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Aamir Jalal Al-Mosawi *

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Review Article

Presbyopia Cure Research progress: An Educational Article and expert Opinion

Aamir Jalal Al-Mosawi

Advisor doctor and expert trainer, The National Training and Development Center, Iran.

***Corresponding Author:** Aamir Jalal Al-Mosawi, Advisor doctor and expert trainer, The National Training and Development Center, Iran.

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Abstract

Presbyopia, commonly known as "old man's eye disease," is a condition that leads to difficulty seeing near objects due to changes in the eye's lens. Historical explanations date back to Aristotle, with significant contributions from figures like René Descartes and Ernst Brücke, who helped identify the ciliary muscle's role in accommodation. Benjamin Franklin devised the first bifocals in the 1780s as a solution for presbyopia. In the 19th century, advancements included the development of eye charts by Heinrich Kuechler and Eduard Jaeger for assessing near vision. Hermann von Helmholtz later explained that presbyopia results from the loss of lens elasticity due to aging. Presbyopia, an age-related decline in near vision, has driven the search for effective and convenient pharmaceutical therapies. Topical parasympathomimetic agents, particularly pilocarpine, have emerged as promising treatments for this condition. The aim of this paper is to provide an understanding and an overview of presbyopia research progress. Pilocarpine has been shown to effectively improve near vision in presbyopic patients. Early studies demonstrated its potential for inducing accommodative changes in the lens. Subsequent research confirmed that pilocarpine combined with diclofenac or phenylephrine can enhance near vision while maintaining distance vision and minimizing side effects. More recent studies affirmed that pilocarpine 0.4% improves near vision with a good safety profile. Additionally, investigations into lipoic acid choline ester suggest new avenues for improving lens elasticity and treating presbyopia.

Conclusion: Topical pharmacologic treatments, especially those involving pilocarpine, represent a significant advancement in managing presbyopia. Current evidence supports the effectiveness of these therapies in improving near vision without severely affecting distance vision. The combination of pilocarpine with other agents like diclofenac or phenylephrine has demonstrated both efficacy and safety. Ongoing research into new compounds and formulations, such as lipoic acid, holds promise for future developments in presbyopia treatment. Further studies are needed to refine these therapies, address side effects, and optimize treatment protocols.

Keywords: presbyopia; pilocarpine; topical agents; near vision improvement; pharmacologic treatments; ocular health; education article; expert opinion

Introduction

Presbyopia, or "old man's eye disease" (where "presbys" is a Greek word meaning "old man" and "ops" means "eye"), is the decreased ability of elderly people to clearly see near objects. Aristotle (384-322 BC) attempted to explain why elderly people do not see as well as younger individuals. Lucius Mestrius Plutarchus, around 100 AD, also tried to explain the occurrence of presbyopia in his book “Symposiacs” [1].

In 1677, René Descartes attributed the insufficiency of accommodation to changes in lens shape, suggesting that lens curvature increases to enable viewing near objects [2]. Descartes's notion was later supported by the recognition of the ciliary body (Figure-1) and the ciliary muscle, known as “Brücke’s muscle,” by Ernst Brücke (Figure 2A) in 1847. Brücke’s anatomical description of the eye remains valid to this day.

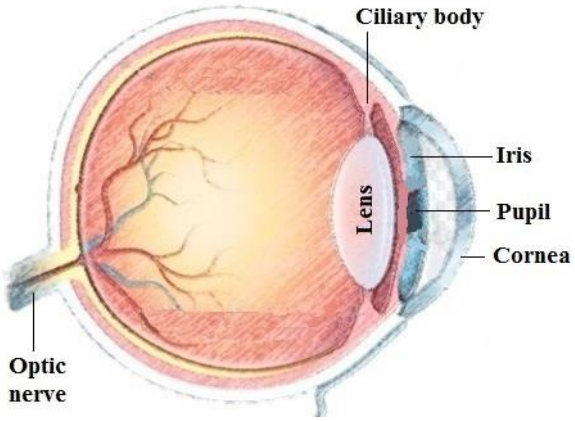

Figure-1: The ciliary body

Figure-2A: Ernst Wilhelm Ritter von Brücke (July 1819- January 1892), a German physician and physiologist

The ciliary muscle is a ring of smooth muscle in the uvea, the middle layer of the eye. It controls accommodation for seeing at various distances and changes the shape of the lens [3].

Most likely, during the 1780s, Benjamin Franklin (Figure-2B) devised the first pair of bifocals (eyeglasses), marking the first treatment for presbyopia [4].

Interestingly, in 1840, James Hunter from Edinburgh reported a case of sudden transient presbyopia in a young boy [5].

Figure-2B: Benjamin Franklin (1705-1790), an American scientist and inventor

In 1845, William White Cooper (Figure-2C) emphasized that between the ages of forty-five and fifty, it is very common for individuals to find that they can no longer see near objects with the same distinctness as before due to changes in their eyes' refractive powers resulting from diminished lens convexity. The rays from near objects are no longer focused on the retina. Cooper pointed out that double convex glasses were used at that time to treat presbyopia because they reduce the divergence of rays from near objects [6].

Figure-2C: William White Cooper (November 1816-June 1886), an English surgeon-oculist

In 1843, German physician Heinrich Kuechler (1811-1873) designed one of the earliest eye charts to test vision, which included one word per line, with the first word at the top being large and the size progressively decreasing with each line. Three different versions of the Kuechler chart were used to prevent patients from memorizing the words.

In 1854, Austrian ophthalmologist Eduard Jaeger (Figure-3A) devised an eye chart consisting of paragraphs of decreasing font sizes to test near vision acuity, which is more relevant to presbyopia. The Jaeger eye chart, also known as the Jaeger card, included text of gradually smaller size rather than a single word per line like Kuechler's chart [7-9].

Figure-3A: Eduard Jäger von Jaxtthal (June 1818-July 1884), an Austrian ophthalmologist

The larger font size on a modern Jaeger chart is J10 (14-point in Times New Roman font), and the smallest is J1 (3-point type in Times New Roman). Some Jaeger charts also include J1+ text, which is even smaller.

In 1867, Hermann von Helmholtz (Figure-4) suggested that the lens becomes more convex with ciliary muscle contraction, contributing to lens elasticity. He proposed that presbyopia occurs due to loss of lens elasticity, a consequence of sclerotic changes associated with aging [10].

Figure-4: Hermann Ludwig Ferdinand von Helmholtz (August 1821-September 1894), a German physicist and physician

In 1976, Dr. J. George Rosenbaum (Figure-5) presented a card-sized vision screener at the American Academy of Ophthalmology, which has been increasingly used to test near vision [11].

Figure-5: Dr. J. George Rosenbaum

In 1976, Ian L. Bailey (Figure-6A) and Jan Lovie-Kitchin (Figure 6B) from the National Vision Research Institute of Australia designed the LogMAR chart test, which can be used to measure distance and near vision acuity. Each line contains five letters, and each correctly read letter represents 0.02 logMAR, so a line read correctly receives 0.1 logMAR [12].

Figure-6A: Ian L. Bailey, an optometrist from Australia

Figure-6B: Jan Lovie-Kitchin, an optometrist from Australia

The increasing demand for convenient treatments for presbyopia has led to renewed interest in topical pharmacologic agents, particularly parasympathomimetic drugs such as pilocarpine. Historical and recent studies highlight various approaches to leveraging these treatments for managing presbyopia, a common age-related vision condition.

Pilocarpine was isolated from the bark and leaves of *Pilocarpus jaborandi* in 1874 by A.W. Gerrard (Figure-7), a pharmaceutical chemist from London, and by H. Hardy in France in 1877. It has been used to treat glaucoma for over 140 years. It is a lactone alkaloid and a cholinergic muscarinic receptor agonist that causes miosis and contraction of the ciliary muscle (accommodative spasm), resulting in lens thickening and forward movement, increasing depth of focus [13].

Figure-7: A.W. Gerrard, a pharmaceutical chemist from London

In 1882, Simeon Snell (1851-1909), an English ophthalmologist, reported the use of pilocarpine in a 70-year-old female patient with an attack of acute glaucoma seen in September 1880. The patient had reduced vision associated with severe pain. After declining treatment with iridectomy, the patient improved with pilocarpine treatment, resulting in complete restoration of vision [14].

The *Pilocarpus jaborandi* species was officially included as a drug in the British Pharmacopoeia in 1914.

In 1968, Lindstrom studied the effects of 2% pilocarpine eye drops on the visual performance of 20 normal individuals. They observed significant individual variability in response, with maximum effects on visual acuity, accommodation, and refraction noted in younger subjects. Older individuals experienced less change. The most significant change was an initial reduction in distance visual acuity. All individuals experienced characteristic miosis without considerable reduction in peripheral fields, with an average decrease in intraocular pressure of 1.7 mm Hg. All subjects showed some reduced dark-adaptive ability [15].

In 1973, David H. Abramson and colleagues reported a study involving presbyopic volunteers aged 60 to 80 years. They performed high-resolution ultrasonic biometry before and at 15-minute intervals after topical instillation of 2% pilocarpine hydrochloride. Pilocarpine had a measurable effect within 15 minutes, resulting in axial thickening of the lens (average 0.25 mm) and 85% of the eyes showing a shallowing of the anterior chamber (average 0.19 mm). The maximum effect of pilocarpine was observed 45 to 60 minutes after instillation [16].

2005 Study by Koeppl et al. demonstrated that pilocarpine induces a forward shift of the lens in presbyopic individuals, showing its effectiveness primarily in those with presbyopia rather than younger individuals.

Koeppl et al. reported a study involving 10 emmetropic young individuals aged 23 to 25 years and 11 emmetropic presbyopic individuals aged 51 to 62 years. They studied the effects of two drops of 2% pilocarpine, measuring anterior chamber depth and lens thickness using partial coherence interferometry. The application of pilocarpine eye drops mainly affected presbyopic individuals, inducing ciliary muscle contraction, which resulted in a significant forward shift of the anterior and posterior lens poles, leading to a translational forward lens shift of about 150 micrometers. This study showed that pilocarpine eye drops had primarily a physiological action in young phakic individuals but acted as a super-stimulus in presbyopic phakic individuals [17].

2012 Research by and colleagues investigated the use of 1% pilocarpine combined with 0.1% diclofenac, finding it improved near vision in presbyopic patients without affecting distance vision, with effects lasting up to five years.

Benozzi and colleagues from Argentina emphasized that presbyopia occurring after age 40 results from a progressive decline in accommodation, which depends on the contraction of the ciliary muscle and iris, lens changes, and convergence. They suggested the possibility of correcting accommodation in emmetropic presbyopic patients and restoring near vision without affecting distance vision using topical cholinergic medication combined with non-steroidal anti-inflammatory drugs.

Benozzi and colleagues treated 100 patients aged between 45 and 50 who had presbyopia with a combination of 1% pilocarpine and 0.1% diclofenac eye drops given six-hourly. These patients initially had a near vision of Jaeger 1 (J1) and a far vision of 20/20. One percent of the patients experienced ocular burning and discomfort, leading them to stop treatment. Over the first year, treatment improved near vision without affecting distance vision, and the vision improvement was maintained for five years. Benozzi and colleagues concluded that a topical muscarinic cholinergic agonist combined with diclofenac can restore accommodation and near vision without affecting far vision [18].

In 2003, Rainer Schalnus from Germany noted that nonsteroidal anti-inflammatory drugs (NSAIDs) eye drops, including diclofenac, are increasingly used in ophthalmology to prevent and manage ocular inflammation and edema from various causes, as well as in the treatment of allergic conjunctivitis [19].

In 2010, Kim and colleagues reiterated the emerging uses of NSAID eye drops in reducing miosis and inflammation, treating scleritis, and preventing and treating cystoid macular edema, among others. They also pointed out that the simultaneous application of topical NSAIDs and pilocarpine can reduce ocular discomfort [20].

2015 Study by Abdelkader explored a combination of carbachol and brimonidine, showing improved near vision and high patient satisfaction.

Almamoun Abdelkader suggested the use of carbachol, a parasympathomimetic medication plus an alpha agonist (brimonidine) to induce optically beneficial miosis to improve near vision in presbyopia. They reported a placebo-controlled study which included emmetropic patients having presbyopia, aged between 43 to 56 years. Thirty patients were treated with single dose of 2.25% carbachol plus 0.2% brimonidine eye drops, and eighteen patients received placebo drops. Drops were applied in the non-dominant eye. Treatment was associated with considerable improvement near visual acuity ($P<0.0001$). In this masked study, all subjects liked and would use this therapy if it was available [21].

2016 Research by Renna et al. evaluated a multi-ingredient eye drop formulation, finding it improved near vision while minimizing negative impacts on distance vision.

In 2016, Renna et al reported a study which included 14 emmetropic patients having presbyopia who were treated with eye drops containing pilocarpine 0.247%, phenylephrine 0.78%, polyethyleneglycol 0.09%, nepafenac 0.023%, pheniramine 0.034%, and naphazoline 0.003%. The eye drops were applied in both eyes.

Renna et al suggested that pilocarpine; parasympathetic agent causes miosis, contraction of the ciliary body, stimulates accommodation, and stimulates lacrimal gland tear production. However, phenylephrine, nepafenac (Nonsteroidal anti-inflammatory drugs), and pheniramine can prevent excessive pupil constriction and counteract ciliary muscle spasm, hyperemia, and vascular congestion caused by pilocarpine.

In addition, naphazoline augments the relaxing effect of pilocarpine on dilator pupillae, increasing acetylcholine release and decreases norepinephrine release. The addition of polyethyleneglycol, a lubricating agent lessens the burning sensation caused by the other ingredients in the eye drops.

Renna et al emphasized that topical parasympathetic treatment which causes small pupil diameter can result in a myopic shift and affect far distance vision.

Treatment was associated with improvement in near uncorrected visual acuity improved by about 2-3 lines. There was no degradation in uncorrected far vision in each eye and binocularly in any patient. The maximum myopic shift was 0.5 D that gradually decreased and disappeared at 4 hours. Therefore, Renna et al concluded that their eye drops treatment can markedly improved near vision in patients with presbyopia without affecting far vision [22].

2019 Study by Vargas et al. found that a combination of pilocarpine and phenylephrine effectively improved near vision in most patients, though some experienced side effects.

Vargas and colleagues reported a prospective study which included 117 patients (Mean age: 50.2 years) who had presbyopia and were treated with pilocarpine (0.247%) plus phenylephrine (0.78%) eye drops. Before treatment, the mean uncorrected distance visual acuity was 0.35 LogMAR. Two hour after the use of eye drops the mean uncorrected distance visual acuity improved to 0.16 LogMAR ($p = 0.000$). However, 9 patients did not show an improvement and 14 patients (11.9%) experienced headaches as a side effect. The eye drops improved near vision by one or more lines (mean improvement 0.18 lines) in 92.3% of the patients at two hours. Patients aged between 41 to 50 years gained more lines after treatment than patients aged between 51 to 65 years [23].

2020 and 2021 Studies by Benozzi et al. confirmed that pilocarpine and diclofenac improve near vision without compromising distance vision [24-25].

In 2020, Benozzi et al from Argentina reported a retrospective study which included 910 patients aged between 40 to 59 years who had presbyopia. The patients had binocular uncorrected near visual acuity of Jaeger 2 or worse. The patients were treated with pilocarpine and diclofenac preservative-free eye drops, twice daily (Benozzi Method).

Benozzi et al emphasized that they used diclofenac in addition to pilocarpine with the aim of lowering the intensity of the contraction ciliary muscle and reducing meiosis to allow a the lens to change shape and position and increasing vision at both near distances and far distance vision.

Treatment side effects include reduction of light perception; headaches, ocular surface dryness symptoms, and dizziness were spontaneously disappeared with continuation of treatment. Treatment was associated with improved uncorrected near visual acuity without affecting uncorrected distance visual acuity [24].

In 2021, Benozzi et al from Argentina reported retrospective multicenter study included 148 patients between 40 to 60 years who had presbyopia. Before treatment, their uncorrected near visual acuity was between J3 and J8.

The patients were treated with a pilocarpine and diclofenac preservative-free eye drops. Treatment was considered safe and was associated with improved uncorrected near visual acuity. After treatment, the patients' uncorrected near visual acuity was between J1 to J2. [25].

2021 Study by Price et al. compared various concentrations of pilocarpine and found optimal concentrations for improving near vision with minimal side effects.

Price et al from the United States reported a study which included emmetropic having presbyopia treated in various combinations and concentrations of pilocarpine (0%, 0.5% 1.0%, and 1.5%) and oxymetazoline (0%, 0.0125%, 0.05%, and 0.125%) eye drops one time daily.

Pilocarpine eye drops was associated with a considerable dose improvement in the average increase of letters ($P < 0.001$).

Oxymetazoline was not associated with important effect ($P=0.4797$). The addition or increase in concentration of oxymetazoline was not associated with a reduction in headache or its severity.

Improvement was seen as early as 15 minutes after the application of eye drops, and a peak effect was observed at one hour. Peak improvement increased from day 1 to day 14 and was maintained up to four weeks.

The study suggested that the optimal pilocarpine concentration is between 1.16% and 1.32% [26].

2023 Study by Vejarano et al. reported that pilocarpine plus phenylephrine improved near vision with minimal changes to pupil diameter.

Vejarano et al. reported a study which included 363 patients (176 females, 48%) with presbyopia aged between 40 to 70 years who were treated with pilocarpine (0.247%) plus phenylephrine (0.78%) eye drops. Instillation of the eye drops was associated with a decrease in the scotopic pupil diameter by 0.97 ± 0.98. The near visual acuity measured logMAR was improved considerably by about two lines ($p < 0.01$).Therefore, Vejarano et al concluded that the use of the pilocarpine plus phenylephrine eye drops can improve binocular near vision acuity in presbyopic patients, and the improvement is independent of pupil change [27].

Recently, Eton et al. from the United States emphasized that pilocarpine 1.25% eye drops should be used in patients with retinal abnormality. They emphasized the reported occurrence of retinal detachment in association with miotic eye drops used to treat glaucoma.

Eton et al. reported two novel cases of unilateral retinal detachment observed within 10 days of the application of pilocarpine 1.25% eye drops for the treatment of presbyopia. Both patients were pseudophakic male patients in their 60s or 70s who had retinal detachment risk factors, such as high myopia, lattice degeneration, and prior retinal detachment [28].

2024 Research by Holland et al. demonstrated that pilocarpine 0.4% improves near vision in a significant proportion of patients without impairing distance vision.

Holland et al. from the United States reported vehicle-controlled which included 613 patients with presbyopia aged between 45 to 64 years (Mean: 54.7 years). 309 patients were treated with either pilocarpine 0.4% eye drops applied twice daily, and 304 patients were treated with a vehicle eye drops for 14 days. Improvement occurred in 40.1% of the treated patients and in 19.1% of patients treated with a vehicle eye drops ($P < 0.0001$). Holland et al. concluded that pilocarpine 0.4% eye drops can improve near vision in patients with presbyopia without impairing distance vision and its use a was associated with good safety profile [30].

Early and Recent Research on Lens Elasticity explored how aging affects lens stiffness and the potential of lipoic acid to improve lens elasticity, showing that this treatment could be beneficial for presbyopia management [30-33].

Recently, the use of lipoic acid choline ester 1.5% eye drops presbyopia has also been suggested [30].

As early as 1999, the work of Glasser and Campbell from the United States suggested that lens changes with aging is not limited to loss of accommodation that contributes to the development of presbyopia but the hardening is an other important contributing factor in the development of presbyopia [31].

In 2004, the work of Heys and colleagues from Australia suggested stiffness of the lens of the eye especially of its nucleus considerably increases with aging. This stiffness significantly decreases the lens ability to change in shape, and thus reduces its ability to accommodate. Heys and colleagues considered the increasing lens stiffness to be an important contributing factor to the development of presbyopia [32].

In 2016, Garner and Garner from the United States reported an experimental study on mouse lens elasticity. The study showed that lipoic acid treatment resulted in a concentration-dependent reduction in lens protein disulfides in association with increased elasticity of the lens. The treated lenses can be more elastic than the lenses of the 8-week-old mice [33].

In 2021, Korenfeld et al. from the United States reported a study which included 75 patients who had presbyopia. 50 patients were treated with lipoic acid choline ester 1.5% eye drops and 25 patients received placebo eye drops for 91 days. Treatment was considered safe and well-tolerated. Treatment was associated with improvement of distance-corrected near visual acuity in 53.1% of the patients while improvement occurred in 21.7% of the patients who were treated with placebo [30].

Conclusion

Recent studies confirm that topical agents like pilocarpine, often combined with non steroidal anti-inflammatory drugs or other drugs, offer effective treatments for presbyopia by enhancing near vision without severely compromising distance vision.

Pilocarpine's ability to induce ciliary muscle contraction and facilitate accommodation has been demonstrated across various studies and formulations, showing lasting benefits for presbyopic patients.

While pilocarpine combined with diclofenac or phenylephrine appears effective and generally safe, side effects such as ocular discomfort and headaches have been noted. Advances in treatment also include exploring new compounds like lipoic acid for improving lens elasticity.

Overall, the ongoing research supports the potential of topical pharmacologic therapies as a viable approach for managing presbyopia, although further studies are needed to refine these treatments and optimize their effectiveness and safety profiles.

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