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Presumed neuroprotective therapies prescribed by veterinary ophthalmologists for canine degenerative retinal and optic nerve diseases

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Abstract

Objective: To investigate veterinary ophthalmologists' use of presumed neuroprotective therapies for degenerative retinal and optic nerve diseases in dogs.

Procedures: An online survey was sent to 663 board-certified veterinary ophthalmologists who were Diplomates of the American College of Veterinary Ophthalmologists (ACVO), Asian College of Veterinary Ophthalmologists (AiCVO), Latin American College of Veterinary Ophthalmologists (Colegio Latinoamericano de Oftalmólogos Veterinarios, CLOVE), or European College of Veterinary Ophthalmologists (ECVO). The survey was created using Qualtrics® software and focused on the prescription of presumed neuroprotective treatments for canine glaucoma, sudden acquired retinal degeneration syndrome (SARDS), progressive retinal atrophy (PRA), and retinal detachment (RD).

Results: A total of 165 completed surveys were received, representing an overall response rate of 25%, which was comparable across the four specialty colleges. Of all respondents, 140/165 (85%) prescribed some form of presumed neuroprotective therapies at least once in the last five years: 114/165 (69%) for glaucoma, 51/165 (31%) for SARDS, 116/165 (70%) for PRA, and 50/165 (30%) for RD. The three most recommended neuroprotective reagents were the commercial Ocu-GLO™ Vision Supplement for animals, amlodipine, and human eye supplements.

Conclusions: Despite lack of published clinical efficacy data, the majority of surveyed board-certified veterinary ophthalmologists previously prescribed a presumed neuroprotective therapy at least once in the last five years in dogs with degenerative retinal and optic nerve diseases.

KEYWORDS

canine, glaucoma, neuroprotection, progressive retinal atrophy, retinal detachment, sudden acquired retinal degeneration syndrome

1 | INTRODUCTION

Degenerative retinal and optic nerve diseases are the most common causes of irreversible vision loss in dogs and include glaucoma, sudden acquired retinal degeneration syndrome (SARDS), progressive retinal atrophy (PRA), and retinal detachment (RD).[1–6] Medical and surgical treatments are available for some of these conditions, such as lowering intraocular pressure (IOP) and reattachment of the retina in canine patients with glaucoma and RD, respectively. Progressive retinal atrophy is a group of genetically heterogeneous diseases with a steadily increasing number of defined mutations.[5] Experimental gene therapies have been developed for a few forms of canine PRA with the intention of future clinical application in homologous human diseases.[5,7,8] Each of these treatments is specific for a mutated gene, and they are currently not available for clinical application in dogs.

Unfortunately, in most degenerative retinal and optic nerve diseases loss of function and death of retinal neurons continue despite treatment attempts, resulting in progressive and irreversible vision loss. The reasons for this phenomenon are not fully understood, but likely include oxidative stress, excitotoxicity caused by disproportionate excitatory amino acid release, such as glutamate and aspartate, excessive intracellular calcium, neurotrophin deprivation, inflammation, and reactive gliosis.[2–4,9–11] In order to optimize treatment outcome and limit, or even prevent, further loss of neurons and eyesight, these complicating factors need to be addressed in addition to the treatment of primary underlying disease mechanisms. Like other mammalian central nervous system (CNS) neurons, retinal neurons do not regenerate and cannot be replaced with the currently available technologies, supporting the need for effective neuroprotection.[12] The retinal neurons mainly affected and requiring protection in PRA, RD, and SARDS are the rod and cone photoreceptors located in the outer retina.[5,13,14] The retinal ganglion cells located in the inner retina, and their axons within the optic nerve are mainly affected as part of the common final pathway in all forms of canine glaucoma; however, in some forms of glaucoma with acute and severe IOP elevation, all retinal neurons are affected, including the photoreceptors in the outer retina.[15,16]

Neuroprotection is defined as the alteration of neurons and/or their environment to improve their survival and function in environments that are deleterious to their health.[9] In general, the inclusion of neuroprotective strategies in the management of degenerative retinal and optic nerve diseases is independent of the treatment of primary disease mechanisms and provides a more comprehensive therapeutic approach.[17] Several neuroprotective strategies have been successfully developed and tested in the laboratory, most importantly in rodent models of retinal and optic nerve disease; however, proof of clinical efficacy in human and companion animal patients has been limited or mixed.[18–21] Challenges include lack of methods for early detection of disease, since neuroprotective treatments are most effective when started early in the disease process, and the ability to deliver neuroprotective agents to the retina and optic nerve.[18] Furthermore, laboratory testing often occurs in acute disease models with neuroprotective reagents being applied before or during the induced damage; this is not a realistic approach considering the chronic degenerative disease processes in most clinical patients, which are often not diagnosed at early stages.[3,9]

Despite the current limitations and lack of clinical efficacy data, presumed neuroprotective therapies are being used by veterinary ophthalmologists in hopes of slowing vision loss or preventing dogs with degenerative retinal and optic nerve diseases from becoming blind.[22] By use of an anonymous online survey, our objective was to estimate the percentage of board-certified veterinary ophthalmologists of four different specialty colleges that prescribe oral and/or topical therapies with the goal of achieving neuroprotection in canine retinal and optic nerve diseases. Furthermore, we wanted to determine which presumed neuroprotective therapies ophthalmologists are utilizing. We believe that the collected data will support the need for currently missing clinical efficacy data.

2 | METHODS

2.1 | Survey

The online survey was generated using the software Qualtrics® (Qualtrics, LLC). An e-mail invitation with a link to the anonymous survey was sent to board-certified veterinary ophthalmologists who were Diplomates of the American College of Veterinary Ophthalmologists (ACVO; $n = 492$), the European College of Veterinary Ophthalmologists (ECVO; $n = 111$), the Latin America College of Veterinary Ophthalmologists (Colegio Latinoamericano de Oftalmólogos Veterinarios, CLOVE; $n = 35$), and the Asian College of Veterinary Ophthalmologists (AiCVO; $n = 25$). A total of 663 veterinary ophthalmologists were contacted via e-mail either by their college's administrator (ACVO) or by the investigators (ECVO, CLOVE, and AiCVO). For the survey to remain anonymous, we did not specifically track individuals who were boarded by more than one of the four listed specialty colleges.

The 33-day duration of the survey period was determined by the funded time period of our 2020 Veterinary Scholars Summer Research Program in which one of the investigators (RGH) was enrolled. Most survey invitations were distributed between June 17 and 20, 2020, and the survey was terminated on July 19, 2020 (Figure 1). Diplomates of the ECVO did not receive the survey until July 10, 2020, in order not to interfere with an ongoing online voting process. All contacted veterinary ophthalmologists received one reminder e-mail

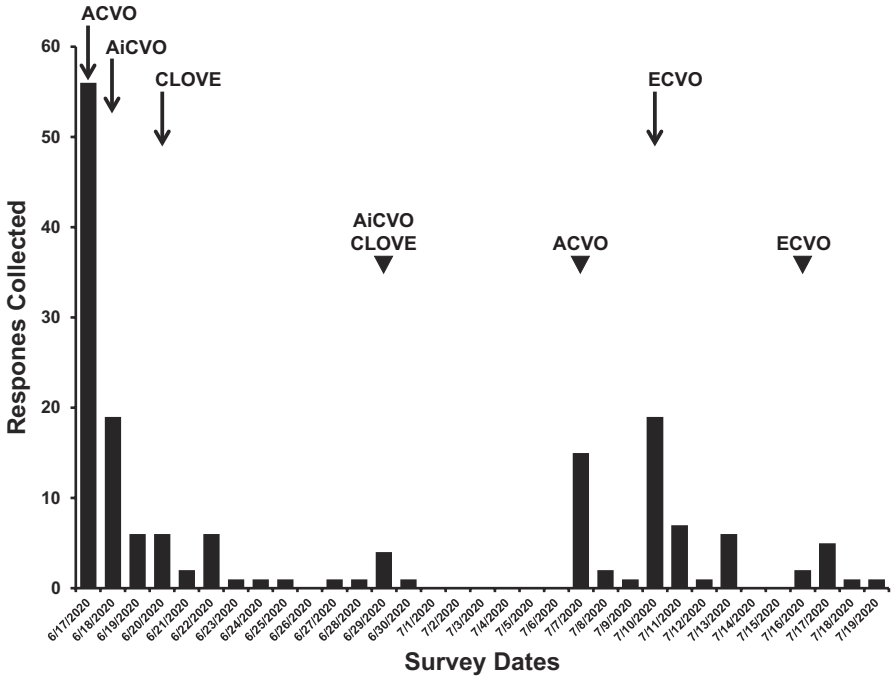


FIGURE 1 Summary of 33-day survey period. Dates of survey invitations (arrows) and reminders (arrowheads) are indicated for the four specialty colleges. The bars show the number of daily responses collected. ACVO, American College of Veterinary Ophthalmologists; AiCVO, Asian College of Veterinary Ophthalmologists; CLOVE, Colegio Latinoamericano de Oftalmólogos Veterinarios (Latin America College of Veterinary Ophthalmologists); ECVO, European College of Veterinary Ophthalmologists

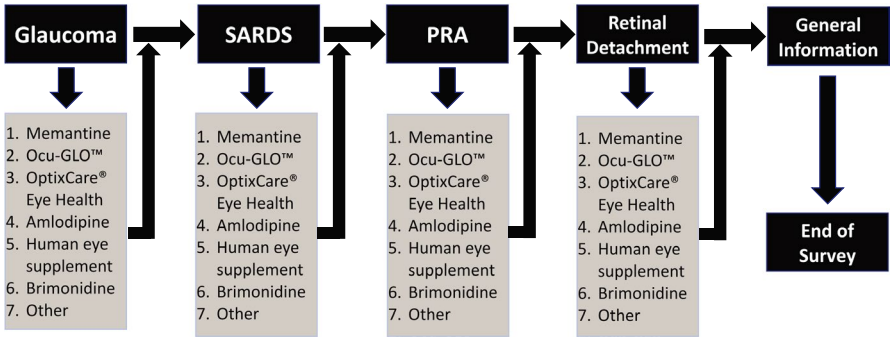


FIGURE 2 Layout of the survey. If respondents answered "yes" to prescribing neuroprotective treatments for a particular disease, they would select any of the treatments listed and answer further questions regarding those treatments. Respondents would not be asked questions regarding treatments they did not select. If a respondent did not prescribe a neuroprotective treatment, they would immediately advance to the next disease. PRA, progressive retinal atrophy; SARDS, sudden acquired retinal degeneration syndrome

partway through the survey period. Diplomates of CLOVE and AiCVO were reminded on June 29, 2020. The reminder was not sent to ACVO Diplomates until July 7, 2020, in order to avoid distraction from concurrent online voting. Because of the late survey beginning, ECVO Diplomates were not reminded until July 16, 2020 (Figure 1).

The survey was programmed not to record IP addresses of participants to aid in maintaining anonymity; however, cookies were generated on the devices used to complete the survey to prevent respondents from submitting multiple survey responses. Regardless, a participant could use different devices to complete more than one survey; this could not be avoided in order to allow respondents to remain anonymous.

Prior to study commencement, the survey was submitted to the Michigan State University (MSU) Institutional Review Board (IRB) and was found to be exempt from further review due to the study's ability to maintain the anonymity of the respondent (MSU Study ID: STUDY00004624).

In the survey's initial screen, a brief description was given to explain the topic and purpose, including the focus on canine degenerative retinal and optic nerve diseases. The survey was broken down into six different sections: (1) introduction, (2) glaucoma, (3) SARDS, (4) PRA, (5) RD, and (6) general information about specialty college membership. The sections that focused on the four specific ophthalmic conditions (glaucoma, SARDS, PRA, and RD) were formatted similarly (Figure 2). Respondents were asked whether they had prescribed medical treatments for the purpose of neuroprotection for a specific disease within the past five years. If the respondents answered "yes," they were shown a list

of potentially neuroprotective treatments. This list consisted of the oral application of memantine, the commercial Ocu-GLO™ Vision Supplement for animals (Animal Necessity LLC), amlodipine, or nutritional supplements originally designed to reduce the risk of disease progression in humans with age-related macular degeneration (AMD).[21] These human supplements are based on the age-related eye disease study formulas AREDS and AREDS2 and included PreserVision® (Bausch & Lomb), Ocuvite® (Bausch & Lomb), and Systane® ICAPS® (Alcon) in the survey (Table 1). The formulas AREDS and AREDS2 are registered trademarks of the United States Department of Health and Human Services (HHS). Topical treatment options were also provided in the survey and consisted of Optixcare® Eye Health (Aventix Animal Health) and brimonidine tartrate 0.2% ophthalmic solution. The respondents could also

TABLE 1 Ingredient comparison among animal and human eye supplements.

Ingredients	Ocu-GLO™	Optixcare® Eye Health	AREDS formula	AREDS2 PreserVision®	Ocuvite®	AREDS2 Systane® ICAPS®	Fish oils
Grape seed extract	X						
Resveratrol		X					
Carotenoids							
Beta-carotene			X				
Lutein	X			X	X	X	
Zeaxanthin				X	X	X	
Asthxanthin		X					
Vitamins and nutrients							
Omega−3 Fatty Acids	X				X	X	X
Pyruvate		X					
Vitamin A						X	
Vitamin C	X		X	X	X	X	
Vitamin D					X		
Vitamin E	X		X	X	X	X	
Vitamin B1	X						
Vitamin B3	X						
Vitamin B6	X					X	
Vitamin B12	X					X	
Folate	X						
Biotin	X						
Pantothenic Acid	X						
Zinc	X		X	X	X	X	
Alpha Lipoic Acid	X						
Coenzyme Q10	X						
Lycopene from tomato extract	X						
Green tea extract 40% ECGC	X	X					
Copper			X	X	X	X	
Niacin						X	
Folic Acid						X	
Selenium						X	
Manganese						X	
Thiamin						X	
Riboflavin						X	

Abbreviations: AREDS, age-related eye disease study formula.

write in a maximum of three additional treatment options that were not listed in the survey by selecting the "other" option. Respondents were then asked to indicate the criteria they used to guide their decisions about the kinds of presumed neuroprotective treatments they had recommended. The options included: (1) published efficacy in laboratory studies, (2) personal experience, (3) colleague's experience, (4) last resort treatment, and (5) "other," which allowed respondents to write in their own answers.

With the use of the Qualtrics® display and skip logic, the survey was programmed only to ask questions related to the specific treatments selected for each condition. This allowed respondents to skip questions not relevant to their experience. Shorter surveys have been shown to improve compliance and response quality by minimizing user fatigue.[23,24]

2.1.1 | Survey analysis

Descriptive survey analysis was conducted using Qualtrics® and Microsoft Excel (Microsoft Corporation). Data were compiled for each question, including response frequency and all manually entered answers provided for open-ended response options. Microsoft Excel allowed effective tracking of specific answers, creation of informative figures, identification of incomplete surveys, which were not included, and tracking of an individual's entire response. This proved useful when respondents would state "see previous answer" or "see comments on disease X" when repeating answers in their survey.

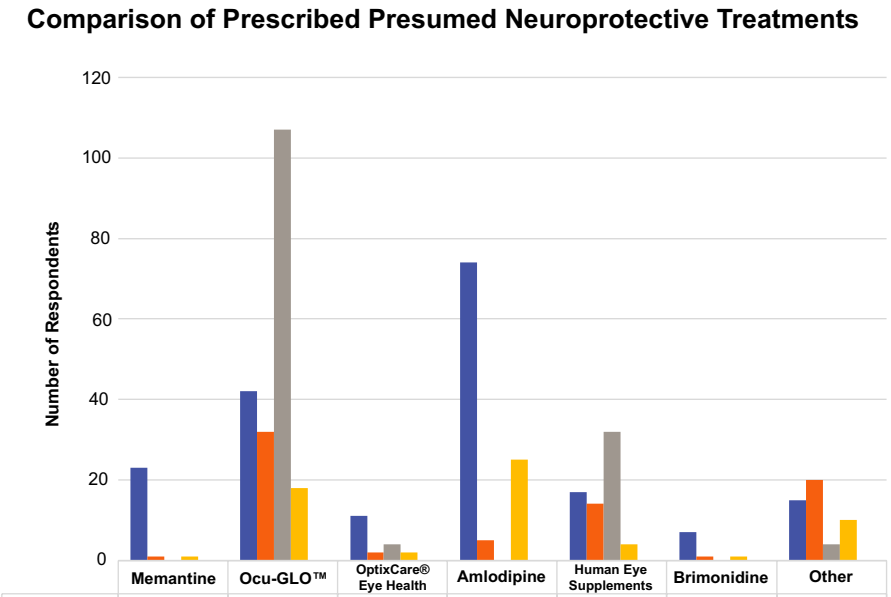
3 | RESULTS

3.1 | General assessment of survey results

Of the 663 veterinary ophthalmologists contacted, we received 176 responses; however, only 165 responses were analyzed, since 11 were incomplete, which resulted in a response rate of 25%. Figure 1 shows when responses were received over the 33-day survey period relative to the e-mail invitations and reminders sent to the four specialty colleges. The response rates were comparable across the four specialty colleges: 112/492 (23%) for ACVO, 39/111 (35%) for ECVO, 9/35 (26%) for CLOVE, and 8/25 (32%) for AiCVO. One respondent also selected the "other" choice and listed the Brazilian College of Veterinary Ophthalmologists (BCVO). Eight veterinary ophthalmologists were double-boarded, and five respondents did not declare their specialty college affiliation.

Overall, 140/165 or 85% respondents had prescribed presumed neuroprotective therapy for at least one of the four conditions in the past five years: 114/165 (69%) for glaucoma, 51/165 (31%) for SARDS, 116/165 (70%) for PRA, and 50/165 (30%) for RD. When stratified by specialty college, the number of respondents prescribing neuroprotection were 100/112 (89%) for ACVO, 30/39 (77%) for ECVO, 8/9 (89%) for CLOVE, and 5/8 (63%) for AiCVO.

Figure 3 depicts the response frequency for the different treatment options listed in the survey. Across all ophthalmic conditions, the three most commonly recommended neuroprotective treatments were Ocu-GLO™ (n = 199 responses), amlodipine (n = 104), and human eye supplements



	Memantine	Ocu-GLO™	OptixCare® Eye Health	Amlodipine	Human Eye Supplements	Brimonidine	Other
Glaucoma	23	42	11	74	17	7	15
SARDS	1	32	2	5	14	1	20
PRA	0	107	4	0	32	0	4
RD	1	18	2	25	4	1	10
TOTAL	24	199	19	104	67	9	49

FIGURE 3 Frequency of respondents prescribing therapies to treat the four neurodegenerative diseases featured in the survey. "Other" depicts individual treatments that were filled in by respondents. These treatments include melatonin, Gingko biloba, and immunosuppressants. PRA, progressive retinal atrophy; RD, retinal detachment; SARDS, sudden acquired retinal degeneration syndrome

($n = 67$). When stratifying the data by specialty college affiliation, Ocu-GLO™ was the most common treatment prescribed by ACVO Diplomates ($n = 151$ responses), amlodipine by ECVO Diplomates ($n = 25$), human eye supplement by AiCVO Diplomates ($n = 6$), and "other" by CLOVE Diplomates ($n = 6$). The "other" treatments are listed in the following sections based on which disease they were recommended for.

3.2 | Treatment of canine glaucoma

Of the 165 respondents, 114 (69%) stated that they prescribe some form of presumed neuroprotective treatment for canine patients with glaucoma: 74/112 (66%) for ACVO, 23/39 (59%) for ECVO, 6/9 (67%) for CLOVE, and 5/8 (63%) for AiCVO. Neuroprotective treatments prescribed for glaucoma by the 114 ophthalmologists in order of decreasing frequency were amlodipine ($n = 74$), Ocu-GLO™ ($n = 42$), memantine ($n = 23$), human eye supplements ($n = 17$), "other" ($n = 15$), Optixcare® Eye Health ($n = 11$), and brimonidine tartrate ($n = 7$) (Figure 3). Those who selected the "other" option manually provided the following therapies: steroid/anti-inflammatories ($n = 6$), Gingko biloba ($n = 3$), curcuma/curcumin ($n = 2$), and melatonin ($n = 2$). Anthocyanin supplement, betaxolol, demecarium bromide, dorzolamide, Monin Cassis, and vitamin E were each mentioned once.

The breakdown of the animal-specific commercial product Ocu-GLO™ between specialty colleges was ACVO ($n = 34/112$; 30%), ECVO ($n = 6/39$; 15%), and AiCVO ($n = 2/8$; 25%). No CLOVE Diplomate used Ocu-GLO™. For Optixcare® Eye Health, the breakdown was ACVO ($n = 10/112$; 9%) and ECVO ($n = 1/39$; 3%). Neither AiCVO nor CLOVE Diplomates prescribed Optixcare® Eye Health.

When asked why the respondents chose to recommend presumed neuroprotective therapies, their responses were colleague's experience (50/179 responses; 28%), success in laboratory (44/179; 25%), personal experience (37/179; 21%), last resort treatment (30/179; 17%), and "other" (18/179; 10%). "Other" responses included advice from human medical glaucoma specialists and "treatment won't cause any harm and has the potential to slow/reverse vision loss."

3.3 | Treatment for SARDS

For SARDS, only 51/165 respondents (31%) indicated they prescribed presumed neuroprotective treatments: 34/112 (30%) for ACVO, 6/39 (15%) for ECVO, 5/9 (56%) for CLOVE, and 2/8 (25%) for AiCVO. Neuroprotective treatments recommended for SARDS, by decreasing frequency, were Ocu-GLO™ ($n = 32$), "other" ($n = 15$), human eye supplements ($n = 14$), amlodipine ($n = 5$), Optixcare® Eye Health ($n = 2$), memantine ($n = 1$), and brimonidine tartrate ($n = 1$) (Figure 2). The following therapies were manually provided by those who selected the "other" option: immunosuppression/corticosteroid ($n = 10$), melatonin ($n = 4$), and doxycycline ($n = 2$). Curcumin, Gingko biloba, intravitreal injection of intravenous immunoglobulin (IVIg), intravitreal injection of triamcinolone acetonide, *omega* fatty acids, pentoxifylline, taurine, vitamin E, and vitamins were each entered once.

The breakdown of the animal-specific commercial products Ocu-GLO™ between specialty colleges were ACVO ($n = 27/112$; 24%), ECVO ($n = 5/39$; 13%), AiCVO ($n = 1/8$; 13%), and CLOVE ($n = 1/9$; 11%). For Optixcare® Eye Health, only two ACVO ophthalmologists ($n = 2/112$; 2%) prescribed this treatment and no respondents from the other specialty colleges.

The most common reason for prescribing presumed neuroprotective therapy for SARDS patients was a last resort treatment (26/71 responses; 37%). With lower frequencies, the choice of neuroprotection prescribed was based on personal experience (17/71; 24%), colleague's experience (14/71; 20%), laboratory data (8/71; 11%), and "other" (6/71; 8%), which included owner request ($n = 2$) and "treatment won't cause any harm and has the potential to slow/reverse vision loss."

3.4 | Treatment of canine PRA

The results for PRA were similar to glaucoma with 116/165 respondents (70%) reporting they used some form of presumed neuroprotective treatment: 84/112 (75%) for ACVO, 23/39 (59%) for ECVO, 7/9 (78%) for CLOVE, and 4/8 (50%) for AiCVO. Neuroprotective treatments, by decreasing frequency, were Ocu-GLO™ ($n = 107$), human eye supplements ($n = 32$), Optixcare® Eye Health ($n = 4$), and "other" ($n = 4$) (Figure 2). No respondents reported the use of amlodipine or brimonidine tartrate for neuroprotective purposes in canine PRA patients. Astaxthanine ($n = 2$) and melatonin ($n = 2$) were manually provided by those who selected the "other" option; fish oil, ForSight™ (Pala-Tech™ Laboratories), multivitamins, *omega* fatty acids, trineurosol, vitamin E, and zeaxthanin were each entered once.

The breakdown of the animal-specific commercial products Ocu-GLO™ between specialty colleges were ACVO ($n = 93/112$; 83%), ECVO ($n = 15/39$; 38%), AiCVO ($n = 2/8$; 25%), and CLOVE ($n = 1/9$; 11%). Optixcare® Eye Health was only prescribed by ACVO Diplomates ($n = 4/112$; 4%).

The influencing factors behind prescribing these treatments were last resort treatment (48/174 responses; 28%), colleague's experience (42/174; 24%), personal experience (39/174; 22%), success in the laboratory (25/174; 14%), and "other" (20/174; 11%). Common answers for the "other" option were the owner's desire/wish to help and "treatment won't cause any harm and has the potential to slow/reverse vision loss."

3.5 | Treatment of canine RD

Retinal detachment had a very similar response as SARDS, with only 50/165 respondents (30%) stating that they have used some form of presumed neuroprotective treatment: 34/112 (30%) for ACVO, 9/39 (23%) for ECVO, 3/9 (33%) for CLOVE, and 3/8 (38%) for AiCVO. The following is the order of treatments used for neuroprotection by frequency: amlodipine ($n = 25$), Ocu-GLO™ ($n = 18$), "other" ($n = 10$), human eye supplements ($n = 4$), Optixcare® Eye Health ($n = 2$), brimonidine tartrate ($n = 1$), and memantine ($n = 1$) (Figure 2). The following treatments were entered by veterinarians for RD under the "other" category: corticosteroids ($n = 8$), methazolamide ($n = 2$), and curcuma ($n = 1$).

The breakdown of the animal-specific commercial products Ocu-GLO™ between specialty colleges were ACVO ($n = 16/112$; 14%), ECVO ($n = 1/39$; 3%), AiCVO ($n = 1/8$; 13%), and CLOVE ($n = 1/9$; 11%). Optixcare® Eye Health was only prescribed by ACVO Diplomates ($n = 2/112$; 2%).

The reasoning behind the prescription of these presumed treatments for RD were colleague's experience (23/76 responses; 30%), personal experience (21/76; 28%), last resort treatment (19/76; 25%), success in laboratory setting (10/76; 13%), and "other" (3/76; 4%). The free text answers for the "other" option were "clinically proven in idiopathic bullous retinal detachments" and owner's desire for treatment.

4 | DISCUSSION

Our results revealed that a majority of surveyed board-certified veterinary ophthalmologists previously prescribed a presumed neuroprotective therapy at least once in the last five years for their canine patients with degenerative retinal and optic nerve diseases. The 85% rate of presumed neuroprotection therapy prescription is likely an overestimation—clinicians using neuroprotection were probably more motivated to respond to our survey than those who are not recommending such treatments. While we were pleased with a 25% response rate, we realize that conclusions must be drawn carefully about clinical practices applied by the 75% of veterinary ophthalmologists who have not responded to our survey. Nevertheless, our study revealed that at least 21% of board-certified veterinary ophthalmologists (140 respondents replying to 663 distributed surveys) use these agents, which is substantial considering the lack of published clinical data. Our findings were true for all four participating specialty colleges: well over half of the respondents used some type of treatment with the goal of achieving a neuroprotective effect on the canine retina and optic nerve.

We specifically asked about the four diseases that were considered the most commonly reported causes of irreversible blindness in pets by veterinary ophthalmologists in a recent international survey: Glaucoma (64% of cases with irreversible blindness), PRA (18%), RD (7%), and SARDS (5%).[1] We assume that presumed neuroprotective therapy is also used for other degenerative retinal and optic nerve diseases, such as optic neuritis and chorioretinitis, but these were not indicated by survey respondents as "other" conditions not listed. In contrast to the previous survey, our study was focused on dogs; however, we cannot rule out that some responding veterinary ophthalmologists also had cats in mind when answering our questions.

Glaucoma and PRA were the two conditions for which most respondents used presumed neuroprotective therapy, approximately 70% for each with overall similar relative frequencies between specialty colleges (glaucoma: ACVO 66%, ECVO 59%, CLOVE 67%, and AiCVO 63%; PRA: ACVO 75%, ECVO 59%, CLOVE 78%, and AiCVO 50%). The most prescribed compounds were amlodipine, Ocu-GLO™ and memantine for glaucoma, and Ocu-GLO™ and human eye supplements for PRA, respectively (Figure 3). Dogs affected by these two disorders may still have some sight at the time of initial diagnosis, and both clinicians and dog owners are eager to consider any treatment option with the potential to slow vision loss. Except for some secondary glaucoma forms, the underlying primary pathogenesis in glaucoma is largely unknown and/or cannot be directly targeted with currently available tools.[3] The ~60% prescription rate for presumed neuroprotective therapies is larger than the 40% of veterinary ophthalmologists declaring the use of neuroprotective agents as part of prophylactic therapy for the normotensive fellow eye in dogs with presumed unilateral primary angle-closure glaucoma (PACG) in a recent survey.[22] This treatment strategy seems crucial considering recent findings by high-resolution OCT imaging that significant retinal thinning occurs before detectable IOP increase.[25] The different results between the two surveys could be explained by (1) difference in clinician population being targeted, and/or (2) different forms of glaucoma being treated. In contrast to our study, which was limited to board-certified veterinary ophthalmologists and included all forms of canine glaucoma, the previous survey was distributed via e-mail listservs to a larger group of veterinarians practicing ophthalmology, but was focused on the prophylactic treatments of primary glaucoma (PACG). In our experience, IOP tends to increase more slowly in many forms of canine secondary glaucoma with slower vision loss than in canine PACG; this results in a longer therapeutic window for presumed neuroprotective therapy.

Compared with glaucoma and PRA, presumed neuroprotective therapy was much less commonly prescribed for SARDS and RD by respondents to our survey (~30%) with overall similar relative frequencies between specialty colleges (SARDS: ACVO 30%, ECVO 15%, CLOVE 56%, and AiCVO 25%; RD: ACVO 30%, ECVO 23%, CLOVE 33%,

and AiCVO 38%). The most prescribed compounds were Ocu-GLO™ and human eye supplements for SARDS, and amlodipine and Ocu-GLO™ for RD, respectively (Figure 3). We assume that the similarly lower prescription frequencies have different explanations for SARDS and RD, respectively. Per definition, dogs with SARDS are generally completely blind with no recordable retinal function and rapid loss of photoreceptors.[2] Recent reports suggest that some SARDS-affected dogs may still have limited sight dependent on the time of diagnosis.[11,26] The low rate of neuroprotection recommendation for SARDS is likely based on the general belief that sight cannot be restored in these canine patients. Only a small percentage of SARDS-affected dogs have been reported to regain some sight with early and aggressive use of immunosuppressive therapies.[2,11,27] In contrast to SARDS, RD is generally more amenable to treatment with medical and surgical methods. With timely and successful intervention, the reattached retina may regain at least some function, and neuroprotective therapy may not be considered necessary by most clinicians.[4,28] Furthermore, if the detached retina cannot be repositioned in time, then neuroprotective therapy will likely not make a difference in treatment outcome as functional rod and cone photoreceptors cannot be maintained in a detached retina.[10] Nevertheless, because the successful reattachment of the retina frequently is not followed by satisfactory visual outcome, there is a need for adjunctive medical neuroprotective therapies in patients with RD.[10]

A minority of veterinary ophthalmologists using neuroprotection based their decision on published laboratory data: 25% for glaucoma and 11%–14% for the photoreceptor diseases SARDS, PRA, and RD, respectively. This indicates that most presumed neuroprotective treatments are used in a rather anecdotal, subjective manner. While many compounds have been shown to be neuroprotective in the laboratory, most importantly in rodent models of retinal and optic nerve disease, successful translation into the clinic for human and companion animal patients has largely failed.[9,18] Possible explanations for these failures include the relatively late disease stage with advanced degeneration at the time of clinical diagnosis, and the inability of many neuroprotective reagents to reach the posterior segment of the eye without intraocular administration.[18] The high prescription rate of presumed neuroprotective treatments in our survey contrasts the absence of published clinical efficacy data in dogs with degenerative retinal and optic nerve diseases. This finding is likely explained by lack of a curative treatment for many of these conditions, the desperate attempt to maintain or restore sight, and low risk of adverse effects caused by the prescribed medications and supplements.

In our attempt to keep the survey short and user-friendly, we did not analyze any responses about efficacy assessment, including timing of treatment initiation in relation with disease progression, dosing of the presumed neuroprotective treatments, and quantifiable outcome measures. Carefully designed clinical or laboratory case-control studies are needed to determine efficacy of presumed neuroprotective therapies in dogs.

The main neuroprotective strategy recommended by veterinary ophthalmologists consisted of inhibiting oxidative stress, which plays an important role in neurodegenerative diseases, whereby cellular damage is caused by increased concentration of reactive oxygen species, most importantly hydrogen peroxide (H_2O_2) and oxy-radicals (O_2-).[9,21,29,30] The two most commonly prescribed antioxidants were Ocu-GLO™ Vision Supplement for animals, which contains 12 antioxidants, and human eye supplements (Table 1). The relative Ocu-GLO™ prescription rate was highest for ACVO, followed by ECVO; both CLOVE and AiCVO had the lowest rates. We believe that these differences can be explained to some extend by the geographic differences of product marketing. According to the manufacturer, Ocu-GLO™ is formally distributed throughout the U.S., Canada, Europe, Australia, New Zealand, and all parts of Asia and is typically shipped to over 70 countries (Jen Palmiotto, Animal Necessity, personal communication).

Comparable to our study, Ocu-GLO™ was the second most commonly prescribed neuroprotectant agent following amlodipine in a recent survey on prophylactic therapy for primary canine glaucoma.[22] Unfortunately, the number of published studies evaluating the use of antioxidants in dogs with ocular disorders is limited. A potential delay in diabetic cataract progression has been shown in dogs and rats with oral administration of Ocu-GLO™.[31,32] The topical application of Optixcare® Eye Health resulted in both prevention and delay of diabetic cataracts in rats.[32] Although the use of oral Ocu-GLO™ did not result in a detectable slowing of pigmentary uveitis in Golden Retrievers,[33] there are indications that application of the anti-oxidative components within Ocu-GLO™ may be beneficial for inhibiting formation and progression of cataracts in dogs, including its main components grape seed proanthocyanidin extract (GSE), lutein, and *omega*-3 fatty acids. For example, GSE has been shown to inhibit reactive oxygen species production and stress-induced cell signaling in primary canine lens epithelial cell culture.[34,35]

Omega-3 fatty acids are also included in the topical lubricant Optixcare® Eye Health and are used by some respondents in the form of fish oils. Combined with vitamin A, a diet high in *omega*-3 fatty acids may slow the rate of visual acuity decline in human patients with retinitis pigmentosa.[36] A systematic literature review described some improvement in human patients with retinitis pigmentosa that received *omega*-3 fatty acid supplementation, but additional studies are required.[37] Unfortunately, dogs affected by progressive rod-cone degeneration (prcd) and supplemented with *omega*-3 fatty acids for up to 21 weeks in a research colony setting did not experience slowing of retinal degeneration.[38] Adding *omega*-3 fatty acids to the AREDS formula also had no additional treatment effect on slowing progression of human AMD.[21] The AREDS

and AREDS2 human eye supplement formulas are based on age-related eye diseases studies that were funded by the U.S. National Eye Institute (NEI) and that demonstrated reduce the risk of AMD progression in human patients.[21,30]

The antioxidative topical lubricant Optixcare® Eye Health was prescribed for all four listed neurodegenerative conditions by some veterinary ophthalmologists participating in our survey. The relative Optixcare® Eye Health prescription rate was highest for ACVO, followed by ECVO; neither CLOVE nor AiCVO Diplomates marked the use of this lubricant. We believe that these differences can be explained to some extend by the geographic differences of product marketing. According to the manufacturer, Optixcare® Eye Health is formally distributed throughout the US, Canada, Europe, the United Arabic Emirates, and Taiwan (Katelynn Jackson, Aventix Animal Health, personal communication). This product contains four antioxidants (Table 1). While we are not aware of any published data demonstrating if and how effectively these compounds reach the canine retina and optic nerve head following topical application on the ocular surface, Optixcare® Eye Health reduced reactive oxygen species significantly in the anterior segment of rat eyes following exposure to oxidative stress and has even delayed the progression of sugar cataracts in diabetic rats.[32] Surprisingly, the topical administration of Optixcare® Eye Health also provided some beneficial retinal effects in a rat model of light-induced retinal damage.[32]

In addition to the commercially available systemic and topical eye supplements, some respondents indicated prescribing other antioxidants that have been suggested to have neuroprotective effects for the photoreceptors and/or retinal ganglion cells, including Gingko biloba, curcumin, and melatonin.[9,29,39]

The calcium channel blocker amlodipine besylate was the second most used treatment in our survey overall, and the most common presumed neuroprotectant used in canine glaucoma patients. Amlodipine was also the leading neuroprotectant agent in a recent survey on prophylactic treatments for canine PACG.[24] The reason for using calcium channel blockers is to inhibit excessive calcium influx from the extracellular space in order to prevent or reverse increased intracellular calcium concentration and calcium-dependent apoptotic cell death.[9,40] While the neuroprotective effects of calcium channel blockers have been well documented in the laboratory, including on photoreceptors and retinal ganglion cells in experimental animals, clinical efficacy data are still lacking.[40] In veterinary medicine, amlodipine is routinely used to lower blood pressure in animals with systemic hypertension.[41] We believe that one reason why amlodipine was the leading presumed neuroprotective drug prescribed for dogs with RD is its common used for hypertensive retinopathy and choroidopathy resulting in RD.[6] Even though our study was focused on dogs, we cannot rule out that some responding veterinary ophthalmologists also had hypertensive cats in mind when marking amlodipine for use in patients with RD. In addition to its potential neuroprotective effect, amlodipine also has the demonstrated benefit of increasing ocular blood flow in dogs.[42] In contrast, calcium channel blockers such as amlodipine have been shown to increase the risk of open-angle glaucoma in humans, possibly because of decreased systemic blood pressure and ocular perfusion.[43]

Memantine was the third most common neuroprotectant used for canine glaucoma both in this and a recent survey on the prophylactic treatment of dogs with unilateral PACG.[22] Some of our respondents also selected memantine for the treatment of SARDS and RD. Memantine, traditionally used for the treatment of Alzheimer's disease, is an N-methyl-D--aspartate (NMDA) receptor antagonist that inhibits the toxic effect of excessive glutamate and aspartate in the extracellular space.[44,45] Memantine was shown to reduce retinal ganglion cell death and functional loss in rats and primates with experimental glaucoma.[46–48] Translation into clinical application failed because protection of visual function by memantine could not be demonstrated in human glaucoma patients enrolled in two phase 3 clinical trials.[19]

Because lowering of IOP is not considered a form of neuroprotection, we did not include routine glaucoma eye drops in our survey.[3,22,39] The exception was the *alpha2*-adrenergic agonist brimonidine tartrate 0.2% ophthalmic solution because of limited IOP-lowering effect in dogs.[49] We assumed that the purpose of any topical brimonidine administration in canine patients would be based on the potential anti-apoptotic neuroprotective effect demonstrated in the laboratory.[50–58] In our survey, very few veterinary ophthalmologists indicated that they were using brimonidine as a neuroprotectant in their canine glaucoma patients.

Even though the use of anti-inflammatory drugs could also be considered a neuroprotective strategy,[9] we did not include them in the survey, since the inhibition of inflammation is part of the treatment of the underlying primary disease mechanism in some of the neurodegenerative diseases, including glaucoma and RD secondary to chronic, severe uveitis. Nevertheless, several respondents added the use of systemic and/or intravitreal injection of corticosteroids under "other" for the treatment of glaucoma, SARDS, and RD.

The inability to examine differences in prescribing behavior between responding ophthalmologists in more detail, such as age, gender, and country of training, is a weakness of our study. This limitation was by design to keep the survey shorter and the response rate higher by minimizing user fatigue.[23,24] For the same reason, we refrained from collecting or interpreting more detailed information about the use of the presumed neuroprotective therapies, such as disease stage at start of treatment and assessment of efficacy of the presumed neuroprotective treatments, since this may have required time-consuming review of medical records. Maintaining the survey anonymous also facilitated the approval process by exemption from further IRB

review. While the 33-day survey period was rather short, our data show that an extended time period would not have resulted in much larger numbers of responses since the majority of completed surveys were received within days of our e-mail invitations (Figure 1).

In conclusion, a majority of board-certified veterinary ophthalmologists who responded to our survey prescribed presumed neuroprotective therapies at least once within the last five years in dogs with the selected four degenerative retinal and optic nerve diseases. Considering the recognized need by clinicians for neuroprotective therapy demonstrated by our survey and the considerable resources invested by owners of dogs with degenerative, blinding retinal and optic nerve diseases, we believe that there is a critical need for clinical efficacy data.

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CONFLICT OF INTERESTS

There are no conflicts of interest related to this study.

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