

Cataract as an Endpoint-Dependent Confounder in Trials of Neuroprotective Therapies for Glaucoma [Letter]

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Dear editor

We read with great interest the review by Rho and Williams, which provides a timely synthesis of neuroprotective therapies for glaucoma and emphasizes that the field's translational challenge is no longer limited to drug discovery, but also concerns endpoint sensitivity, patient selection, and trial design.¹ Their discussion of the negative memantine Phase III program and the subsequent movement toward PhNR, PERG, OCT-based progression metrics, artificial intelligence-guided visual-field endpoints, and molecular biomarkers is particularly valuable.

In this context, we would like to highlight cataract not as a universal limitation, but as an endpoint-dependent confounder in glaucoma neuroprotection trials. In the memantine trials summarized in the review, progression was assessed using standard automated perimetry, frequency-doubling technology, and optic-disc photography.¹ These contrast-dependent and media-sensitive endpoints are vulnerable to cataract progression. Lens opacity can reduce visual-field sensitivity and mimic glaucomatous worsening, whereas cataract extraction can improve visual-field indices and create an apparent functional benefit unrelated to retinal ganglion cell preservation.^{2,3} Therefore, cataract could contribute to either false-negative or false-positive interpretation of neuroprotective efficacy when visual-field endpoints dominate. This issue is also relevant to artificial intelligence-selected "High-5" visual-field endpoints, because improved spatial targeting of vulnerable test locations does not by itself eliminate optical-media noise.⁴

The same concern applies, although differently, to structural endpoints. Rho and Williams appropriately emphasize OCT-based retinal nerve fiber layer and ganglion-cell measurements as important tools for future trials. However, cataract can reduce OCT signal strength and alter measured retinal nerve fiber layer thickness, and recent evidence continues to show measurable retinal nerve fiber layer changes after cataract surgery in glaucoma-related populations.^{5,6} Although modern OCT devices incorporate signal-strength and image-quality indices, residual cataract-related measurement bias may persist, particularly when longitudinal change is interpreted near progression thresholds. Thus, in CNTF or other studies using visual-field and OCT outcomes, cataract progression or postoperative improvement in image quality may distort structural trajectories.

By contrast, not all endpoints are equally susceptible. PERG, used in citicoline studies, and PhNR, adopted in nicotinamide-based trials, may be less directly confounded than conventional perimetry because they provide retinal functional readouts.^{7,8} Nevertheless, media opacity may still influence retinal illuminance, stimulus delivery, pupil-related testing conditions, and electrophysiological test quality. Even more importantly, DARC, aqueous neurofilament light chain, and multi-omics biomarkers discussed by Rho and Williams are less vulnerable to cataract-related optical confounding than perimetry or OCT thickness metrics.⁹ Recognizing this hierarchy of endpoint vulnerability could help trialists select, weight, and interpret outcomes more appropriately.

Cataract surgery itself also deserves prespecified handling. Phacoemulsification may lower intraocular pressure, reduce medication burden, change postoperative inflammation and steroid exposure, and improve imaging quality.¹⁰ In trials intended to demonstrate IOP-independent neuroprotection, failure to model cataract surgery may lead to erroneous

attribution of benefit or harm to the investigational agent rather than to altered intraocular pressure exposure or optical conditions. This issue is especially important when a treatment effect is interpreted as retinal ganglion cell protection independent of IOP lowering.

We therefore suggest an endpoint-specific cataract-aware strategy. Future studies should record baseline lens status, phakic/pseudophakic status, OCT signal strength, planned cataract surgery, and cataract extraction during follow-up. For visual-field and OCT outcomes, cataract surgery should be prespecified as a time-varying covariate in longitudinal mixed-effects models, with sensitivity analyses excluding perioperative visits. Post-surgical re-baselining may reduce discontinuities caused by improved optical clarity and imaging quality, but it may also reduce continuity between preoperative and postoperative longitudinal data; therefore, it should be used as a sensitivity approach rather than as the sole analytic strategy. For PhNR, PERG, and biomarker-based endpoints, cataract-related adjustment may be less intensive but should still include standardized optical and test-quality documentation.

In conclusion, accounting for cataract in an endpoint-specific manner would strengthen the translational roadmap proposed by Rho and Williams. Without such adjustment, future glaucoma neuroprotection trials may underestimate true retinal ganglion cell protection or overestimate apparent benefit caused by cataract extraction, reduced IOP exposure, or improved media clarity.

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References

1. Rho S, Williams PA. Prospects for neuroprotective therapies in glaucoma: drug targets and emerging clinical strategies. *Drug Des Devel Ther.* 2026;20:612176. doi:10.2147/DDDT.S612176
2. Seol BR, Jeoung JW, Park KH. Changes of visual-field global indices after cataract surgery in primary open-angle glaucoma patients. *Jpn J Ophthalmol.* 2016;60(6):439–445. doi:10.1007/s10384-016-0467-8
3. Hayashi K, Hayashi H, Nakao F, Hayashi F. Influence of cataract surgery on automated perimetry in patients with glaucoma. *Am J Ophthalmol.* 2001;132(1):41–46. doi:10.1016/S0002-9394(01)00920-5
4. da Costa DR, Scherer R, Swaminathan SS, et al. Artificial intelligence-guided endpoint selection for neuroprotection trials in glaucoma. *Am J Ophthalmol.* 2026;284:88–100. doi:10.1016/j.ajo.2025.12.038
5. Mwanza JC, Bhorade AM, Sekhon N, et al. Effect of cataract and its removal on signal strength and peripapillary retinal nerve fiber layer optical coherence tomography measurements. *J Glaucoma.* 2011;20(1):37–43. doi:10.1097/IJG.0b013e3181d787a5
6. Menna F, De Luca L, Calabro M, Meduri A, Lupo S, Vingolo EM. Retinal nerve fiber layer changes following cataract surgery in patients with and without preperimetric glaucoma. *J Clin Med.* 2025;14(20):7255. doi:10.3390/jcm14207255
7. Parisi V, Centofanti M, Ziccardi L, et al. Treatment with citicoline eye drops enhances retinal function and neural conduction along the visual pathways in open angle glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 2015;253(8):1327–1340. doi:10.1007/s00417-015-3044-9
8. Hui F, Tang J, Williams PA, et al. Improvement in inner retinal function in glaucoma with nicotinamide: a crossover randomized clinical trial. *Clin Exp Ophthalmol.* 2020;48(7):903–914. doi:10.1111/ceo.13818
9. Cordeiro MF, Normando EM, Cardoso MJ, et al. Detecting retinal cell stress and apoptosis with DARC: progression from lab to clinic. *Prog Retin Eye Res.* 2022;86:100976. doi:10.1016/j.preteyeres.2021.100976
10. Brízido M, Rodrigues PF, Almeida AC, Abegão Pinto L. Cataract surgery and IOP: a systematic review of randomised controlled trials. *Graefes Arch Clin Exp Ophthalmol.* 2023;261(5):1257–1266. doi:10.1007/s00417-022-05911-3

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