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EDITORIAL

Pilocarpine: The Renaissance

Shibal Bhartiya

Department of Ophthalmology, Fortis Memorial Research Institute, Gurugram, India

The crownless again shall be king.

—*J. R. R. Tolkien*

Pilocarpine, a muscarinic acetylcholine agonist, first introduced, in 1877, as an antiglaucoma medication, just a year after Eserine, the first ever glaucoma drug.[1] With time, and newer, more efficacious and safer drugs, the use of pilocarpine was relegated to the bottom drawer.[2] Almost a 150 years since its introduction into the modern-day pharmacopoeia, the drug finds itself in the news again, although in a very different avatar.

Vuity (pilocarpine 1.25%, Allergan, an AbbVie Company) has been approved by the USFDA as treatment for presbyopia,[3] while CSF-1, (undisclosed low concentration of pilocarpine and a proprietary vehicle, Orasis) Phase III clinical trials have ended as of January 2022.[4] There is considerable excitement among clinicians and patients alike, as eye drops may replace eyeglasses, providing an on-demand solution for the progressive near-vision loss that affects individuals for more than half of their working lives.

Global Burden of Disease

Presbyopia is marked by an individual's inability to see details clearly at the near working distance. Age-related decrease in accommodation of the natural lens of the eye maybe attributed to its thickening, and to its loss of elasticity due to intraprotein cross linkages through oxidized protein sulfhydryl groups.[5]

Presbyopia usually becomes apparent around or after 40 years, affecting more than 50% of the population – ranging between 54.7% and 90.0% in adults ≥35 years.[6] The estimated worldwide prevalence of presbyopia ranges from of 1.1[7] to 1.8 billion in 2020.[8,9] Given that the refractive error affects individuals for more than half their working life, if nor corrected, it results in increased visual stress, and loss of productivity. Increasing use of digital devices has only compounded the problem with more and people requiring vision correction for near, as well as intermediate distances for comfortable use of screen devices. Presbyopia is found in almost all cataract patients and presents in all patients who undergo cataract surgery with a monofocal intraocular lens that only corrects for distance vision.

Uncorrected presbyopia makes routine tasks arduous and distressing. A decrease of up to 22% in quality-of-life score has been reported in presbyopia patients, with more than one in ten requiring help for routine activities, and eight out of ten reporting a difficulty in performing near-vision-related tasks. Uncorrected patients have reported that routine near-vision tasks are twice as difficult, while very demanding near-vision-related tasks are eight times as difficult as usual.

Annual global productivity losses due to presbyopia, across 244 million working-age subjects <50 years of age, have been estimated to be US$ 11.0 billion, increasing to US$ 25.4 billion, if individuals younger than 65 years are to be considered productive.[10]

The most common and accepted treatment of presbyopia is optical correction, including spectacles and contact lenses. Surgical modalities, such as presbyopic LASIK, scleral implants, refractive lens exchange, and corneal inlays, have not really become popular.[11,12] Without doubt, there is an urgent need, as yet unmet, for the optimized correction of presbyopia, globally. The use of eye drops may just prove to the best therapeutic option for presbyopia: to be used as and when required, effective, accessible, low cost, and non-invasive.

The Not so New Kid on the Block

Pilocarpine continues to be an essential part of the anti-glaucoma armamentarium, unlike almost all of its contemporaries. It is of particular use in angle closure disease, before laser peripheral iridotomies and often, selective laser trabeculoplasty, during trabeculectomy and implantation of glaucoma shunts, and also as a backup drug in open angle glaucomas, refractory to maximal medical therapy.

Mechanism of Action

Pilocarpine acts on the muscarinic receptors (M_3) found on the iris sphincter, causing its contraction, and miosis. This

relieves the pupillary block in angle closure, contracts the ciliary muscle in open angle glaucoma, increasing the outflow of aqueous humor, thereby decreasing intraocular pressure. There is limited evidence to show that pilocarpine may also decrease aqueous production. Pilocarpine also causes a contraction of the ciliary body, relaxing the connected zonular fibers that control the accommodation of the lens, by changing its curvature.[13]

Pilocarpine is known to decreases uveoscleral outflow, causing a paradoxical rise in eye pressures in individuals dependent on the secondary drainage pathways.

Side Effect as Primary Therapeutic Function

The underlying mechanism for the successful treatment of presbyopia using pilocarpine is the induced pupillary miosis. This is associated with an adverse effect on distance vision, scotopic and mesopic vision, and the visual field. Other concerns include the incidence of frequent headaches, brow ache, and redness of eyes. These side effects are why pilocarpine fell into disrepute, as first-line glaucoma therapy.

The low dose of pilocarpine (1.25%, as against the 2% and 4% used in glaucoma therapy), along with special proprietary vehicles, may help combat these side effects, since both the GEMINI and NEAR trials have reported on its acceptability as treatment for presbyopia.

Side Effects and Contraindications

Local side effects of pilocarpine eye drops are usually transient and include: stinging, burning, swelling, redness, photophobia, decreased scotopic vision, brow ache, headache, and eye pain. Potentially, serious adverse events include retinal tears and detachment and uveitis.

Systemic side effects include sweating, tremors, and gastrointestinal symptoms such as nausea vomiting and diarrhea, shortness of breath, and other muscarinic symptoms.

Contraindications: Asthma, intestinal disease, ulcers, high blood pressure, heart disease, an overactive thyroid gland, seizures, Parkinson's disease, urinary tract obstruction, history of retinal tears and/or detachment, and history of uveitis. There is limited data available for its use in the geriatric population, as well as during pregnancy and breastfeeding, and must therefore be avoided.

Pilocarpine 1.25%, GEMINI 1 Trial

Pharmacologic therapy has the potential to revolutionize presbyopia management: drops are effective, acceptable, and represent a reversible therapy. The newly approved Vuity is not a new drug, but has a safety profile that has been tracked through decades. The novel, optimized formulation of pilocarpine, delivered by a proprietary vehicle, is to be used once daily. The results of the Phase III GEMINI 1 clinical trials have demonstrated an acceptable safety and tolerability profile. After 30 days of once daily dosing with 1.25% Pilocarpine, 30.7% subjects showed an improvement of 3 or more lines in mesopic distance-corrected near visual acuity (DCNVA), versus 8.1% subjects in the control; the values dropping to 18.4% and 8.8% in the two groups, respectively. At the end of 8 h, the difference in 3 or more lines of mesopic DCNVA gains was not statistically significant, but the test group showed superiority in least-squares mean (SE) mesopic DCNVA change from baseline and photopic distance-corrected intermediate visual acuity. It is of interest to note that no participants, who reported a mesopic DCNVA improvement of 3 or more lines at hour 3 lost more than five letters in mesopic, high-contrast, and binocular-corrected distance visual acuity.[14]

So, what does this mean in clinical practice?

At least, one third of the patients, after 30 days of using the eye drops, may experience an improvement of more than three lines in near-vision acuity, with the improvement in vision experienced within 15 min, with the improvement remaining significant for at least 6 h. None of these patients will experience a significant decrease in distance vision, or any significant side effects requiring an emergency intervention. Moreover, more than 75% of patients may achieve a ≥2-line improvement in mesopic DCNVA, and more than 90% may achieve ≥20/40 vision in photopic DCNVA. These improvements may be variably expected to past for up to 10 h.

Pilocarpine (Undisclosed "Low" Concentration) NEAR 1 Trial

CSF-1 (Orasis), that contains an undisclosed, but low, concentration of pilocarpine with a proprietary vehicle just finished its Phase III NEAR-1 and NEAR-2 clinical trials, in January 2022. Even though the results are not in the realm of peer review, it is believed that the results are similar to Phase IIb trials,[15] with a gain of at least two lines of near-vision in 80%, and more than three lines of near-vision in 47% subjects, with no decrease in distance or mesopic vision.

Microdose Pilocarpine 2%, VISION 1 Trial

A novel proprietary pilocarpine solution, MicroLine (Eyenovia, New York, USA) uses a proprietary Opteject spray dispenser, uses an automated push-button, to administer 7 ml of pilocarpine, potentially decreasing its systemic absorption and toxicity, and thereby, improving its therapeutic index.

The Phase III VISION-1 clinical trials evaluated the safety and efficacy of the 1% and 2% pilocarpine Micro-Array Print formulations in comparison to a placebo, using the Opteject dispenser.[16] They reported a higher efficacy with 2% MicroLine

and also found that the peak effect of the treatment is observed 1 h after administration, resulting in a gain of up to three lines in near acuity, and lasting for up to 3 h or more.[17] They have also reported the incidence of headache and brow ache to be <3%, as against a 20–25% to incidence reported with conventional formulations of the eye drops, which deliver 20–50 ml of the drug.

Almost 70% of study participants reported said that they will be strongly interest in using MicroLine for presbyopia correction, should it be approved by the USFDA, when asked during a post study survey. Given that the formulation is designed for on-demand use, it was interesting to note that these patients expected to use the spray, on an average of 3–4 times a week.

Pilocarpine Plus 0.4%, LYNX 1 Trial

Another emerging pharmaceutical treatment of low light vision disturbances is Nyxol (Ocuphire Pharma, Farmington Hills, Michigan). This consists of low-dose pilocarpine (0.4%) in combination with phentolamine ophthalmic (0.75%), nonselective alpha-1, and alpha-2 adrenergic antagonist, administered as a topical eye drop.

The Phase III interventional LYNX 1 trial, evaluating the safety and efficacy of once daily dosing (at bedtime) of Nyxol in subjects with dim light vision disturbances, has just concluded in May 2022,[18] and the results are yet to be made available. Initial impressions are promising with a reported increase of least three lines (15 letters or more) of binocular DCNVA in photopic lighting conditions, without any loss of distance vision, or changes in pupillary diameter.[19]

The Pilocarpine Renaissance

Pilocarpine is not the first drug whose side effects have caught the attention of scientists worldwide. The side effects of sildenafil, the PDE5 inhibitor developed for heart disease, and angina in 1989, have garnered more attention than its proposed primary use.[20] The increased blood flow and vasodilation were considered to be an adverse effect, making it less suitable for use for angina patients. It was famously, and serendipitously, rebranded as the miracle cure for erectile dysfunction a decade later, and the "little blue pill" is now a part of urban folklore.

The pilocarpine renaissance comes over a 100 years later from when it was first introduced, but may just be just as life changing for many, many of our patients. Indeed, in the immortal words of T. S. Elliot,

"We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
TS Eliot, from Little Gidding ("Four Quartets")

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Address for correspondence:
Shibal Bhartiya,
Department of Ophthalmology,
Fortis Memorial Research Institute, Gurugram, India
E-mail: shibalbhartiya@gmail.com

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