesis.[23] The multitude of pathways offers a variety of potential targets. Multiple strategies have been implemented in the current literature to discover medications that can be repurposed for other indications. These strategies range from signature matching with integrative omics data, virtual structural screens, and genomic association studies, to population-level studies of association.[20,24] To date, drug-gene association and population-level studies are the most well-characterized methods for AMD drug repurposing.

Population-level studies may fall under the umbrella of big data from compiled patient records. This approach yields high statistical power, which better elucidates the relationship between drugs and the disorders they could be repurposed to treat. Furthermore, it can simultaneously screen a wide array of candidates, which have biologically plausible impacts considering AMD's multifactorial etiology. Other methods have harnessed the power of bioinformatics to synthesize inputs from pharmacological, clinical, and genomic data in a manner that is described as systems biology.[25] A strength of systems biology lies in its ability to avoid a reductionist framework. In other words, diverse data sets are brought together to best model how certain drugs may interact within the complex network of a disease, as opposed to a singular pathway.

In this review, we provide an overview of population-level studies and bioinformatics tools that may help to identify and repurpose existing medications for the treatment of AMD. We highlight important preliminary results that detail candidates such as metformin, statins, L-DOPA (levodopa), fluoxetine, and so on. We also provide evidence from a systems biology approach that further supports potential candidates from population-level studies. When available, we offer an interpretation of basic science studies and prospective clinical trials that have provided further validation of such medications.

Metformin in population-level studies

Metformin, a first-line medication for the treatment of type 2 diabetes, has traditionally been thought to inhibit gluconeogenesis in the liver, possibly through stimulation of AMP-dependent kinase (AMPK).[26] However, in addition to its antidiabetic properties, metformin has also been shown to have antiaging effects that reduce mortality from diabetes, cardiovascular disease, and cancer.[27] These properties may stem from metformin's interactions with the metabolic and cellular processes that are associated with aging, which

include direct suppression of the inflammatory response,[28] attenuation of reactive oxygen species,[29] and augmentation of autophagy.[30] With the purported roles of inflammation, oxidative damage, and aging in AMD pathogenesis, interest in metformin's therapeutic potential for AMD has grown. Several population-level studies have reported a promising relationship between metformin and AMD thus far and are detailed below.

Blitzer *et al.*[31] performed a case-control study using the IBM MarketScan Commercial and Medicare Supplemental Databases to determine the association of AMD with metformin use. This study included patients aged 55 years and older who were newly diagnosed with AMD between the years of 2008 and 2017 and had a minimum of two eye examinations in the year preceding diagnosis. These criteria yielded 312,404 cases with AMD and 312,376 controls matched for age, hypertension, region, anemia, and Charlson Comorbidity Index (CCI) score. To our knowledge, this is the largest population-level study to date that has studied the relationship of AMD with metformin exposure. In multivariable logistic regression, it was found that the use of metformin was associated with reduced odds of AMD development (odds ratio [OR] = 0.93; 95% confidence interval [CI] = 0.91–0.95), especially at low and moderate doses. Interestingly, in a subgroup of patients with diabetic retinopathy, metformin did not demonstrate the same protective effect (OR = 1.07; 95% CI = 1.01–1.15). This result may suggest that metformin's protective effect is diminished in patients with poorly controlled diabetes that is associated with the development of retinopathy.

Stewart *et al.*[32] performed a retrospective cross-sectional study of diabetic patients with electronic medical records at the University of California, San Francisco. They identified 3120 diabetic patients who were at least 60 years old and had an encounter with an ophthalmologist between 2012 and 2019. Of these patients, 122 had dry AMD, and 26 had wet AMD at their first ophthalmology visit. They identified potential confounders, including age, smoking status, metabolic syndrome, and socioeconomic status, to create a propensity score that accounted for systematic differences across groups in logistic regression analysis. Patients exposed to metformin had significantly reduced odds of any AMD development (OR = 0.70; 95% CI = 0.55–0.88) and significantly decreased risk development of wet AMD (OR = 0.59; 95% CI = 0.46–0.77).

In a retrospective case-control study, Brown *et al.*[33] identified patients older than 55 years of age who visited a University of Florida health clinic between 2011 and 2017. Cases and controls were both required to have four visits to a University of Florida health clinic. Cases of AMD were not separated into dry and wet forms due to the large number of patients with unspecified AMD in procedural coding. Propensity score matching was performed to ensure 1947 AMD cases and 5841 controls were matched for age and baseline health through variables, including age, CCI, hypertension, and anemia. Brown *et al.* demonstrated in their multivariable analysis that metformin decreased the odds of AMD development (OR = 0.58; 95% CI = 0.43–0.79). These reduced odds were not attributable to another class of antidiabetic medications, dipeptidyl peptidase 4 (DPP4) inhibitors, in the multivariable analysis (OR = 0.80; 95% CI = 0.45–1.34). Hence, metformin may protect against AMD development in a mechanism independent of its tight regulation of blood glucose levels. In addition, the study was unable to study the effect of metformin dosing and length of metformin treatment on the odds of AMD development.

Chen *et al.*[34] conducted a retrospective cohort study of subjects with type 2 diabetes in the Taiwan National Health Insurance Research Database from 2001 to 2013. A total of 45,524 subjects were identified that had used metformin, while 22,681 subjects had no history of metformin use. They performed a multivariable Cox regression analysis that included the following variables: age, sex, metformin use, hypertension, hyperlipidemia, coronary artery disease, obesity, diabetic retinopathy, chronic kidney disease, and insulin treatment. Those in the metformin group had a lower risk of any AMD development (hazard ratio [HR] = 0.54; 95% CI = 0.50–0.58). This effect was preserved in a Cox regression after propensity matching for potential confounders for the above comorbidities and other antidiabetic oral agents, antihypertensive medications, and lipid-lowering medications (HR = 0.57; 95% CI = 0.52–0.63). Interestingly, longer duration of metformin treatment (greater than 4 years) and greater average metformin dose per day (greater than 2.1 g) were both associated with lower AMD risk compared to shorter duration and lower average daily doses, respectively. The authors did not investigate differences in the development of dry and wet AMD.

Lee *et al.*[35] conducted a nested case-control study of the Korean National Health Insurance Service database. A total of 2330 combined cases of dry and wet AMD were matched 1:10 to 23,278 controls, all of whom were older than the age of 60 years and had a diagnosis of diabetes or cardiovascular disease. They performed a conditional logistic regression adjusted for income level, health care utilization, CCI, type of health insurance, and various medications. Metformin was not associated with decreased odds of AMD development in the studied population (OR = 1.15; 95% CI = 0.91–1.45). Interestingly, long-term use of metformin (greater than 300 days) also failed to demonstrate a protective effect on AMD development. Analyses of separate dry and wet AMD subgroups were not performed.

Eton *et al.*[36] conducted a retrospective cohort study of a nationwide insurance claims database from 2002 to 2016, including patients with diabetes, age greater than 55 years, and two years of enrollment prior to dry AMD diagnosis. They excluded patients with a history of AMD, choroidal neovascularization, use of anti-VEGF agents, or retinal conditions similar to AMD prior to the index date. A total 1,007,226 diabetic patients were identified, 166,115 of whom were taking metformin upon enrollment in the study. They defined prior use of metformin as exposure before the index date and current use as exposure during the study period. In a multivariable Cox proportional hazard regression, current use of metformin was associated with an increased risk of dry AMD (HR = 1.08; 95% CI = 1.04–1.12), while prior use was associated with decreased risk of dry AMD (HR = 0.95; 95% CI = 0.92–0.98). They also observed a trend of increasing HR of AMD development with increasing metformin exposure. Although a low cumulative dose of metformin (less than

290,000 mg) was associated with a slightly decreased risk of AMD (HR = 0.95; 95% CI = 0.91–0.99).

Gokhale *et al.*[37] carried out a retrospective cohort study of patients older than 40 years of age diagnosed with type 2 diabetes in the United Kingdom from 1995 to 2019 using the IQVIA Medical Research Data. They included age, sex, smoking status, ethnicity, socioeconomic status, CCI, body mass index (BMI), blood pressure, hemoglobin A1c, diabetes-related complications, cardiovascular disease, statin use, chronic kidney disease, and hypothyroidism as covariates. They identified 173,689 patients with type 2 diabetes, and 154,016 of them were prescribed metformin. Using a Cox proportional hazards model, there was no association between the use of metformin and the development of AMD (HR = 1.02; 95% CI = 0.92–1.12). Given the poor coding of AMD in the data set, the authors did not differentiate between the odds of dry and wet AMD development.

Domalpally *et al.*[38] studied patients enrolled in the Diabetes Prevention Program Outcomes Study, a follow-up phase of an initial randomized clinical trial that investigated the effects of metformin treatment and intensive lifestyle modifications compared with placebo on preventing the development of type 2 diabetes. At 16 years of follow-up, patients underwent retinal imaging, which offered the opportunity to assess the prevalence of AMD in patients treated with metformin as compared to those assigned to the lifestyle modification arm or placebo arm. Retinal imaging was available in 1587 patients, and there was no significant difference in the prevalence of AMD between the three groups: 29.6% in the lifestyle arm, 30.2% in the metformin arm, and 30.7% in the placebo arm ($P = 0.09$). Furthermore, there were no significant differences observed in the severity of AMD (absent, early, intermediate, or advanced) across the different arms. In a pooled analysis of patients who were treated with metformin regardless of the arm to which they were originally assigned, there was also no association between either any metformin use or total duration of metformin use and AMD. However, this study was severely limited by its methodology. Baseline imaging was not available, and retinal imaging was only carried out at a single visit after a long duration of follow-up. Hence, it is unclear how well-matched patients were at baseline with regard to their ocular health. The single imaging date also limits the study's ability to determine the relationship between metformin exposure and the progression of AMD. In addition, out-of-study use of metformin could have occurred, as needed, in patients assigned to the placebo arm. The long duration of the follow-up period may fail to capture the timing between AMD diagnosis and metformin exposure, such that AMD may have been evident in patients before they were prescribed out-of-study metformin. Overall, this could have limited or attenuated any potential associations between metformin and AMD.

The mechanistic role of metformin in protecting against AMD may involve both AMPK-dependent and AMPK-independent pathways. Using three different mouse models of retinal degeneration, Xu *et al.*[39] showed that metformin crossed the blood-retina barrier to stimulate APMK, thereby protecting photoreceptors from light damage, making RPE cells more resistant to injury from oxidative stress, and delaying retinal degeneration. The authors additionally generated AMPK retinal knockout mice that were deficient in either AMP-dependent kinase alpha 1 (AMPKα1) or AMP-dependent kinase alpha 2 (AMPKα2), separate isoforms of the α-catalytic subunit of AMPK. Metformin protected mice with an AMPKα1 knockout from light damage, while it did not protect mice with an AMPKα2 knockout from light damage. This suggested that metformin acts on or through AMPKα2 to provide localized protection within the retina. Foretz *et al.*[40] found that metformin exerted an antihyperglycemic effect in mice where hepatocytes were depleted of AMPK which was similar to its effect in wild-type mice. In addition, the inhibition of glucose production by metformin correlated with a drop in adenosine triphosphate content. These results suggest that metformin inhibits gluconeogenesis independently of AMPK, instead mediating this effect through a decrease in the hepatic energy state. Furthermore, *in vivo* and *in vitro* activation of AMPK requires suprapharmacological dosing of metformin, which is not used in a clinical setting.[41] Hence, the potential beneficial effect of metformin in AMD may be due to AMPK-independent pathways.

Retrospective studies of metformin use have yielded contrasting findings, with many finding it to have a protective effect on AMD development,[31–34] while others have reported no effect.[35–37] However, current studies of metformin are limited by their use of cohorts comprised primarily of diabetic patients, given the common indication for metformin among diabetics. As of yet, it is unclear the effect of metformin on AMD development in non-diabetic patients, and further study in this population is warranted. Furthermore, many retrospective studies are unable to distinguish between dry and wet forms of AMD. Hence, it is difficult to discern whether metformin may protect against the progression of AMD and, in particular, the development of wet AMD and geographic atrophy. Studies are also inconsistent in their interpretations of ideal metformin dosing. Blitzer *et al.*[31] and Eton *et al.*[36] found lower doses to have the greatest potential protective effect, while Chen *et al.*[34] identified larger doses to have the greatest potential protective effect. Prospective clinical trials are warranted to elucidate the nuances of metformin as a potential therapeutic for the treatment of AMD. A phase II, single-blind, randomized clinical trial is investigating an 18 month course of metformin among non-diabetics over the age of 55 years with advanced dry AMD as it relates to progression to geographic atrophy.[42] It is estimated to be completed in December 2024 and will provide the first clinical insights into repurposing metformin for AMD.

Statins in population-level studies

Although the pathophysiology of AMD is not fully understood, epidemiological studies have demonstrated that AMD and cardiovascular disease may share multiple certain risk factors, including atherosclerosis, smoking, hypertension, and hypercholesterolemia.[43–45] Furthermore, studies have long drawn parallels between the accumulation of lipid-rich drusen deposits characteristic of AMD and the atherosclerotic changes present in cardiovascular disease, and it has thus been posited that lipid-lowering drugs may be protective against AMD.[45,46] Curcio *et al.*[47] have even proposed an

"oil spill" hypothesis that attempts to explain the process by which the RPE takes up lipoproteins to meet metabolic demands within the retina before recycling them through Bruch's membrane, where they build up over time to form a lipid wall, eventually interacting with reactive oxygen species and fusing to form the lipoprotein-derived debris that makes up soft drusen. Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are the most prescribed lipid-lowering drug and have been proven to reduce cardiovascular morbidity and mortality.[48] In addition, these drugs have been noted to have anti-inflammatory, antiangiogenic, and antioxidant effects.[48,49] As a result, numerous population studies have attempted to characterize the relationship between AMD and statins.

A case-control study by McGwin *et al.*[50] investigated 12,588 individuals who underwent screening fundus photographs between 1993 and 1995 as part of the Atherosclerosis Risk in Communities study, including 871 individuals with AMD and 11,717 controls. Medication use was evaluated prior to screening visits to determine those taking cholesterol-lowering medications. Notably, cholesterol-lowering medications in this study included multiple drug classes, including statins, cholestyramine, clofibrate, colestipol, gemfibrozil, and so on. Of the participants with AMD, 11% utilized cholesterol-lowering medications, compared to 12.3% in the control group (OR = 0.89; 95% CI = 0.71–1.11). When adjusted for age, gender, and race, the results revealed a statistically significant relationship, and those with AMD were roughly 20% less likely to have used cholesterol-lowering medications than those without AMD (OR = 0.79; 95% CI = 0.63–0.99).

A prior study by McGwin *et al.*[46] more specifically examined the relationship between statin use and AMD, utilizing a nested case–control design to study patients at the Veterans Affairs Medical Center in Birmingham, Alabama between 1997 and 2001. Based on International Classification of Diseases, Ninth Revision (ICD-9) codes, the investigators identified 550 incident cases of AMD, which were age matched to 5500 controls over the same period. The individuals with AMD were noted to be significantly more likely to have diabetes, hypertension, cardiovascular disease, and cerebrovascular disease. The prescription file was queried to determine statin usage in study participants, as well as the usage of non-statin lipid-lowering medications. The percentage of individuals with AMD who filled a prescription for a statin prior to the study start date was significantly lower than that of controls (6.7% vs 13.6%, OR = 0.45; 95% CI = 0.32–0.64). This finding was not restricted to those with a longer duration of use, and it persisted regardless of whether statin use was current or past. In addition, associations were stronger when results were adjusted for comorbidities (OR = 0.30; 95% CI = 0.21–0.45). The use of non-statin lipid-lowering agents was also significantly lower among cases when adjusted for comorbidities, but significant risk reduction was not observed in those who did not use statins in conjunction with the non-statin agents.

A later case-control study by McGwin *et al.*[51] also examined the association between cholesterol-lowering medications and AMD using data from the Cardiovascular Health Study. Based on fundus photographs taken during clinic visits between 1997 and 1998, 390 of the 2755 participants were classified as having AMD (cases) and 2365 were classified as controls. Cholesterol-lowering agents were classified by medication class, and participants were considered to be users of any medications they reported taking at one or more study visits. Ultimately, similar rates of statin use were found among cases and controls (OR = 0.98; 95% CI = 0.73–1.30), and these results paralleled those of cholesterol-lowering medication use in general among the two groups. After controlling for age, sex, and race, statin users were discovered to possibly have an increased risk for AMD, though this finding was not statistically significant (OR = 1.40; 95% CI = 0.99–1.98).

An early investigation by van Leeuwen *et al.*[52] in 2003 also examined this association as part of the Rotterdam study, a population-based cohort study of individuals aged 55 years and older. A total of 4822 patients were included, and continuous data on the use of cholesterol-lowering medications was obtained from a register of prescriptions filled by local pharmacies. Over the course of follow-up, 457 patients used cholesterol-lowering agents, and 419 incident cases of AMD were observed. The authors utilized Cox proportional hazards regression analysis to calculate HRs associated with the development of AMD. Overall, the use of cholesterol-lowering agents was not found to be associated with the incidence of AMD (HR = 1.0; 95% CI = 0.7–1.5). This finding persisted when statins were independently analyzed, including when results were adjusted for comorbidities.

Population-based cohort studies published in 2003 and 2007 by Klein *et al.*[53,54] studied the relationship between statins and AMD over two consecutive five-year periods. These investigations utilized a population from Beaver Dam, WI, which was initially examined in 1987–1988 and then reexamined at five-year intervals. The 2003 investigation included 2780 participants aged 48–91 years who participated in the 1998–2000 follow-up, utilizing the 1993–1995 examination as a "baseline" to assess statin usage and AMD incidence and progression. Medication use was determined via standardized questionnaires, and participants were asked to bring all current medications to each examination. Fundus photographs were also obtained, and the Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of AMD lesions. For each eye, a six-level severity scale for AMD was defined. Utilizing logistic regression analysis and controlling for age and sex, the authors determined that there was no statistically significant relationship between baseline statin use and AMD prevalence (early AMD: OR = 1.12; 95% CI = 0.74–1.69; late AMD: OR = 1.14; 95% CI = 0.27–4.83), incidence (early AMD: OR = 1.12; 95% CI = 0.47–2.67; late AMD: OR = 0.41; 95% CI = 0.12–1.45), or progression (OR = 1.22; 95% CI = 0.54–2.76). Interestingly, in participants who began using statins between the 1993–1995 and 1998–2000 examinations, there was a statistically significant reduction in the prevalence of soft indistinct drusen (OR = 0.68; 95% CI = 0.49–0.95), drusen 125 µm or more in diameter (OR = 0.64; 95% CI = 0.48–0.86), and incident late AMD (OR = 0.29; 95% CI = 0.09–0.95).

The 2007 investigation by Klein *et al.*[54] largely replicated the same protocol, instead examining 2087 participants aged 53–96 years who participated in the 2003–2005 follow-up

as the study population and the 1998–2000 examination as "baseline." Controlling for age and sex, the authors found no statistically significant associations between statin usage and AMD incidence (early AMD: OR = 1.16; 95% CI = 0.71–1.91; late AMD: OR = 1.27; 95% CI = 0.60–2.69) or progression (OR = 1.16; 95% CI = 0.75–1.78). This finding persisted when results were controlled for vitamin use, smoking status, total serum cholesterol levels, cardiovascular disease history, and antioxidant supplement use. In addition, in a secondary analysis, the duration of statin use showed no association with any AMD endpoint studied.

An investigation by van Leeuwen *et al.*[55] in 2004 pooled data from three prospective, population-based cohort studies: the Beaver Dam Eye Study ($n = 3012$), the Rotterdam Study ($n = 3434$), and the Blue Mountains Eye Study ($n = 2203$). The investigation by van Leeuwen *et al.* only included those who did not have early or late AMD at baseline, as determined by the presence of drusen on fundus photographs, and included a total of 8649 individuals aged 43–93 years. In all three studies, medication use was evaluated through a standardized interview, and commonly used medication classes were studied for the pooled analysis. Notably, lipid-lowering medications, such as statins, were grouped to increase the power of the study. Gender, BMI, systolic blood pressure, diastolic blood pressure, smoking, serum total cholesterol, and high-density lipoprotein cholesterol were potential confounding variables available from each of the included studies. The association between medication use and the incidence of AMD was analyzed using logistic regression, and analyses were conducted using a pooled data set as well as each individual population's data. There was not a statistically significant difference in the use of lipid-lowering medications at baseline among the three study populations. No statistically significant association was found between lipid-lowering agent use and the incidence of early AMD when results were adjusted for age and follow-up time, as well as the confounding variables mentioned above (OR = 1.0; 95% CI = 0.6–1.6). Furthermore, a statistically significant relationship was not found between the use of lipid-lowering agents and the incidence of early AMD when any of the three studies were analyzed separately.

A study by Tan *et al.*[56] aimed to assess the relationship between statin use and the long-term incidence of AMD as part of the Blue Mountains Study conducted in Australia. Of the 3654 individuals aged 49 years and older who originally participated in the population-based cohort study (1992–1994), 2335 were reexamined after five years (1997–1999) and 1952 after 10 years (2002–2004). A total of 2254 participants had retinal photographs taken, which were graded for AMD using the Wisconsin Age-Related Maculopathy Grading System. Medication utilization was assessed using standardized questionnaires, and discrete linear logistic models were used to estimate HRs for the association of current statin use and the five-year development of AMD. After adjusting for age, gender, and other confounding variables, statin users were found to have a significantly reduced long-term risk of developing indistinct soft drusen, the principal precursor lesion for late AMD (HR = 0.33; 95% CI = 0.13–0.84). However, a significant association was not found between statin use and overall early AMD incidence (HR = 0.54; 95% CI = 0.26–1.11).

Smeeth *et al.*[44] conducted a population-based case-control study utilizing the United Kingdom General Practice Research Database, comparing 18,007 individuals with diagnosed AMD to 86,007 controls matched on age, sex, and general practice. The database contains comprehensive prescribing and diagnostic information for over three million people in the United Kingdom. Eligible cases were those at least 50 years of age who had a first diagnosis of AMD while participating in a practice contributing to the database. Notably, early AMD was not able to be distinguished from advanced AMD. Each case was matched with five controls who had not been diagnosed with AMD, and cases and controls were matched by age (within 5 years), sex, and practice. Exposure to statins was considered as a binary variable and modeled using conditional logistic regression for the primary analysis. A series of bivariate models were fitted, and variables significantly associated with both AMD and statin exposure were retained. In additional analyses, the effects of different doses and types of statins, as well as the total number of prescriptions for statins, were analyzed. In the primary analysis, there was no significant relationship between statin exposure and diagnosis of AMD (OR = 0.93; 95% CI = 0.81–1.07) when results were adjusted for consultation rate, smoking, alcohol intake, and several other variables. Furthermore, the authors found no relationship when analyzing results by statin dose, type, and duration of use (median observation period of 4 years).

A later study by Smeeth *et al.*[57] in 2009 assessed the relationship between statin use and several health outcomes in a population-based cohort study based on the United Kingdom Health Improvement Network database, which includes extensive prescribing and diagnostic information. A total of 129,288 individuals who initiated treatment with a statin were compared with 600,241 matched controls who did not initiate treatment, and the median follow-up period was 4.4 years. The source population included individuals contributing to the database between 1995 and 2006, and each statin user was matched with up to five non-users. Propensity scores for statin prescription were estimated for all patients utilizing conditional logistic regression and numerous patient factors. Cox regression was used to evaluate the association between statin use and several health outcomes. The first year of follow-up was excluded from analysis for long-term outcomes, such as the development of AMD, and results were adjusted for propensity score, as well as other patient factors. Statin effect sizes on clinical endpoints were validated against data from established randomized controlled trials, which suggested adequate control of confounding variables. The authors found that statin was associated with a slightly increased risk of AMD, though this relationship was not statistically significant (OR = 1.17; 95% CI = 1.00–1.38).

In a case-control study, Kaiserman *et al.*[58] analyzed the electronic medical records of individuals in the "central district" of the Clalit Health Services health maintenance organization (HMO) in Israel. A total of 139,894 members over 50 years old were included, 283 of whom underwent photodynamic therapy (PDT) for AMD. A total of 29,417 individuals used statins between 1992 and 2002, before receiving PDT, and a total of 471,232 statin prescriptions

were documented during this time. PDT was used as a surrogate for predominantly classic subfoveal neovascular AMD. The dose and potency of various statin formulations were standardized by conversion to defined daily dose (DDD), as outlined by the World Health Organization. In a substudy, 334 PDT cases were matched to 1670 controls who did not undergo PDT. Student's *t*-test and chi-square test were used to compare variables, and a logistic regression analysis was performed to control for various patient factors. Overall, the authors found that PDT was more prevalent among statin users. However, after adjustment for several patient factors, such as age, gender, and chronic diseases, the association between statin use and PDT for wet AMD was not statistically significant. Furthermore, no association was found between total statin DDDs and treatment with PDT. Similarly, statin use in those who underwent PDT for AMD was not significantly different from that in those who did not undergo PDT (OR = 1.0; 95% CI = 0.8–1.3).

Fong and Contreras[59] conducted a case-control study at Kaiser Permanente Southern California to evaluate the association between statin use and newly diagnosed exudative AMD. Outpatient diagnosis data were utilized, and eligible cases included those with a diagnosis of exudative AMD in 2007 who did not have this diagnosis in 2006. Participants were also 60 years of age or older and had been enrolled in the health system for at least five years. Controls were designated as patients who underwent an eye examination the same year without a diagnosis of AMD (of any type). Overall, 86,635 patients were included in the investigation, 719 of whom were newly diagnosed with exudative AMD. Statin usage was determined by querying the health system's pharmacy information management system. Proportions were compared using chi-square tests and means with *t*-tests; confounding variables were adjusted for using logistic regression. The authors ultimately found that statin use was not associated with newly diagnosed exudative AMD (OR = 0.89; 95% CI = 0.77–1.03). This finding persisted after adjustment for confounding variables (OR = 0.9; 95% CI = 0.8–1.0).

Shalev *et al.*[60] conducted a historical prospective cohort study among members of Maccabi Healthcare Services, an HMO in Israel. A total of 108,973 members who were at least 55 years of age were identified, and 2732 incident cases of AMD were observed (based on ICD-9 coding) over an average follow-up period of 4.75 years. Individuals were included if they were being newly treated with statin agents between 1998 and 2006 and had no prior AMD diagnosis. Data were obtained from the health system's automated database, which included information on dispensed prescriptions and health records. Statin therapy was classified as one of three levels of relative efficacy, based on expected low-density lipoprotein reduction; these levels included low, moderate, and high efficacy. Cox regression was used to estimate HRs and CIs, as well as to identify variables associated with AMD. Results were adjusted for numerous variables in the final model. Ultimately, the authors found that patients in the highest quintile for persistent use of statin therapy had no significant difference in AMD risk than those in the lowest quintile (HR = 1.05; 95% CI = 0.92–1.20). When analyses were confined to those with more than five years of follow, the results remained non-significant (HR = 0.99; 95% CI = 0.76–1.29). Similar findings were obtained when results were stratified by efficacy levels or statin type, suggesting no relationship between statin use and AMD risk over the follow-up period.

In a cross-sectional study utilizing the National Health Nutrition Examination Survey (NHANES), Barbosa *et al.*[61] also studied the association between statin use and AMD. The authors identified 5604 survey participants in the 2005–2008 NHANES who were at least 40 years of age and underwent both the interview and examination portions of the survey. Of these participants, 1231 were receiving statin agents and 441 presented with AMD. NHANES questionnaires provided self-reported data on statin use, as well as the number of days each participant used statins. Evaluation for early or late AMD was conducted through gradable retinal photographs, as part of the ophthalmology examination. Demographic variables were obtained through the interview portion of the survey. The authors utilized multivariable logistic regression models to assess the relationship between statin use and AMD and to adjust for confounding variables. In the initial, unadjusted model, statin intake was associated with a significantly increased risk of AMD (OR = 1.77; 95% CI = 1.32–2.38); however, after adjusting for several confounding factors, statin therapy was not found to be significantly associated with AMD (OR = 0.91; 95% CI = 0.67–1.24). When analyzed separately, neither early nor late AMD was significantly associated with statins (early: OR = 0.95; 95% CI = 0.67–1.33; late: OR = 0.78; 95% CI = 0.34–1.80). Similar findings were observed when individuals 40–67 years of age were analyzed separately. In individuals who were 68 years of age or older, however, statin intake was significantly associated with lower odds of AMD compared with no statin intake, even after adjustment for confounding variables (OR = 0.69; 95% CI = 0.51–0.94). These results suggest that statin use may significantly lower the odds of developing AMD in this older population.

Al-Holou *et al.*[48] completed a prospective cohort study utilizing observational data obtained as part of the Age-Related Eye Disease Study 2 (AREDS2) to study statin use and AMD. A total of 4203 participants aged 50–85 years of age were enrolled at 82 retinal specialty clinics between 2006 and 2008. Individuals were included if they had bilateral large drusen or unilateral large drusen with late AMD in the other eye. Comprehensive eye exams were performed on participants at baseline as well as at annual eye examinations, and stereoscopic fundus photographs were assessed using the Wisconsin Age-Related Maculopathy Grading System. Questionnaires administered at study visits collected information on several patient factors, including medications and treatment compliance. Ultimately, 3791 individuals with complete information on statin use and AMD were included. Propensity scores were estimated using logistic regression based on numerous risk factors predisposing individuals to statin use, and statin users and non-users were matched based on these scores. The authors used age-adjusted proportional hazards regression models to evaluate the relationship between statin utilization and progression to any late AMD. After adjusting for several patient factors, a significant association was not found between statin use and the development of AMD (HR = 1.08; 95% CI = 0.83–1.41). Similar

models that separately evaluated each component of late AMD (central geographic atrophy, any geographic atrophy, and neovascular AMD) also found no statistically significant relationship between statin use and the development of any of these outcomes. However, among a subgroup of patients with large drusen in both eyes, there was a statistically significant association between statin use and the outcome of any late AMD after adjusting for the competing risk of death (HR = 0.53; 95% CI = 0.31–0.89).

A study by VanderBeek *et al.*[62] examined i3 InVision Data Mart, a national insurance claims database, and identified subjects aged 60 years or older who had at least one visit with an eye care provider. The database provided demographic data, socioeconomic information, outpatient medication data, and other patient information for included beneficiaries. ICD-9 codes were utilized to determine the diagnoses of non-exudative and exudative AMD. Cox regression analyses were conducted to evaluate the relationship between statin usage and the development of AMD. Non-exudative AMD, exudative AMD, and AMD progression were analyzed in three separate analyses. Overall, 486,124 individuals were included in the study, including 107,007 eligible for the non-exudative AMD analysis, 113,111 eligible for the exudative AMD analysis, and 10,753 eligible for the progression of AMD analysis. After multivariate analysis, the authors found that the development of non-exudative AMD was not significantly associated with statin use of any duration. The development of exudative AMD was also not significantly associated with statin use for 6–12 months. However, individuals prescribed statins for 13–18 months demonstrated a statistically significant association with developing exudative AMD (HR = 1.57; 95% CI = 1.16–2.13), as well as individuals using statins for 19–24 months (HR = 1.48; 95% CI = 1.17–1.88). Furthermore, statin use for 19–24 months was associated with an increased hazard of progression from non-exudative AMD to exudative AMD (HR = 1.63; 95% CI = 1.16–2.29). Overall, these results indicate a higher hazard of developing exudative AMD in individuals receiving statin therapy for over one year.

Ludwig *et al.*[63] conducted a retrospective cohort study of the IBM MarketScan database, including 231,888 commercially insured individuals diagnosed with non-exudative AMD from 2007 to 2015. Patients who utilized lipid-lowering agents within a year of diagnosis were included in the exposure group, while those who did not were placed in the control group. International Classification of Diseases (ICD) codes (as well as procedural codes) were utilized to identify AMD diagnoses, while National Drug Codes were used to identify medications. Lipid-lowering medication usage was categorized as the use of any lipid-lowering agent, use of a statin, use of a fibrate, or use of both a statin and a fibrate. Statins were classified as either hydrophilic or lipophilic, and lipophilic statins were further subdivided into categories based on dosage. The authors conducted a time-to-event analysis to assess the relationship between lipid-lowering medication utilization and time from a diagnosis of non-exudative AMD to a diagnosis of exudative AMD. Unadjusted and adjusted Cox proportional hazards models were utilized to assess the time to first diagnosis of exudative AMD and time to first intravitreal injection. The adjusted results demonstrated no significant association between utilization of lipid-lowering medications prior to diagnosis and progression to exudative AMD or risk of receiving an anti-VEGF injection (statin: HR = 0.94; 95% CI = 0.87–1.03). Furthermore, no significant association with AMD progression was found in individuals taking lipophilic statins (HR = 1.03; 95% CI = 0.90–1.19) or hydrophilic statins (HR = 0.98; 95% CI = 0.77–1.23). No statistically significant results were found in any subgroup analysis. Interestingly, no patients receiving very-high-dose lipophilic statins (atorvastatin 80 mg) progressed to exudative AMD or required anti-VEGF injection.

Vavvas *et al.*[64] performed an open-label prospective clinical study including 26 patients diagnosed with AMD featuring multiple large drusen deposits who were assigned to 80 mg daily of atorvastatin. A total of 23 patients completed 12 months of follow-up. Treatment with high-dose atorvastatin resulted in regression of drusen deposits in ten patients, who additionally gained a mean of 3.3 letters of visual acuity. Furthermore, no patients progressed to advanced neovascular AMD, which would be expected to occur in 14% of enrolled cases. While this study was limited by its open-label status and small patient enrollment, it does provide evidence that intensive statin therapy can cause regression of certain high-risk AMD features.

Guymer *et al.* performed a randomized placebo-controlled trial to assess the effect of simvastatin on the progression of AMD. A total of 114 patients with normal lipid profiles and either bilateral intermediate AMD or unilateral non-advanced AMD with advanced AMD in the fellow eye were assigned 1:1 to 40 mg of daily simvastatin or placebo. Patients were followed for a total of three years with the primary endpoint of progression of non-advanced AMD to either advanced AMD or higher severity scores of non-advanced AMD. After adjustment for age, sex, smoking, and baseline AMD status, the intent to treat multivariate logistic regression analysis revealed a significant reduction in AMD progression in the simvastatin group compared to the placebo group (OR = 0.43; 95% CI = 0.18–0.99). After stratification, simvastatin did not have a significant effect on AMD progression in patients who had advanced AMD in the fellow eye, while simvastatin did have a significant effect compared to placebo on AMD progression in patients with bilateral intermediate drusen (OR = 0.23; 95% CI = 0.07–0.75). The effect of simvastatin was greatest in patients who had the at-risk C allele at Y402H of the complement factor H gene (OR = 0.08; 95% CI = 0.02–0.45). This finding suggested that genotype should be considered when studying the potential role of statins in treating AMD.

Population studies investigating the association between statin utilization and AMD have demonstrated largely inconsistent findings. While some have reported a protective effect, many have found no association with AMD development, and still, others have posited an increased risk. Limitations in research methodologies, as well as the multifactorial nature of AMD, may have contributed to this uncertainty. Several studies have been restricted by the inability to analyze specific statin types or doses, which has resulted in the grouping of low-potency and high-potency statins, and statin utilization itself has increased over the years. It

is unclear if different types and dosing of statins may have implications concerning the prevention of AMD development and slowing AMD progression. However, in a mouse study, Mast *et al.*[65] found that simvastatin had a greater concentration in the retina compared to atorvastatin and pravastatin when administered in equal concentrations, while the blood-retina barrier appeared impermeable to rosuvastatin. These findings are made further important in the context of findings from Lin *et al.*[66] that local biosynthesis accounts for the majority of cholesterol input within the mouse retina. Hence, retinal delivery of statins may be required to disrupt the synthetic pathway for cholesterol. Furthermore, studies of statins and their therapeutic potential in other diseases have found differing results based on intensity. For example, Zissimopoulos *et al.*[67] found that high exposure to statins was associated with decreased incidence of Alzheimer's disease compared to low exposure to statins in men and women, among a sample of Medicare beneficiaries. Moreover, resorption of atherosclerotic plaques has only been demonstrated in subgroups receiving a high-intensity statin.[68,69] In addition, studies have often been unable to differentiate among specific types of AMD, and many have been limited by inadequate control for confounding variables. Ultimately, there has been insufficient evidence to conclusively define the role of statins in AMD development and progression. The current body of literature has reported many interesting findings, however, highlighting the need for further nuanced research in this area.

Other medications may protect against AMD in population-level studies

Variation in the incidence and prevalence of AMD across different races has been reported, with white populations facing the greatest rates of AMD as compared to Black, Hispanic, and Chinese racial/ethnic groups.[70,71] These differences persist even after accounting for various AMD risk factors. L-DOPA, which is a byproduct of melanin pigment synthesis, has been found to bind GPR143, a G-protein coupled receptor found in the RPE.[72] Stimulation of this receptor by L-DOPA enhances the expression of pigment epithelial-derived factor (PEDF) while simultaneously abating the expression of VEGF.[73] PEDF is antiangiogenic,[74] while VEGF is the main target of wet AMD therapies. Taken collectively, these findings may help to explain why increased ocular pigmentation is protective against AMD. They also suggest that L-DOPA may drive this protective role due to its agonism of GPR143 in the RPE. Population-level studies have just begun to examine L-DOPA, which is used to treat movement disorders such as Parkinson's disease, and its association with AMD development.

Brilliant *et al.*[75] studied the incidence of AMD in patients taking L-DOPA compared to patients who were not taking L-DOPA in three independent patient cohorts. Two of these cohorts were derived from the Marshfield Clinic, and an additional cohort was derived from the Truven MarketScan outpatient databases. In the MarketScan database, the mean age of first AMD diagnosis in 12,387 patients with an L-DOPA prescription was 79.3 years, compared to 71.4 years in patients without an L-DOPA prescription ($P < 0.001$). The mean onset of wet AMD also occurred at 80.8 years in patients with an L-DOPA prescription compared to 75.8 years in patients without an L-DOPA prescription ($P < 0.001$). To evaluate the association of AMD diagnosis and L-DOPA use, the authors carried out a multinomial regression analysis and controlled for the potential confounding variables, age, and gender. Patients with a history of an L-DOPA prescription were less likely to have an AMD diagnosis (OR = 0.78; 95% CI = 0.76–0.80). Patients with an L-DOPA prescription were also less likely to be diagnosed with wet AMD in the multinomial regression (OR = 0.65; 95% CI = 0.65–0.69).

Figueroa *et al.*[76] have reported initial results from two AMD cohorts treated with oral carbidopa-levodopa in proof-of-concept studies. The first cohort was composed of patients with newly diagnosed wet AMD without a history of anti-VEGF injections, while the second cohort included patients previously treated with anti-VEGF injections. After six months of escalating treatment, patients in the first cohort had significantly improved best-corrected visual acuity (BCVA) in addition to significant decreases in central retinal thickness (CRT) and retinal fluid. After six months, patients in the second cohort were observed to have significant improvements in BCVA with accompanying reductions in the mean frequency of anti-VEGF injections compared to the prestudy period. These results are undoubtedly limited by their small numbers of patients enrolled, 15 and 11 in the first and second cohorts, respectively. However, they do suggest that levodopa has promise as an additional therapeutic tool for AMD. In addition, these findings validate the approach of using big data in population-level studies.

Ambati *et al.*[77] studied the association of fluoxetine, a selective serotonin reuptake inhibitor used to treat clinical depression, and its association with dry AMD in two separate clinical databases. A total of 112,165 patients with an exposure(s) to fluoxetine were identified in the Truven database, while 83,845 such patients were identified in the PearlDiver Mariner database. Patients exposed to fluoxetine were matched 1:1 to controls without an exposure to fluoxetine using propensity scores. Hazard ratios were estimated using multivariable Cox models that included age, smoking, BMI, gender, and CCI as matching variables. In the Truven database, patients exposed to fluoxetine had a reduced hazard of developing dry AMD (HR = 0.91; 95% CI = 0.85–0.97), and an even greater effect was observed in the Mariner database (HR = 0.78; 95% CI = 0.69–0.89). The authors performed a random-effects meta-analysis to estimate the combined HR of the two databases and found that the protective association of fluoxetine against dry AMD development persisted.

In the same study, the authors sought to provide a mechanistic explanation for their findings that fluoxetine was associated with a reduced hazard of AMD development.[77] Briefly, they identified that fluoxetine shared a structural moiety with a small molecule that had been previously shown to bind to NLRP3 and prevent inflammasome assembly.[78] Activation of the NLRP3 inflammasome contributed to RPE degeneration and death in a prior study.[79] However, the role of NLRP3 in AMD has not been well-replicated, with an additional study finding that the RPE may not contain a sufficient amount of NLRP3 to contribute to AMD pathogenesis.[80]

Wang *et al.*[81] performed a nested case-control study to screen approximately 4000 generic drugs and their association with progression to wet AMD. Participants were identified from Medicare data covering New Jersey and Pennsylvania, in addition to national data from the IBM MarketScan Research Database. The Medicare database yielded 2517 wet AMD cases, while the MarketScan database yielded 41,887 wet AMD cases. Cases of wet AMD were matched 1:4 with controls for age, gender, and recent health care use. Cases were required to be at least 65 years old and to have a code for an intravitreal injection within 90 days of the index date, or the first date of wet AMD diagnosis. Exposures to hierarchical drug classifications were evaluated in the six months, 7–24 months, and all months preceding the index date using a tree-based scanning method. Statistical alerts were generated at $P \leqslant 0.01$ and a relative risk of at least two, meaning that cases of wet AMD were less frequently exposed to these medications. Such criteria yielded 19 alerts, and the authors identified several suitable candidates for preventing and treating wet AMD: megestrol acetate, erlotinib, epoetin alfa, and donepezil. These candidates, in particular, were highlighted due to previous findings that would support a causal relationship in slowing or preventing wet AMD. The authors recommended further studies tailored to these particular drugs.

Bioinformatics tools to support repurposing medications

Nadeem *et al.*[82] used advanced bioinformatics modeling to identify drug classes that affect the genes integral to AMD pathogenesis. This was the first time a systems medicine approach was used to predict drugs for AMD treatment. The authors generated a comprehensive list of the genes involved in AMD by searching studies deposited in the National Center for Biotechnology Information (NCBI). The NCBI search identified genes from human genome-wide association studies, known gene-phenotype relationships from the Online Mendelian Inheritance in Man database, and GeneRIFs, which are functional annotations to a gene added by authors of relevant studies that can come from any source (humans and animal models). GeneRIFs all undergo review. The authors used Medical Subject Headings terms related to AMD, while manually removing genes not associated with AMD. They reviewed the full text of selected publications that revealed substantial associations between genes and AMD, ensuring that publications with negative or insignificant associations were excluded. Genes were identified from different AMD subtypes, including dry AMD, wet AMD, intermediate AMD, geographic atrophy, and combinations thereof. They performed drug-gene enrichment analysis using the ToppGene platform on AMD genes against 77,146 drug compounds. Deleterious compounds were manually filtered from inclusion, resulting in a final list of 27 relevant compounds with 174 genes and 886 total interactions. Predicted beneficial drugs for AMD included metformin, simvastatin, atorvastatin, antioxidants, and cardiovascular agents such as aspirin. In addition, curcumin and acetylcysteine were the most significantly enriched drugs for all AMD genes. Curcumin, a natural antioxidant, may scavenge free radicals and prevent an inflammatory response by blocking nuclear factor (NF)-kappa B activation.[83] Several clinical trials are currently ongoing and investigating the effect of oral curcumin on drusen size in patients with AMD.[84,85] Acetylcysteine, an additional antioxidant, may also prevent retinal neurodegeneration and is being studied in a clinical trial for retinitis pigmentosa, an inherited condition characterized by retinal degeneration.[86] It is notable that antioxidants including ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E) were enriched in various subtypes of AMD, as AREDS supplements are the only therapy that has been proven to decrease progression to advanced AMD. This finding is considered to validate the study design as a positive control, while also bolstering confidence that other enriched drugs may provide a similar protective effect.

In the study by Nadeem *et al.*, metformin had the strongest association with risk genes for AMD and was a top candidate among dry AMD subtypes. This computational finding provides further support for results from observational studies, which have identified that metformin may be associated with decreased risk of AMD development. Notably, simvastatin and atorvastatin were also significantly associated with AMD risk genes, including wet AMD, intermediate AMD, and geographic atrophy subtypes. This finding should prompt further testing of these two medications, in particular, through big data studies where dosing can be closely monitored. The study did not identify candidates such as L-DOPA, fluoxetine, megestrol acetate, erlotinib, epoetin alfa, or donepezil to be associated with AMD risk genes.

Conclusions

A variety of promising candidates have emerged in recent years that may eventually be repurposed into therapies for preventing or delaying AMD. However, the vast majority of these candidates have been identified through observational studies, which are limited in demonstrating only association as opposed to causation. Furthermore, dosing for these various agents has remained largely unexplored. Future preclinical studies and analysis of large-scale patient databases should attempt to determine optimal doses for these candidates, if this type of data is available to researchers. Advanced bioinformatics studies may also help to elucidate the associations between AMD and proposed candidates, although systems medicine approaches have mostly been untapped at this time. Metformin, high-dose statins, L-DOPA, and fluoxetine appear to demonstrate the most promise for AMD repurposing among agents that are already available and approved for other indications. Additional candidates may also include antioxidants such as curcumin and acetylcysteine. Prospective clinical trials for several of these agents are justified given findings from observational and bioinformatics studies.

AUTHORS' CONTRIBUTIONS

All authors contributed to the literature review. JM and SA drafted the paper, while DS critically reviewed the manuscript and revised the paper before submission.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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