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Possible Association Between Dopamine Antagonists and Increased Conversion to Exudative Age-Related Macular Degeneration

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Abstract

Purpose: To investigate whether modulating dopamine signaling affects conversion to exudative age-related macular degeneration (AMD). **Methods:** A retrospective cohort study was performed using the Duke Epic database. Eyes from patients with a diagnosis of nonexudative AMD with at least 1 year of follow-up were evaluated for conversion to exudative AMD. Eyes with an AMD diagnosis were evaluated for age, sex, smoking history, hypertension, Age-Related Eye Disease Study (AREDS) or AREDS2 prescription, dopamine-modulating therapy prescription, and indication for dopamine-modulating therapy. Generalized estimating equations were used to calculate odds ratios for individual variables on conversion from nonexudative to exudative AMD. **Results:** Five hundred fifty-eight eyes of 354 patients with an initial diagnosis of nonexudative AMD were evaluated for conversion to exudative AMD. Conversion to exudative AMD was significantly higher in patients who had been on dopamine antagonist therapies for at least 3 years than in patients who were not on any dopamine-modulating therapies. After controlling for other variables, dopamine antagonists were associated with an increased risk for conversion to exudative AMD at 3 years of follow-up ($P = .005$). **Conclusions:** These findings suggest that antagonizing dopamine signaling may be associated with the development of macular neovascularization in eyes with nonexudative AMD. Although the data are observational, these findings warrant further investigation of dopamine signaling in conversion to exudative AMD.

Keywords

levodopa, dopamine antagonist, dopamine agonist, exudative age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is a leading cause of visual impairment globally, affecting nearly 200 million individuals worldwide.[1,2] The condition consists of nonexudative AMD, characterized by varying degrees of drusen deposition and retinal pigment epithelium (RPE) abnormalities without macular neovascularization (NV), and exudative AMD, which is additionally defined as having macular NV.

The development of AMD has been linked to aging, smoking, cardiovascular disease, and hypertension.[3–5] Current therapeutic options to decrease conversion rates to exudative AMD are limited, with Age-Related Eye Disease Study (AREDS) and, more recently, AREDS2 vitamin supplementation offering modest risk reductions in conversion rates. Previous studies found that AREDS supplementation conferred a 38% decreased risk for developing exudative AMD at 5 years,[6] which was not dramatically altered with the addition of lutein and zeaxanthin and the removal of beta carotene (AREDS2).[7] Although anti-vascular endothelial growth factor (anti-VEGF) injections are the mainstay treatment for exudative AMD,[8–10] 2 recent clinical trials failed to show a benefit of offering patients prophylactic anti-VEGF therapies in an attempt to prevent conversion at 2 years.[11,12] Given the limited effectiveness of using anti-VEGF therapy to inhibit angiogenic drive in eyes with nonexudative AMD, alternative mechanisms underlying the initiation of macular NV in eyes with nonexudative AMD should be further explored.

Several retrospective studies have investigated the effectiveness of levodopa, a dopamine precursor, in reducing the risk for AMD.[13,14] Claims-based data from the Vestrum Health database showed that exposure to levodopa reduced the risk for conversion to exudative AMD by 35% at 3 years and led to an average of 1 less intravitreal injection over 2 years in eyes diagnosed

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with exudative AMD.[14] Furthermore, a small clinical study involving patients diagnosed with exudative AMD found a fluid decrease of 29% 1 month after the administration of levodopa.[15] Although there have been a few studies assessing the effectiveness of levodopa on conversion to exudative AMD, to our knowledge, none looked at how other dopamine-modulating therapies (ie, dopamine agonists and antagonists) affect this conversion. The current study evaluated whether pharmacologic modulation of dopamine signaling pathways might affect conversion to exudative AMD.

Methods

Patient Selection

The built-in SlicerDicer function of the Duke Epic database (Epic Systems) was used to identify patients presenting to the Duke Eye Center for evaluation of AMD between January 1, 2014, and January 1, 2024. Individuals who had at least 1 eye with an initial diagnosis code of nonexudative AMD were included in the study. Subsequent parsing was performed of the electronic health record of patients with at least 1 year of follow-up from the first diagnosis of nonexudative AMD diagnosis to assess for age, sex, race, comorbid diagnoses, and prescription history and duration. Medication use was collected including Age-Related Eye Disease Study (AREDS) and AREDS2 prescriptions, levodopa, dopamine agonists (ropinirole, pramipexole, and rotigotine), monoamine oxidase-B inhibitors (rasagiline and selegiline), and dopamine antagonists (quetiapine, olanzapine, risperidone, aripiprazole, metoclopramide, and haloperidol).

The patients were subsequently grouped into 1 of the following 3 categories: not on any dopamine-modulating therapies, on therapies that promote dopamine signaling, or on dopamine antagonists. Individuals on both dopamine-promoting therapies and dopamine antagonists were not included in the analysis. Those not on any dopamine-modulating therapies were propensity score matched to patients on therapies that promote dopamine signaling with regard to sex, age at first diagnosis, and total follow-up time, which was defined as the time in years between the initial diagnosis and the last documented clinic visit. Patients not on dopamine-modulating therapies were matched at a 3:1 ratio to patients on therapies that promoted dopamine signaling, and the balance was assessed by standard mean difference and variance ratio.[16]

Eye-Level Evaluation

A manual chart review of the ophthalmology note and optical coherence tomography (OCT) images of eyes included in the study was performed to evaluate staging when it was excluded from the diagnosis code (ie, nonexudative AMD) and to confirm that the diagnosis code matched the diagnosis documented in the ophthalmology note. Cases were not included when a questionable diagnosis of exudative AMD was documented in the ophthalmology note. Subsequent comparisons were performed for AMD diagnoses and prescription history and duration. Eyes were excluded if the end date of a prescription preceded the start date of the first AMD diagnosis or the dopamine-modulating therapy prescription was active for less than a year. In addition, eyes with a prescription for dopamine-modulating therapy were only evaluated for conversion during the time period in which there was an active prescription.

Statistical Analysis

Demographic features and comorbidities pertinent to dopamine-modulating therapies were compared across groups at the participant level using a 1-way analysis of variance (ANOVA) for continuous variables and a χ^2 test of proportions for categorical variables. Post hoc comparisons were conducted for variables that displayed significant differences on the ANOVA or χ^2 test. Generalized estimating equations (GEEs) with exchangeable correlation structure were used to account for 2 eyes of the same patient, and both univariate and multivariate logistic regression were performed with conversion from nonexudative to exudative AMD as the outcome variable. Logistic regression modeling included age, sex, follow-up time, smoking history, hypertension, Parkinson disease, history of insomnia, mood disorders, schizophrenia, AREDS/AREDS2 use, and dopamine-modulating therapies (separating dopamine-promoting therapies from dopamine antagonists). Statistical significance was set at $P < .05$. All statistical analyses were completed using R software (R Project for Statistical Computing).

Results

Of the patients with an initial diagnosis of nonexudative AMD between January 1, 2014, and January 1, 2024, 80 were identified to be on dopamine-promoting therapies and 34 were identified to be on dopamine antagonists. The primary indication for dopamine-promoting therapies was Parkinson disease or Parkinsonism, while the primary indication for dopamine antagonists was either insomnia, mood disorders, or schizophrenia. Table 1 shows the demographic features and pertinent medical and prescription histories of enrolled participants. Compared with individuals not on any dopamine-modulating therapies, patients on dopamine-promoting therapies had higher rates of Parkinson disease, insomnia, and mood disorders ($P < .05$). In addition, a higher percentage of patients on dopamine antagonists were women, were significantly younger, and had higher rates of schizophrenia compared with patients not on dopamine-modulating therapies and patients on dopamine-promoting therapies (Table 1). The rates of insomnia and mood disorders were higher for patients on dopamine antagonists than for patients not on dopamine-modulating therapies; however, they were not significantly different from the rates for patients on dopamine-promoting therapies.

Of the eyes included in the study, 558 had an initial diagnosis of nonexudative AMD. At 1 and 2 years of follow-up, there were no significant differences in the initial staging of AMD or the rates of conversion across all 3 groups. Although the number of eyes in the study was substantially reduced at 3 years of follow-up (207 eyes not on dopamine-modulating therapies (63 eyes on

Table 1. Demographic Data for Patients With Nonexudative AMD and at Least 1 Year of Follow-up.[a]

Variable	Patients Not on DA Therapy (n = 240)	Patients on DA Promoters (n = 80)	Patients on DA Antagonists (n = 34)
Age at diagnosis, y (SD)	77.3 (7.3)	77.3 (7.8)	71.6 (9.3)[b]
Female sex, n (%)	119 (49.6)	41 (51.3)	28 (82.4)[b]
Smoking history, No. (%)	31 (12.9)	10 (12.5)	4 (11.8)
Hypertension, n (%)	177 (73.8)	68 (85)	26 (76.5)
Parkinson disease, n (%)	1 (0.4)	25 (31.3)[b]	1 (2.9)
Insomnia, n (%)	27 (11.3)	19 (23.8)[c]	16 (47.1)[c]
Mood disorder, n (%)	31 (12.9)	24 (30.0)[c]	18 (52.9)[c]
Schizophrenia, n (%)	0	0	4 (11.8)[b]
AREDS/AREDS2 use, n (%)	142 (59.1)	43 (53.8)	20 (58.9)
Length of follow-up (y)			
Mean	3.8	3.6	2.8
Range	1, 10	1, 10	1, 8
Length of therapy (y)			
Mean	N/A	2.8	3.5
Range	N/A	1, 13	1, 8

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; DA, dopamine.
[a]One-way analysis of variance (ANOVA) was performed across all 3 groups for age at diagnosis and length of follow-up. The χ^2 test was performed across all 3 groups for the remaining binomial variables. Post hoc comparisons were performed when the ANOVA or χ^2 test were significant.
[b]$P < .05$ when compared with the other 2 groups.
[c]$P < .05$ when compared with the patients not on DA therapy group.

dopamine-promoting therapies; 22 eyes on dopamine antagonists), the rate of conversion to exudative AMD in eyes exposed to dopamine antagonists was significantly higher than for unexposed eyes (27.3% vs 6.8%) ($P = .02$) (Table 2). In contrast, eyes exposed to dopamine-promoting therapies did not experience different rates of conversion to exudative AMD compared with unexposed eyes. In addition, time on dopamine-promoting therapies or on dopamine antagonists was not significantly different between eyes that converted and eyes that did not. Rates of conversion to exudative AMD were, however, significantly higher in eyes when the fellow eye was previously diagnosed with exudative AMD (Supplemental Table 1).

A GEE analysis was performed at the 3-year timepoint to evaluate which factors might be associated with a difference in conversion rates from nonexudative to exudative AMD. Table 3 shows the odds ratios derived from univariate and multivariate regressions for nonexudative to exudative conversion based on demographic features, pertinent medical comorbidities, AREDS/AREDS2 prescriptions, and different types of dopamine-modulating therapies. On the univariate regression, age at initial diagnosis and sex were included as covariates to control for the differences in the rates of these covariates in eyes exposed to dopamine antagonists compared with unexposed eyes. Eyes exposed to dopamine antagonists were associated with significantly increased odds of conversion to exudative AMD compared with unexposed eyes ($P = .005$). Other risk factors for the development of AMD, including smoking history and hypertension, as well as dopamine-promoting therapies, did not confer a significant difference to the odds for conversion. Exposure to dopamine antagonists was still associated with significantly increased odds of conversion to exudative AMD when accounting for other comorbidities, such as insomnia, mood disorders, and schizophrenia, which occurred at higher rates in these patients.

Conclusions

We investigated the potential impact of pharmacologic modulation of dopamine signaling on conversion from nonexudative to exudative AMD and found a significant difference in conversion rates only after eyes had been exposed to therapies for 3 years. In our study, dopamine-promoting therapies were not associated with any difference in conversion to exudative AMD; however, eyes exposed to dopamine antagonists for 3 years had significantly greater odds of conversion to exudative AMD.

Our findings differ from those in a study by Hyman et al,[14] which showed significantly reduced rates of conversion at 2 years in eyes of patients with a levodopa prescription. Conversion rates were more pronounced at 3 years compared with the rates for eyes not exposed to levodopa. Notable differences between our studies include that our analysis comprised eyes that were not only on levodopa but also on dopamine agonists. However, conversion rates in our study did not differ between eyes exposed to levodopa and eyes exposed to dopamine agonists only. In addition, the prescription history was evaluated for each individual prescribed levodopa or a dopamine agonist. Patients who discontinued either of these dopamine-promoting therapies before any AMD diagnosis were excluded. Furthermore, patients who were on dopamine-promoting therapies for less than 1 year were also excluded, because these eyes would not have met the criteria for a 1-year follow-up for AMD while on dopamine-promoting therapy. These 2 exclusion criteria reduced

Table 2. Conversion Rates for Eyes With Nonexudative AMD.[a]

	Eyes With 1-Year Follow-up			Eyes With 2-Year Follow-up			Eyes With 3-Year Follow-up		
	No DA Therapy	DA-p Therapy	DA-a Therapy	No DA Therapy	DA-p Therapy	DA-a Therapy	No DA Therapy	DA-p Therapy	DA-a Therapy
Variable	(n = 379)	(n = 128)	(n = 51)	(n = 273)	(n = 90)	(n = 42)	(n = 207)	(n = 63)	(n = 22)
Early, n (%)	112 (29.6)	36 (28.1)	14 (27.5)	84 (30.8)	21 (23.3)	10 (23.8)	60 (29.0)	10 (15.9)	4 (18.2)
Intermediate, n (%)	227 (59.9)	73 (57.0)	30 (58.9)	157 (57.5)	57 (63.3)	30 (71.4)	123 (59.4)	43 (68.3)	17 (77.3)
Advanced, n (%)	40 (10.6)	19 (14.8)	7 (13.7)	32 (11.7)	12 (13.3)	2 (4.8)	24 (11.6)	10 (15.9)	1 (4.5)
Conversion, n (%)	4 (1.1)	2 (1.6)	2 (3.9)	13 (4.8)	3 (3.3)	3 (7.1)	14 (6.8)	6 (9.5)	6 (27.3)[b]

Abbreviations: AMD, age-related macular degeneration; DA, dopamine; DA-a, dopamine antagonist; DA-p, dopamine promoting.
[a]The χ^2 test was performed across all 3 groups for each stage. Post hoc comparisons were performed when the χ^2 test detected significant differences between groups.
[b]$P < .05$ when compared with the No DA Therapy Group.

Table 3. Factors Affecting Conversion to Exudative AMD Within 3 Years.

	Univariate Logistic Regression			Multivariate Logistic Regression		
Variable	Odds Ratio	95% CI	*P* Value[a]	Odds Ratio	95% CI	*P* Value[a]
Age at diagnosis (y)	1.01	0.97, 1.05	.70	1.03	0.98, 1.08	.28
Female sex	Reference population			Reference population		
Male sex	1.02	0.43, 2.43	.97	1.04	0.40, 2.70	.94
Follow-up time	1.00	1.00, 1.00	.78	1.00	1.00, 1.00	.68
Smoking history	0.28	0.04, 2.18	.23	0.21	0.05, 0.86	.03
Hypertension	0.83	0.30, 2.25	.71	0.78	0.28, 2.20	.64
Parkinson disease	2.38	0.65, 8.67	.19	5.45	1.01, 29.30	.05
Insomnia	1.66	0.57, 4.89	.35	1.87	0.76, 4.64	.17
Mood disorder	0.86	0.30, 2.45	.78	0.22	0.06, 0.83	.03
Schizophrenia	4.22	0.33, 53.11	.27	0.76	0.06, 9.94	.83
AREDS	0.68	0.28, 1.64	.39	0.63	0.25, 1.59	.32
No DA therapy	Reference population			Reference population		
DA-p therapy	1.41	0.50, 3.97	.51	0.78	0.20, 3.02	.72
DA-a therapy	6.67	1.79, 24.86	.005	14.01	2.59, 75.74	.002

Abbreviations: AMD, age-related macular degeneration; AREDS, age-related eye disease study; DA, dopamine; DA-a, dopamine antagonist; DA-p, dopamine promoting.
[a]*P* values were derived from generalized estimating equation analysis.

our sample size but allowed greater confidence that the effect of dopamine-promoting therapies overlapped with the timeframe of AMD evaluation. Although our sample is smaller than in the Hyman et al study, it is possible that several confounding features addressed in our study may have also contributed to the difference in findings.

In our study, we observed significantly higher rates of conversion to exudative AMD at 3 years in eyes exposed to dopamine antagonists than in unexposed eyes. In contrast, the rate of conversion to exudative AMD was not significantly different between eyes exposed to dopamine antagonists and eyes exposed to dopamine-promoting therapies. It is likely that this difference is a result of the smaller sample of patients on dopamine-promoting therapies compared with unexposed patients. Larger retrospective and prospective studies are warranted to specifically understand how modulating dopamine levels may alter the conversion to neovascular AMD. To better understand the underlying mechanism of this effect, it is important to consider the physiologic role of dopamine in the retina.

Nearly all dopamine in the retina is produced by amacrine cells.[17–19] Dopamine release follows diurnal cycles and is heightened during daylight[20,21] and reduced at night.[22] All forms of the dopamine receptor (D_1 to D_5) are present in the retina; however, RPE cells appear to primarily express the D_2 and D_5 receptors.[23] Moreover, dopamine acting on D_2 receptors was noted to modulate vascular permeability on endothelial cells through VEGF signaling,[24,25] which may directly regulate macular angiogenesis. Although no previous reports have specifically assessed the impact of dopamine antagonists on conversion to exudative AMD, a study by Shome et al[26] showed that dopamine antagonists promote angiogenesis in wound healing. Thus, it is plausible that dopamine antagonists could also promote angiogenesis within the retina. Moving beyond its role in angiogenesis, dopamine's response to light adaptation is noteworthy,[27] in particular in lieu of the success of new therapies that use light to prevent the progression of nonexudative AMD (eg, LumiThera, LumiThera, Inc).[28,29] Given that dopamine signaling appears to decline with age,[30,31] it can be speculated that preservation of dopamine signaling may be important to prevent progression or conversion in eyes with nonexudative AMD.

Our finding that a 3-year exposure to dopamine antagonists was associated with increased odds of conversion to exudative AMD highlights the importance of evaluating associations between systemic drugs and disease progression in AMD to better understand the mechanisms that underlie the conversion to exudative AMD. The rates of conversion were higher for eyes exposed to dopamine antagonists for 1 or 2 years; however, they were not significantly different from eyes exposed to dopamine-promoting therapies or unexposed eyes. It is possible that the sample sizes were too small to capture this difference in conversion to exudative AMD or that a significant amount of time on dopamine antagonists is required to confer an increased risk for conversion.

In addition, a strength of our study is that it is the first to our knowledge to evaluate rates of exudative conversion while considering the duration of dopamine-modulating therapy. Prescription duration does not necessarily indicate that the patient adhered to prescription instructions; however, this approach could be expanded to larger retrospective studies to more carefully evaluate the role of dopamine modulation on macular NV in AMD. Moreover, given the expression of both D_2 and D_5 receptors in the RPE,[24,25] it will be critical to evaluate whether therapies that specifically target these pathways are associated with greater differences in rates of conversion to exudative AMD.

In addition to assessing a large number of patients with AMD on dopamine-modulating therapy and their responses, specific characteristics of the OCT images should be evaluated in future studies. The effect of these distinct therapies will enable a better understanding of the heterogeneity of AMD in addition to factors involved in its conversion to an exudative form.

Ethical Approval

Ethical approval for this study was obtained from the Duke University Health System Institutional Review Board (Pro00114162). The study complied with the tenets of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996.

Statement of Informed Consent

Informed consent was waived because the study was a retrospective review of de-identified data and posed no substantial risk to participants.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material is available online with this article.

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