Review Article

Advances in Glaucoma Drug Therapy

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Abstract

Glaucoma remains the leading cause of irreversible blindness, but timely treatment to lower intraocular pressure is effective at slowing the rate of vision loss from glaucoma. Medical management remains the first line of treatment in adult glaucoma, and the evolution of medical therapy for glaucoma has followed an exponential curve. This narrative review briefs the rapid development of new medications and drug delivery systems in recent years. Newer medications may be able to extend the duration of medically controlled glaucoma, delaying or possibly eliminating the need for glaucoma surgery for some patients. Alternative methods of delivery for glaucoma medications may be a key factor in improving outcomes with currently available medications.

Keywords: Glaucoma, glaucoma medications, medical therapy

Introduction

Glaucoma, the leading cause of irreversible blindness, is a chronic progressive optic neuropathy that is caused by both, intraocular pressure (IOP)-dependent and -independent mechanisms.[1] However, the only modifiable risk factor for glaucoma is the IOP.[2] After nearly two decades, there has been an attempt to identify novel mechanisms for lowering outflow resistance, which are efficacious during both diurnal and nocturnal periods. Additionally, neuroprotection is another key area to focus on. Figure 1 shows the classification of newer medical approaches to glaucoma.

Topical agents

Rho-associated protein kinase (ROCK) inhibitors[3]

ROCK is a small guanosine triphosphate (GTP)-binding protein that is involved in cellular events that regulate cell shape motility, proliferation, and smooth muscle contraction. Figure 2 shows the mechanism of action of ROCK inhibitors.

Ripasudil

This was the first ROCK inhibitor approved in Japan in 2014. It Inhibits both ROCK1 and ROCK2 thereby:

- Increasing conventional outflow through the trabecular meshwork (TM).
- Increasing permeability of endothelial cells of the Schlemm's Canal
- Decreasing episcleral venous pressure.

Dosage: Twice a day

Efficacy: A report from the K-115 Clinical Study Group in Japan showed that Ripasudil monotherapy reduced the mean IOP by 2.6 mm Hg at the trough and 3.7 mm Hg at peak over usage for 52 weeks.[4]

Safety and tolerability: The most common side effect is conjunctival hyperemia due to the relaxation of the vascular smooth muscles. Other side effects include blepharitis and allergic conjunctivitis

Availability: Not yet United States Food and Drug Administration (FDA) approved, but available in India as a topical formulation of 0.4%.

Netarsudil

Approved by the FDA in 2017, Netarsudil is a ROCK + norepinephrine transport inhibitor thereby causing

- Increase in conventional aqueous outflow

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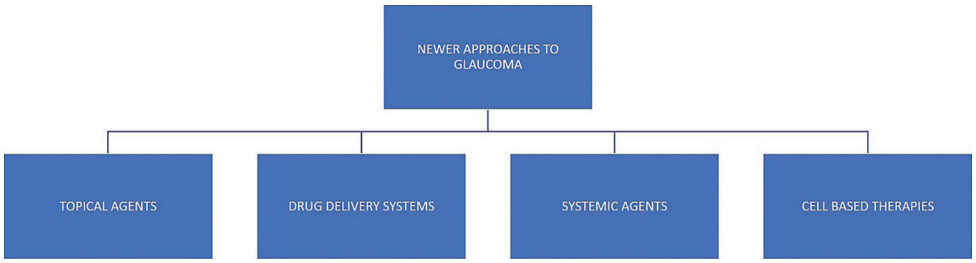

Figure 1: Classification of newer medical approaches to glaucoma

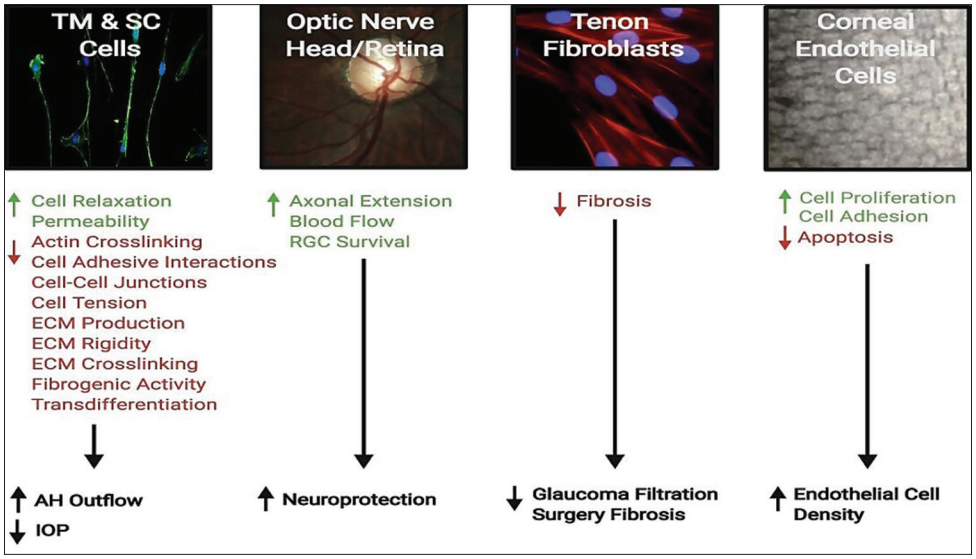

Figure 2: Mechanism of action of ROCK inhibitors

- Decrease in episcleral venous pressure (EVP)
- Decreased aqueous production.

Dosage: Once daily in the evening

Efficacy: Two double-masked randomized control trials called ROCKET-1 and ROCKET-2 concluded clinically relevant and statistically significant IOP lowering by Netarsudil as compared to timolol in patients with baseline IOP below 25 mm hg. However, Netarsudil did not meet this noninferiority criterion in patients with baseline IOP above 27 mm Hg.[5]

Safety and tolerability: Netarsudil has a favorable safety profile. The reported ocular side effects are conjunctival hyperemia, cornea verticillate, honeycomb/reticular bullous epithelial edema, subconjunctival hemorrhage, and contact dermatitis

Availability: Available in India

Rocklatan[6]

It is a fixed dose combination of 0.02% Netarsudil with 0.005% Latanoprost.

FDA-approved in 2019, this fixed-dose combination provides the strong IOP lowering efficacy of prostaglandin analog with the additional efficacy of Netarsudil.

Dosage: Once daily in the evening

Availability: Not available in India

Latanoprostene bunod[7]

Approved by the FDA in 2017 and available under the brand name Vyzulta, Latanoprostene bunod is a prostanoid analogue that works in two ways

Figure 3 shows the mechanism of action of Latanoprostene bunod.

Dosage: One drop in the evening

Efficacy:

APOLLO trial[8] - Mean IOP lowering by Latanoprostene bunod was significantly lower than timolol at all time points

VOYAGER trial[9] - Once daily dosing of Latanoprostene bunod provides greater IOP reduction than latanoprost

Other trials include- LUNAR,[10] CONSTELLATION[11]

Safety and tolerability: Well-known adverse effects of prostaglandin analogs have been reported. The butanediol mononitrate does not lead to any adverse effects.

Availability: Not available in India

Figure 4 shows the summary of efficacy and action of currently available new glaucoma drugs.

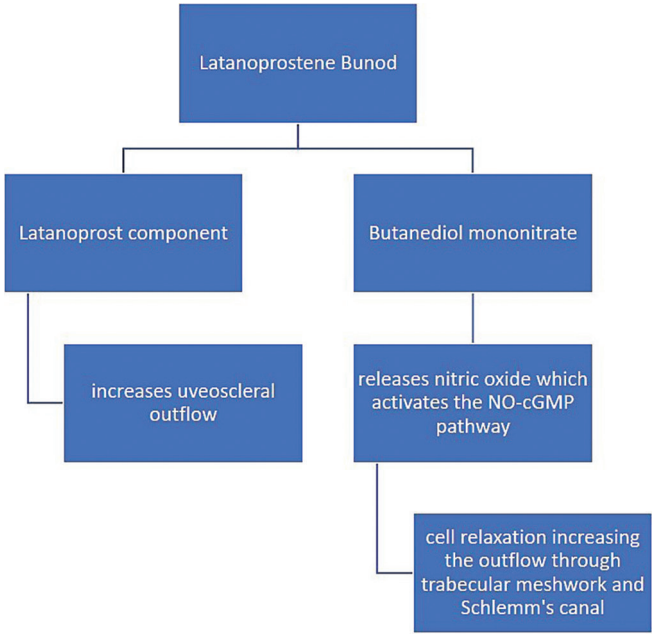

Figure 3: Mechanism of action of Latanoprostene bunod

Medication	Class	IOP reduction	Primary Target			
			Increases trabecular outflow	Increases uveoscleral outflow	Decreases aqueous production	Decreases episcleral venous pressure
Ripasudil 0.4%	ROCK inhibitor	15-18%	Yes	No	No	Yes
Netarsudil 0.02%	ROCK + Norepinephrine transporter inhibitor	16-21%	Yes	No	Yes	Yes
Netarsudil 0.02% + Latanoprost 0.005%	ROCK inhibitor and Prostaglandin analogue	30-34%	Yes	Yes	Yes	Yes
Latanoprostene bunod 0.024%	Prostaglandin analogue and NO donator	32-34%	Yes	Yes	No	No

Figure 4: Summary of efficacy and action of newer glaucoma drugs available in the market

Omidenepag isopropyl (OMDI, Santen)[12]

Approved by the FDA in 2022, OMDI is a selective, non-prostaglandin, prostanoid EP2 receptor agonist

Mechanism of action: It is found to increase both conventional and uveoscleral outflow. It binds to a prostanoid receptor, which has Gs-coupled transmembrane properties within the ciliary body and TM. Upon binding it stimulates an increase in intracellular adenosine 3',5-cyclic monophosphate (cAMP) levels, which promotes aqueous humor outflow by increasing trabecular and uveoscleral outflow.

Efficacy:

- The AYAME study compared OMDI at 0.002% to Latanoprost at 0.005% once-daily and found that the OMDI was just as well tolerated and not inferior at reducing IOP in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).[13]
- Other studies: FUJI,[14] RENGE[15]

Safety and tolerability: As it is a non-prostaglandin, it does not have other side effects such as cystoid macular edema, periorbital atrophy, or periorbital pigmentation. Ocular adverse effects include conjunctival hyperemia and corneal thickening.

Availability: Not available in India

Drugs undergoing clinical trials

NCX 470 (NICOX SA)[16]

A prostaglandin analogue, formed from a nitric oxide-donating compound has shown promise in trials.

Initially, an animal study displayed this drug's superiority over Bimatoprost in lowering IOP and treating both glaucoma and ocular hypertension. More recently in 2021, the company reported the outcomes of the dose-response Phase II trial (Dolomites), which showed that patients on the novel drug experienced significantly greater IOP-lowering effects than those on Latanoprost.[16]

Phase II trials, involved the use of topical NCX 470 (0.065% concentration) vs 0.005% Latanoprost, over a 28-day period. NCX 470 was found to be superior to Latanoprost at all time points during the day coupled with a drop in IOP, up to 1.4 mmHg more than Latanoprost.

Currently, two multi-regional Phase III clinical trials, known as Mont Blanc and Denali trials are underway, with the primary objective being to evaluate whether 0.1% NCX 470 solution surpasses the efficacy of IOP control provided by Latanoprost 0.005%, or not. Both these trials are expected to be completed by 2025.

Cromakalim prodrug 1 (CKLP1)[17]

Cromakalim prodrug 1 (CKLP1) is a water-soluble, adenosine triphosphate (ATP) sensitive potassium channel opener.

Mechanism of action: It uses a new mechanism of action involving the reduction of EVP. It is currently being studied, with the hope that may offer clinical results equivalent to what may be achieved only via surgical intervention. EVP and IOP share a one-to-one relationship and reduction in EVP brings about an equal reduction in IOP. As opposed to the floor effect on IOP produced by prostaglandin analogs, drugs that lower EVP it is possible to achieve pressures as low as 8–10 mm Hg, which is particularly important in advanced glaucoma.

Efficacy: A study published in 2021 studied its effect on normotensive animals and found that CKLP1 was able to significantly lower IOP by 18.9 percent in monkeys and 16.7 percent in dogs compared with control eyes, without any effect on systemic blood pressure.

QLS-101 and QLS-111[18]

QLS-101 is also an ATP-sensitive potassium channel opener. Its mechanism of action is the reduction of EVP. The drug has shown excellent safety profile and efficacy during human trials.

QLS -111 is the second-generation formulation that has undergone, both high-dose and low-dose testing in humans. It brings about an extra reduction of 3.5 mm Hg from the

baseline IOP, as compared to its predecessor, without any ocular adverse effects.

PDP-716[19]

It is a once-daily ophthalmic formulation of brimonidine, in development, for the treatment of ocular hypertension and open-angle glaucoma.

Mechanism of action: PDP-716 has been formulated using patented TearAct™ fine resin technology, which provides slow, consistent, and sustained drug delivery to improve drug bioavailability.

The Phase III trials were carried out in 682 participants, which demonstrated functionally equivalent IOP reduction for Alphagan-P and PDP-716.

Trabodenoson[20]

It is an adenosine mimetic, which selectively targets the A1 receptor (A1R) subtype, involved in multiple signaling pathways, including matrix metalloproteinase (MMP-2) associated with glaucoma, thereby providing trabecular rejuvenation.

Its Phase 3 clinical trials failed at the wrong dose and dosing regimen because of the misinterpretation of results from the Phase 2 monotherapy.

Tetrahydrocannabinol (SBI-100)[21]

Tetrahydrocannabinol is the main psychoactive component of cannabis. Its IOP-lowering mechanism is not fully understood. There are three proposed pathways through which cannabinoids exert their neuroprotective effect: inhibition of glutamate, nitric oxide, and endothelin-1. It is known that glutamate is toxic to retinal ganglion cells in glaucoma and has been implicated in progressive degeneration in chronic optic neuropathies.[22]

SBI-100 ophthalmic emulsion is a synthetic tetrahydrocannabinol derivative molecule in a nanoemulsion formulation, which binds to CB1 receptors and lowers IOP in glaucoma and ocular hypertension.

Systemic agents

Nicotinamide and pyruvate[23]

Patients who continue to progress despite IOP lowering measures may benefit from neuroprotective and neuroenhancement therapies. Neuroprotection refers to the prevention of retinal ganglion cell death, whereas neuroenhancement is an effort to improve the functioning of damaged retinal ganglion cells.

Mechanism of Action: Nicotinamide, a form of vitamin B3, produced by the body from niacinamide, is a precursor to nicotinamide adenine dinucleotide (NAD). NAD of the retina and optic nerve declines as a function of IOP, thereby compromising energy and redox metabolism.

Pyruvate is involved in energy production pathways in the body. Animal studies show an IOP-mediated decrease in retinal pyruvate levels.

It has been hypothesized that a combination of nicotinamide and pyruvate may improve retinal ganglion cell function in glaucoma.

Efficacy: 32 patients underwent a Phase II randomized clinical trial for nicotinamide and pyruvate for neuroenhancement in open-angle glaucoma. Patients were randomized to high oral doses of nicotinamide (1,000–3,000 mg) and pyruvate (1,500–3,000 mg) or a placebo. The study concluded that this combination provided significant short-term visual function improvement without any adverse effects.

Citicoline[24]

Citicoline (cytidine 5'-diphosphocholine) is an endogenous compound that provides benefits in glaucoma.

Mechanism of Action:

- Normalization of visual evoked potential amplitude and implicit time in glaucomatous eyes
- Improved retinocortical time in chronic POAG patients treated with oral citicoline.

Drawbacks: These results were not apparent until after 1-year of citicoline therapy, suggesting that extended treatment is needed.

Efficacy: Further studies have demonstrated that continued therapy for up to 8 years stabilized or improved visual dysfunction in glaucoma patients, suggesting the need for repeated dosing to achieve optimal results.

Memantine[25]

It is a non-competitive N-methyl D-aspartate (NMDA) antagonist with anti-glutamate excitotoxicity effects. Memantine was shown to protect against retinal ganglion cell loss in animal models of glaucoma. Despite these promising findings, its Phase III clinical trials failed to demonstrate significant benefits.

Gingko Biloba[26]

Ginkgo biloba extract is derived from ginkgo tree leaves, which contain free radical scavengers like flavonoids, terpenoids, and various bioactive compounds. Ginkgo has not only shown short-term improvement in visual field indices, but it also has antithrombotic properties that may produce adverse ocular effects such as retinal hemorrhage and hyphema.

Bilberry[27]

Bilberry fruit (Vaccinium myrtillus) or European blueberry contains the flavonoid anthocyanin and is hypothesized to provide neuroprotective and anti-inflammatory effects.

Neurostimulation

Neurostimulation therapies aim to reactivate the malfunctioning retinal ganglion cells by applying an electrical current that relaxes muscles in the head thereby improving ganglion cell blood flow.[28]

A randomized clinical trial involving repetitive transorbital alternating current stimulation demonstrated the following results:

- Mean visual field improvement
- Improved reaction times
- Improved near-threshold visual fields in the central 5 degrees

- Increased static perimetry thresholds.

The results are found to be better in patients with advanced disease.

Drug delivery systems

Patient adherence is impossible to guarantee while using topical glaucoma agents. Around half of glaucoma patients do not follow the dosing instructions properly, as convenience is a major factor negatively impacting patient adherence.[29] Approximately one-third of patients are incapable of effectively self-administering their eye drops.[30] Also, the bioavailability of topical drugs was less, and they caused damage to the ocular surface.[31] Studies have shown fluctuations in IOP after treatment with topical drugs, whereas systemic medications are less effective and tend to increase the risk of visual field deterioration.[32,33] In an attempt to overcome these issues, mainly non-compliance to chronic medication use, sustained drug delivery systems have been developed in the past two decades.

Durysta[34]

Structure: The Bimatoprost implant (Durysta™, Allergan plc, Dublin, Ireland) is a biodegradable sustained-release implant that utilizes the NOVADUR drug delivery system.

Dose: It contains 10 micrograms of Bimatoprost and its action lasts for 90 days, following which the biodegradable polymers of the implant disintegrate into carbon dioxide and water.

Procedure: It is available as a single-use pre-filled applicator

- Before use, the safety tab is pulled out perpendicular to the long axis of the applicator
- With adequate stabilization of the eye, the needle is advanced through the cornea.
- The anterior chamber is entered with the needle bevel visible through clear cornea and parallel to the iris plane, adjacent to the limbus, in the superotemporal quadrant.
- The needle should be inserted approximately 2 bevel lengths within the anterior chamber
- The back half of the actuator button is depressed firmly until an audible and/or palpable click is noted.
- Following the release of the implant, the needle is removed via the same track in which it was inserted. The injection site is checked for leaks.
- The patient is instructed to remain upright for at least 1 hour after the procedure so the implant can settle.

Efficacy: The ARTEMIS 1 trial demonstrated the efficacy of Durysta (10 and 15 mcg) and concluded that it was as efficacious as timolol 0.5%.[35]

Safety and tolerability: While eyelash growth, skin hyperpigmentation, and periorbital fat atrophy are not caused by Durysta; the main concern is a drop in corneal endothelial cell density.

Availability: Not available in India

Bimatoprost ocular ring[36]

Structure: It is a silicone and polypropylene ring ranging from 24 to 29 mm in diameter.

Dose: 2.5 mg Bimatoprost- The rate of drug release ranges from 35 µg per day on the day of insertion to 6 µg per day at 6 months, after which it needs to be replaced.

Procedure: It is designed for insertion between the upper and lower fornices.

Efficacy: IOP control over 6 months was found to be comparable to 0.03% Bimatoprost topical drops, with the main adverse effect being mucinous discharge from the eye in some patients.

Safety and tolerability: Adverse effects include foreign body sensation, itchiness, and epiphora.

Availability: Not available in India

Travoprost punctum plugs (OTX-TP)[37]

Structure: It consists of a polyethylene glycol resorbable hydrogel rod. The rod contains Travoprost particles, which are encapsulated in polylactic acid microparticles. The rod also contains fluorescein which helps in easy visualization.

Procedure: It is inserted into the upper or lower punctum and provides a sustained delivery of Travoprost over 90 days.

Efficacy: The OTX-TP produced an IOP lowering of 4.5–5.7 mm Hg, as opposed to 6.4–7.6 mmHg produced by timolol. A possible reason for this may be the longer contact time of timolol with the ocular surface due to the presence of a placebo punctal plug.

Safety and tolerability: Adverse effects include foreign body sensation, itchiness, epiphora, and retention of the plug.

Availability: Not available in India

iDose TR[38]

iDose Travoprost implant (Glaukos) was FDA approved in December 2023.

Structure: It is a 1.8 × 0.5 mm biocompatible titanium implant. It has three parts:

- A scleral anchor that affixes into the TM
- The body of the device that serves as the drug reservoir
- Elution membrane that titrates Travoprost release.

Procedure: After creating a 2.4 mm incision, the surgeon uses an ab interno approach to visualize the anterior chamber angle. The scleral anchor is implanted into the TM, and the surgeon ensures secure attachment by nudging the device.

Rationale: This bypasses the barrier of corneal permeability, allowing the device to release micro-amounts of the active drug molecule, directly at the level of TM.

Efficacy: In both the phase III iDose TR pivotal trials, both implant arms (fast- and slow-release), achieved the prespecified primary efficacy endpoint of non-inferiority to

the active comparator arm (topical timolol) through 3 months. 93% of slow-release participants had well-controlled IOP with the same or fewer antiglaucoma topical medications at 12 months versus screening after a single iDose TR implant administration, compared with 67% of participants receiving timolol in both trials. Nearly 81% of slow-release implant participants were free of the topical antiglaucoma medications at 12 months.[39]

Safety and tolerability: Adverse effects include conjunctival hyperemia, iritis, and a possible drop in corneal endothelial cell density.

Availability: Not available in India

Spyglass drug (Bimatoprost) eluting intraocular lens[40]

Structure: It consists of a single-piece, hydrophobic acrylic intraocular lens with Bimatoprost-eluting pads located over the haptics.

Efficacy: In a trial, 23 patients underwent cataract extraction with implantation of the drug-eluting IOL, following which the mean reduction in intraocular pressure was 45%, without the need for additional therapy.[40]

Safety and tolerability: No significant adverse events

Availability: Not available in India

Cell-based therapies

Nanotechnology[41]

A novel route of drug delivery, nanoparticles range from 1 to 100 nm in size. They can bypass biological barriers and provide piggybacked medications directly at the target site.

- Subconjunctival injection of Dorzolamide-loaded polymer microparticles
- Supraciliary injection of Brimonidine-laden microspheres
- Intravitreal injection of Brimonidine, Travoprost, and Bimatoprost-laden nanosponges.

Ribonucleic acid (RNA) interference[42]

It involves specific gene silencing using small bits of RNA called small interference RNA (siRNA). SYL040012 is a siRNA developed to specifically silence the Beta 2 adrenergic receptor (ADRB2) at the ciliary body, thereby reducing the aqueous humor production.

Gene therapy[43]

Gene therapy for glaucoma is still in the early stages of research.

- Disruption of Aquaporin 1 by gene therapy with CRISPR-Cas9 RNA reduces IOP in animal models.
- Adeno-associated virus (AAV) gene therapy (intravitreally) for glaucoma that targets the BDNF has been successful in mouse models.

NT-501 encapsulated cell therapy (or NT-501 ECT)[44]

This experimental treatment involves the use of a capsule filled with human cells that have been genetically modified to secrete ciliary neurotrophic factor (CNTF). This promotes nerve growth and activity. The capsule, once implanted into the eye, provides a constant source of CNTF to protect the optic nerve.

Conclusion

The burden of irreversible vision loss from glaucoma continues to rise. The past few decades have opened up multiple new horizons in glaucoma treatment. Newer topical agents are effective in IOP lowering with a reasonably good safety profile. However, the drugs which may be useful as first-line of treatment are still not available in our country. Sustained drug release platforms may improve patient adherence. Nevertheless, such innovations will only be widely adopted when efficacy and safety have been established through large-scale trials. While the dearth of evidence for most new therapies may make clinicians hesitant to recommend them to their patients, experts also acknowledge that there may be seeds for future therapeutics in some of them. With the pace and scale of ongoing research, we have reason to look forward to newer medications, delivery systems, and novel therapeutic modalities including personalized treatment through genetic risk profiling, and exploration of potential advanced cellular and gene therapies being available for patient care.

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The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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Conflicts of interest

There are no conflicts of interest.

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