Original Article

Overview of pharmacological treatments for presbyopia

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ABSTRACT

Background: Presbyopia is the normal progressive waning of accommodation with loss of the visual ability to focus on objects residing at different distances. Presbyopia exacts a cost in quality of life and professional efficiency of many people over 40 years of age. Presbyopia is likely to be 1 of the main pressing visual concerns of the 21st century, given that life expectancy is increasing, resulting in an aging population. This review aimed to address the 3 strategies of the pharmacological treatment for presbyopia.

Methods: A review on PubMed/MEDLINE, Google Scholar, and Clinicaltrials.gov was performed to investigate the English literature on pharmacological treatment for presbyopia from beginning-of-year 2012 to September 30, 2020.

Results: In addition to the treatment of presbyopia with glasses or contact lenses, new surgical strategies have been developed, some of which have been successful. However, during the last decade, a new, promising, non-invasive option for treating presbyopia has emerged: the pharmacological approach. Many researchers have developed 3 different lines of investigation from different assumptions, on a pharmacological basis. The first consisted of producing miosis, to take advantage of a pharmacologically induced pinhole effect, increasing depth-of-focus, and thus improving uncorrected near visual acuity. The second aimed to rehabilitate accommodation binocularly to enable good vision at all distances. Finally, the third approach attempted to rehabilitate lost elasticity in the human crystalline lens.

Conclusions: None of the 3 discussed pharmacological strategies for treating presbyopia, prescribed globally, but patients of restoring accommodation strategy can adhere locally, where they are sold so far as master prescriptions.

KEY WORDS

presbyopia, pharmacological presbyopia treatment, accommodation, eye-drops, miosis, crystalline lens, pinhole, uncorrected near visual acuity, UNVA

INTRODUCTION

Presbyopia is a refractive condition occurring with aging that involves the gradual loss of accommodation, resulting in loss of visual performance when focusing on objects residing at different distances [1, 2]. Symptoms begin in nearly all people at around 40 years of age [3, 4] and are 1 of the first indicators of "the passage of time." People who still feel young, experience, for the first time in their life, the need to wear spectacles for near tasks, such as reading, stitching, doing handcrafts, cooking, and using a computer and cellphone.

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Furthermore, our eyes are stimulated with accommodative stimuli in daily activities, intended or not, and this decrease in vision exacts a cost in quality of life and professional efficiency in many people aged over 40 years [5]. The world is facing the Fourth Industrial Revolution, in which innovative information and communication technologies, such as artificial intelligence, Internet of Things, big data, and smartphones are increasingly being used, causing the need for the best possible vision and accommodation [6]. Presbyopia is likely to be 1 of the main visual concerns of the 21st century, as the population is aging. It has been predicted that in 2050, 21% of the global population will be 60 years or older [7], and this percentage is likely to increase to nearly 50% in developed countries [8]. Thus, treatment of presbyopia is 1 of the greatest challenges of the 21st century.

The pathophysiology of presbyopia has not been completely elucidated. However, the Helmholtz theory is the most widely recognized theory, based on an accommodation mechanism. It indicates that the crystalline lens thickness increases as its diameter decreases, and its anterior and posterior curvature increase; therefore, this results in augmentation of the crystalline lens power [9]. This is a passive process, because the crystalline lens changes are reliant on ciliary muscle contraction. In humans, the triad of accommodation also requires contraction of the iris sphincter, called miosis, and the convergence of both eyes [4, 10]. Contraction of the ciliary muscle and iris sphincter is mediated by parasympathetic, cholinergic stimulation of muscarinic receptors [11], resulting in an increase in the depth-of-focus and a change in the crystalline lens shape and axial thickness [12].

Currently, there are a few different treatments for presbyopia, ranging from non-invasive options to a succession of surgical techniques. The less-invasive option includes reading spectacles, bifocal, trifocal, or progressive spectacles. Although spectacles fulfill the goal of correcting presbyopia, they are sometimes not very comfortable. For instance, the need for different focal distances or learning how to direct the visual axes in a specific direction for suitable vision can be unpleasant. In addition, some people may not like their appearance when wearing spectacles or their dependence on spectacles for performing any near activity. Another option for optical treatment is contact lens correction, which can include contact lenses for distance correction, adding near vision spectacles to read, or monovision contact lenses, whereby the dominant eye is adjusted for distance and the fellow eye for near, and bifocal or multifocal contact lenses [13]. This option is more convenient for those who do not like to wear spectacles or take part in more athletic activities, but for using them all day long, good lacrimal production and tear stability are required, which is sometimes lacking in presbyopes. Additionally, use of contact lenses require proper care and hygiene [10-13].

Various surgical procedures have been proposed for presbyopia, although not all patients are suitable for all possible surgeries, and each technique has its own limitations. Through the use of new laser procedures and ablation profiles, corneal refractive surgery for presbyopia is growing. Presby laser in situ keratomileusis (PresbyLASIK) utilizes the principles of LASIK to generate a multifocal corneal surface using different profiles, central, peripheral, or blended vision. Depending on the profile of choice, far vision will be preserved, but near vision will be compromised or the other way around [14]. Although the reported spectacle independence is good, the main limitation is the corneal structure itself, the inconvenience of implanting a multifocal intraocular lens (IOL) in future, and different possible complications, which sometimes cause irreversible effects [15, 16].

Another approach for correcting presbyopia is intracorneal inlay implantation, whereby a lenticule is placed at the interface of the cornea. The procedure is minimally invasive and reversible. The main complications include decentration; biological intolerance, with corneal opacity; late hyperopic shift; and poor visual performance resulting from corneal irregularity [17]. In addition, some cases of explantation have been reported [18]. Another reversible treatment option is the implantation of a phakic lens in either the anterior or posterior chamber. The main complications described with this approach are corneal endothelial cell loss, uveitis, glaucoma, pupil deformation, and cataract development [19].

The emergence of a wide range of IOLs, including monofocal, extended depth-of-focus (EDOF), and multifocal with multifocal effects, make refractive lens exchange one of the most popular treatments for presbyopia [20]. Although multifocal IOLs increase spectacle independence and yield good visual results for near and distance vision, the main complications consist of an unpredictable neuroadaptation process, the presence of halos, and glare [17, 21]. With a monofocal alternative, using correction for emmetropia in the dominant eye and a selected degree of myopia in the non-dominant eye, it is possible to have successful visual results, with less dysphotopsia symptoms than with multifocal IOLs, but at the cost of stereopsis and reduced contrast sensitivity [22]. The newest options are EDOF IOLs; reports show that these IOLs can deliver suitable vision for near and intermediate distances, with fewer halos and glares [23]. All these options raise the possibility of common complications of intraocular surgery and invasive procedures. Thus, performing clear lens surgery in young patients with presbyopia, low refractive error, and healthy eyes is promising but remains controversial at present [24, 25].

During the last decade, a new promising option for treating presbyopia has emerged, in the form of a pharmacological approach [26-28]. In contrast to all the above-described techniques, this method is not invasive and provides good vision at all distances. Many researchers have developed different lines of investigation based on different assumptions, on a pharmacological basis. To date, 3 main guidelines have been followed. The first consists of inducing miosis to take advantage of a pharmacologically induced pinhole effect, enhancing the depth-of-focus, and thus improving the uncorrected near visual acuity (UNVA) [29-31]. The second approach aims to rehabilitate accommodation binocularly, allowing good vision at all distances [5, 32]. Finally, the third method attempts to rehabilitate the lost elasticity of the crystalline lens by decreasing the effect of aging [33]. The aim of this review was to summarize the publications on these 3 modalities.

METHODS

We conducted a comprehensive search of PubMed/MEDLINE, Google Scholar, and Clinicaltrials.gov to identify the English literature on pharmacological treatment for presbyopia. We identified relevant articles using the keywords "presbyopia", "presbyopia treatment", "eyedrops", and "pharmacological presbyopia treatment" deposited in these databases from beginning-of-year 2012 to September 30, 2020. Finally, the authors outlined

Table 1. Studies evaluating the efficacy of pharmacological treatment for presbyopia by the pinhole effect

Authors/ Owners	Active Substance	Patients	Duration	Main Outcomes	Side Effects
Liquid vision (PRX100), Presbyopia Therapies, Dell Krader [30, 34, 35]	Aceclidine Tropicamide	Instilled in both eyes 4 -8 hours Miosis 1.5 – 2 mm Age: 46-63 years Placebo: no	N/A	3-7 lines improvement of UCNVA on the Jaeger scale with constant distance vision	Conjunctival injection, stinging upon instillation. Although some minimal dimming indoors is likely for the first few days of use, subjects claimed that this effect was limited to the first few days of treatment.
Abdelkader [36, 37]	Carbachol 2.25-3% Brimonidine 0.2% Pilocarpine 1%	Instilled in non-dominant eye, once daily 48 emmetropic, presbyopic subjects Age: 43-56 years	3 months	4-line mean improvement of UNVA following 1 hour of eye drops instillation with progressive regression to 1-2 lines at 10 hours, with constant UDVA	Mild burning sensation Dull headache Dimness
PresbiDrops CSF-1, Orasis Pharmaceuticals [29, 38]	Oil-based formulation Parasympathomimetic NSAID (unknown exact active ingredients)	Instilled in both eyes 81 Patients: 10 eyes pseudophakic, 4 eyes cataracts, 10 eyes postLASIK/ PRK, 57 presbyopic without lens opacity. Age: 42–74 years Placebo: no	N/A	After treatment with 1-2 drops, the mean pupil diameter decreased significantly from 3.77 mm to 2.63 mm. Mean depth-of-field increased significantly from 1.6 D to 2.6 D. Both mean UDVA (from 0.9 to 1.1) and UNVA (0.3–0.6) improved significantly.	Nausea: quickly resolved Headache: 10–15 min Dryness or burning Stinging Blurry distance vision
Rodriguez et al. [39]	Pilocarpine 1% Bromfenac 0.0018% Monocular	Unilateral post-LASIK patients	N/A	N/A	N/A
Allergan [30, 40]	AGN-190584 AGN- 199201 (Oxymetazoline) - Pilocarpine	Unilateral and bilateral Mean age: 49.2 years Placebo: no	3 days	Instillation of AGN-190584 alone revealed at least 2 lines of improvement from baseline UNVA in 70.6% of patients, while using both agents in both eyes resulted in improvements in 68.8%, and using AGN-199201 alone resulted improvements in 46.7%	**AGN-199201 (Oxymetazoline):** Eyelid retraction in 26% of the group using oxymetazoline alone. **AGN-190584:** AGN-190584 group had 1 case each of blurred vision, hyperemia, lacrimation, and eye irritation. **Pilocarpine:** None

Abbreviations: h, Hours; mm: milimiters; N/A, not available; UNVA, uncorrected near visual acuity; UDVA, Uncorrected distance visual acuity; NSAID, non steroid antiinflammatory drug; D, diopter; min, minutes.

the results by summarizing 3 lines of investigation of pharmacological treatment for presbyopia, namely producing miosis to take advantage of a pharmacologically induced pinhole effect, restoring accommodation, and attempts to rehabilitate the lost elasticity of the crystalline lens.

Table 2. Studies evaluating the efficacy and security of pharmacological treatment for presbyopia by restoring accommodation

Authors	Active Substance	Duration	Patients	Main outcomes	Side Effects
Orman and coworkers	Pilocarpine Diclofenac	5 years	100 Patients Age:45-50 years [11]	All patients improved CNVA to J1 and it was maintained for 5 years. CDVA remained at 20/20 and was constant during the study period.	1% of the patients discontinued treatment due to ocular burning and discomfort, and 4% preferred treatment with glasses.
		1 year	15 male patients Age: 45-55 years [41]	All patients improved CNVA to J1 and CDVA remained at 20/20 during the year. Patients showed an improvement in the lachrymal film and the cornea-conjunctival surface. The results for eyelid and bulbar conjunctival impression cytology showed no changes during the study.	None
		8 years	917 patients Age: 40-59 years [5]	All the patients maintained an UNVA between J1 and 2 during the 8-year period. The mean ± SD of UDVA at baseline was 0.00 ± 0.01 logMAR and after 8 years of follow-up was 0.03 ± 0.04 logMAR.	Dimness, headaches, symptoms of ocular surface dryness, and dizziness were spontaneously resolved in patients who continued with the treatment.
		1 hour	20 patients Age: 40-55 years [42]	The mean ± SD of UNVA was 0.197 ± 0.02 LogMAR and 30 min after eye drop instillation, CNVA improved to 0.02 ± 0.06 LogMAR (18 cases with J1 and 2 with J2). Pre-treatment mean ± SD of stereopsis was 200.5 ± 190.85 s of arc, which improved to 58 ± 22.38 s of arc after pharmacological treatment.	None
Renna et al.	Pilocarpine 0.247% Nepanefac 0.023% Phenylephrine 0.78% Pheniramine 0.034% Naphazoline 0.003% Polyethylenglycol 0.09%.		14 patients, 9 natural emmetropes and 5 post-LASIK cases with stable emmetropy surgery, aged 41–55 years [32]	Improvement of CNVA by 2–3 lines.	None
Vargas et al.	Pilocarpine 0.247% Nepanefac 0.023% Phenylephrine 0.78% Pheniramine 0.034% Naphazoline 0.003% Polyethylenglycol 0.09%.		117 Presbyopic patients, divided into 2 groups: 41–50 and 51–65 years old [43]	CNVA improved by 1 or more lines (mean 0.18 lines) in 92.3% of the patients, while 7.7% did not show improvement, at 2 hours after eye drop instillation. The group with the youngest patients achieved more lines of improvement than the group with the oldest patients.	Headaches in 11.9% of the patients

Abbreviations: CNVA, corrected near visual acuity; CDVA, corrected distance visual acuity; UNVA, uncorrected near visual acuity; UDVA, uncorrected distance visual acuity; s of arc, seconds of arc; SD, standard deviation; logMAR, logarithm of the minimum angle of resolution; J, Jaeger.

RESULTS

Pinhole Effect

Some new pharmaceutical treatments have been proposed that are based on the pinhole rationale to take advantage of pharmacologically induced miosis through the judicious use of miotics [44]. Small aperture optics blocks peripheral light waves, which are most distorted by refractive error, and allow only the most central rays of light to enter the retina, resulting in clearer vision and an increase in the depth-of-field. Moreover, other options for presbyopia are founded on a similar effect, such as the Kamra corneal inlay [45] and IOLs that contain a central aperture [46] and claim to achieve an expanded depth-of-focus, without significant visual degradation when implanted in the non-dominant eye. Pinhole glasses have also been studied and proved to reduce the required accommodation by 10-15% [6].

The approach proposed by the company Presbyopia Therapies is known as liquid vision PRX-100. This is a binocularly instilled drop with a combination of aceclidine and tropicamide, which has a pure miotic effect with minimal stimulation of accommodation [30]. This combination produces a pinhole effect with strong miosis and without inducing significant ciliary body spasms, such as brought about by pilocarpine, and thus avoids brow ache and any myopic shift that would disturb distance vision. Aceclidine is less potent than pilocarpine and carbachol muscarinic agonists. Opposing this effect, tropicamide induces pupil dilatation with minimal influence on accommodation because it has a stronger affinity for iris M3 receptors than other antimuscarinic agents [47]. A 1-day pilot study examining nine presbyopic subjects treated with PRX-100 drops revealed that the effect on the pupil was achieved 30 min after application, reaching a pupil diameter of approximately 1.6 millimeters (mm, for 5 and 8 h) [34]. According to Presbyopia Therapies, Dr. Castillejos in Mexico performed a preliminary trial where UNVA improved three to seven lines on the Jaeger scale without impairing distance vision [30]. Additionally, a clinical trial phase II to verify the dosing, safety, and efficacy of PRX-100 in the treatment of early to moderate presbyopia in 2017 recruited 58 patients, but the results have not been released to date [35].

Abdelkader in 2015 proposed another concept for pharmacological control of presbyopia [36]. The principle is driven by the rationale of stimulating parasympathetic innervation and increasing depth-of-focus via miosis by instilling a combination of carbachol 2.25% and brimonidine 0.2% eye drops monocularly [36]. On the 1 hand, brimonidine, an α2-receptor agonist used in glaucoma, induces pupillary action, producing significant miosis, mainly under low light conditions [48]. Brimonidine binds to receptors on the presynaptic nerve endings of the dilator muscle and obstructs further release of the neurotransmitter into the synaptic cleft, thus reducing the activity of the dilator muscle, generating a more miotic pupil [37]. In contrast, carbachol, unlike pilocarpine, is a full parasympathomimetic agent that stimulates the muscarinic and nicotinic receptors on the iris sphincter muscle to produce miosis, increase the depth-of-focus [34], and promote acetylcholine release from parasympathetic nerve endings. To induce miosis, the most commonly used strength of carbachol is 2.25%, which corresponds to approximately 3% pilocarpine [49, 50].

In 2015, Abdelkader A. published a prospective randomized double-masked placebo-controlled clinical trial that recruited 48 emmetropic presbyopic patients aged 43-56 years. The study aimed to evaluate the efficacy of the use of eye drops containing carbachol 2.25% and brimonidine 0.2% monocularly once daily for 3 months [36]. This achieved a mean improvement in UNVA of 4 lines on the Jaeger scale at 1 h after instillation of the drops, which gradually reverted to 1-2 lines at 10 hours, without deteriorating the uncorrected distance visual acuity (UDVA). The described side-effects were reported by patients as a mild burning sensation in 3.3%, a dull headache in 10%, and difficulty in low luminosity (dimness) in 3.3% for the first 2 weeks [36].

Another study from the same study group compared 3% carbachol with 0.2% brimonidine in 10 patients with presbyopia, between 42 and 58 years old, and found statistically significant improvement in mean near visual acuity following use of combined eye drops as compared with use of separate forms [37].

In addition, the researchers evaluated the effects of various concentrations of pilocarpine and brimonidine, pilocarpine alone, and carbachol with and without brimonidine, compared with a placebo. To produce a pharmacological pinhole effect, in addition to clear vision in the eye, they instilled drops for the non-dominant eye. The near vision of the fellow eye, with the normal pupil, was blurred to some extent, but distant vision was clear, and there was no dimmed light perception. They also aimed to determine whether brimonidine could prolong the effect of cholinergic agonists and achieve an 8-hour effect using carbachol and brimonidine once daily [48]. This approach was also attempted in pseudophakic patients between 30 and 80 years of age. It was found that the use of 1 eye drop daily of a combination of carbachol and brimonidine could obtain adequate reading vision for 25 pseudophakic patients [51].

Based on these previous studies, in September 2020, Visus Therapeutics Inc. announced that Brimochol phase

II trials would commence in 2021. This formulation combines carbachol and brimonidine tartrate [52].

The use of parasympathomimetic drops, such as pilocarpine and carbachol, and physostigmine, an anticholinesterase inhibitor, likely results in chronic inflammation due to muscarinic stimulation of the anterior uveal tract and causes fixed pupil, posterior synechiae, and spasmodic contractions of the iris, pigment dispersion, and myopic shift [47]. Furthermore, it has been described that non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) activity and act as anti-inflammatory agents in the anterior uveal tract, reducing miosis and spasmodic ciliary contractions, pigment dispersion, and posterior synechia; thus, NSAIDs are combined with miotics [11, 53].

PresbiDrops (PresbiDrops, FEPASAET Group, Israel) include an oil-based undisclosed combination of a parasympathomimetic agent with an NSAID [29]. The basis of PresbiDrops is consistent with the eye drops studied by Abdelkader. The study presented by Feinbaum C. included 81 heterogeneous patients aged 42-74 years (10 eyes were pseudophakic, 4 had cataracts, 10 were post-LASIK or PRK, and 57 were presbyopic with a clear crystalline lens). The patients received binocularly instillation of 1 or 2 eye drops, and the mean pupil diameter reduced significantly from 3.77 mm to 2.63 mm. The pseudophakic group presented substantial improvements in both UNVA and UDVA, while post-refractive surgery patients maintained 20/20 distance UDVA and had a significant improvement in UNVA from 0.4 to 0.7 [29]. The local side effects described were dryness or burning (2 patients), stinging (4 patients), and blurry distance vision (4 patients). Three-fourths of the patients showed no adverse events, 4 patients had nausea after instillation (with rapid resolution), and 4 patients had a headache with gradual reversibility within 10–15 min [29]. PresbiDrops is undergoing phase II clinical trials to evaluate is safety and efficacy in presbyopia treatment. This was a 15 days study with 166 participants, although the final results are not yet available [38].

A Spanish patent of Rodríguez and Carrera combined pilocarpine with bromfenac as an NSAID [39]. Bromfenac was used to target COX-2 pro-inflammatory mediator production. In contrast to both COX-1 and COX-2 inhibitors, the agents that selectively inhibit COX-2 are thought to block inflammation without altering the regular homeostatic body mechanisms [54]. Furthermore, bromfenac is considered to extend the activity up to 24 hours, allowing for a once-daily topical application. They use this combination monocularly in patients after the LASIK procedure [39]; however, to date, no published studies are available based on this formulation.

Allergan Inc. announced phase IIa data from a study comparing oxymetazoline (AGN-199201), low-dose pilocarpine, or both drugs combined [31, 40]. Oxymetazoline, as an α-adrenergic agonist, produces mydriasis by acting on the α-receptor of the iris dilator muscles, thus diminishing the depth-of-focus. Moreover, it is used as an ocular anti-hyperemia agent due to its vasoconstrictive effect. However, AGN-199201 may be combined with AGN-190584 to reduce its side effects, such as hyperemia, or to strengthen its effect by weakening systemic absorption and extending maintenance time in the eye [30].

In a clinical trial with a 3-day study period, 65 participants with a mean age of 49.2 years were recruited to investigate the safety and efficacy of two types of eye drops labeled as AGN-199201 and AGN-190584. UNVA was assessed without corrective lenses in the non-dominant eye. The percentage of patients with at least 2 or more lines of improvement in UNVA in the non-dominant eye was 70.6% in the group treated with AGN-190584 alone, 68.8% when both agents were used binocularly and only 46.7% in the group that received AGN-199201 alone [55]. Table 1 summarizes studies which evaluated the efficacy of pharmacological treatment for presbyopia by the pinhole effect.

Restoring Accommodation

Accommodation is the physiological, active process that allows changing of the optical power of the crystalline lens to perceive a clear image of objects when changing focus at all distances [9].

Accommodation takes place via ciliary muscle contraction by modifying the shape and position of the crystalline lens, accompanied by the iris sphincter contractions and convergence [9]. Presbyopia is the progressive loss of accommodation and, consequently, the inability to focus on objects situated at different distances. The amplitude of accommodation decreases gradually up to 65-year of age, when it is almost completely lost. However, the amplitude of accommodation allows enough adaptive diopters to focus on objects until the sudden onset of a deficit in most people, and thus presbyopia appears [56]. Accommodation at near depends on ciliary muscle contraction, depth-of-focus, and stereopsis. However, over time, the possibility of focusing on distant objects would also decrease, arriving at the impossibility of accommodation at all distances [9].

The following 2 methods to treat presbyopia, Benozzi's method [57] and FOV tears [32], are based on binocular accommodation restoration through the stimulation of parasympathetic receptors, and consequently restoring the ability to focus at all distances. This rehabilitation was evaluated by measuring UNVA and UDVA.

Pharmacological treatment of presbyopia began in 2012 with the publication of the first results of Benozzi's method [11]. Since then, this group has published 3 more full papers concerning the different aspects of this treatment. The development of this method involves the use of eye drops containing a combination of pilocarpine at different concentrations and a fixed concentration of diclofenac. The treatment is personalized, and its prescription is based on the initial condition of the patient and their ophthalmology follow-up [5, 11, 41].

The first paper on this topic referred to a study of 100 patients who were followed for 5 years, with an age range of 45-50 years. The treatment consisted of eye drop instillation twice in each eye at a 6-hour interval during daytime hours. All patients reached Jaeger 1 for near vision, and distance vision remained at 20/20 in the first year of treatment. The improved vision was maintained for 5 years. Of all the patients, 1% stopped treatment due to ocular burning and discomfort, and 4% preferred treatment with glasses [11].

The second paper is a study of the ocular surface integrity and tear production in patients under Benozzi's pharmacological treatment for presbyopia for 1 year. Fifteen male patients aged 45–55 years were included. In this case, near and distance visual acuity was evaluated in addition to the Schirmer test, tear film break-up time, corneal staining with fluorescein, and conjunctival staining with lissamine green and rose Bengal; and conjunctival impression cytology at baseline and 1 year later. The UNVA baseline values ranged between Jaeger 2 and Jaeger 5, and UNVA reached Jaeger 1 at the first appointment and remained steady after 1 year of pharmacological treatment. The UDVA was 20/20 following treatment initiation and remained constant after 1 year of treatment. The tear film break-up time increased significantly, indicating recovery of the tear film, whereas the Schirmer test showed no changes during this period. The results of fluorescein, lissamine, and rose Bengal stains indicated the recovery of the corneal-conjunctival surface of the patients receiving the treatment. The results of eyelid and bulbar conjunctival impression cytology showed no changes during this study. These results indicate that the pharmacological treatment for presbyopia produced a corneal-conjunctival surface recovery, with no changes in tear production and corneal epithelium following 1 year of chronic eye drop use [41].

The third paper reports on an 8-year prospective study of 910 patients aged 40–59 years, to evaluate the safety and efficacy of topical treatment with Benozzi's method for presbyopia. This study included patients with emmetropia with binocular UDVA of 25/20 logMAR or better and with UNVA at least Jaeger 2 or worse. The baseline UNVA was 4.74 ± 1.53 Jaeger scale and at 8 years of follow-up was decreased to 1.36 ± 0.48 Jaeger scale. All patients were maintained for 8 years with a UNVA between Jaegers 1 and 2. The mean ± standard deviation (SD) of binocular UDVA at baseline was 0.00 ± 0.01 logMAR and after 8 years of follow-up was 0.03±0.04 logMAR. The side effects reported were a decrease in light perception, headaches, symptoms of ocular surface dryness, and dizziness, which were spontaneously resolved in patients who continued with the treatment [5].

A topic directly related to accommodation was addressed in the fourth study, i.e., stereopsis. A non-randomized case-series prospective study investigated 20 emmetropic patients aged 40–55 years. Measurements of the spherical equivalent (SE) refraction, UDVA, monocular UNVA, monocular corrected distance visual acuity (CDVA), corrected near visual acuity (CNVA), ocular motility, and stereopsis were performed in 3 situations: at baseline, with optical correction (wearing eyeglasses), and 30 min after treatment (eye-drop instillation). The mean ± SD of SE refraction in the right eye was 0.34 ± 0.32 D and in the left eye, it was 0.23 ± 0.22D. Orthophoria was found in 85% of patients while 15% had exophoria. The mean ± SD of UNVA was 0.197 ± 0.02 LogMAR; with optical correction patients achieved Jaeger 1 (0 LogMAR) and after pharmacological treatment, the mean ± SD of CNVA was 0.02 ± 0.06 LogMAR (18 cases with Jaeger 1 and 2 with Jaeger 2). Pre-treatment mean ± SD of stereopsis was 200.5 ± 190.85 seconds of arc using a Titmus Stereo Optical test, which improved to 52.5 ± 19.70 seconds of arc ($P < 0.0018$) after the optical correction and to 58 ± 22.38 seconds of arc ($P < 0.002$) after pharmacological treatment. Both methods exhibited similar stereoscopic results, thus adding more evidence that the treatment re-established near visual acuity as well as stereopsis [42].

A group from South America, developed another pharmacological treatment. In this case, the ophthalmic formulation combined pilocarpine 0.247%, with the NSAID nepafenac 0.023%, with the addition of phenylephrine (0.78%), pheniramine (0.034%), naphazoline (0.003%), and polyethylene glycol (0.09%). This group has published 2 papers regarding their pharmacological treatment results [32, 43].

The first paper, from 2016, by Renna et al., studied the safety and potential efficacy of this ophthalmologic formulation in 14 patients (9 natural emmetropes, 5 stable emmetropes post-LASIK), with an age range of 41–55 years. For each patient, the UDVA, UNVA, near and distance refraction, CDVA, CNVA, photopic and scotopic pupil size, Schirmer's test, endothelial cell count, intraocular pressure, keratometry, pachymetry, and anterior chamber depth were assessed before eye drop administration, and then again at 0.5, 1, 2, 3, 4, and 5 h, 1 week, and 1-month after administration in each eye and binocularly. The results revealed about a 2–3 lines of UNVA improvement from baseline in each eye and binocularly. There were no changes in UDVA measured in

each eye or binocularly in the study population. The refractive measurements showed that there was a maximum myopic shift of 0.5 D, which decreased gradually and disappeared at 4 h [32].

The second paper, by Vargas et al., in 2019, reported a prospective, consecutive, interventional, non-comparative clinical study on 117 patients with presbyopia, using 1 drop FOV tears (composed of 0.247% pilocarpine, 0.78% phenylephrine, 0.09% polyethyleneglycol, 0.023% nepafenac, 0.034% pheniramine, and 0.003% naphazoline) in each eye, and assessed UNVA and UDVA 2 hours after instillation of eye drops. The patients were divided into 2 age groups: group 1, aged 41-50 years; and group 2, aged 51-65 years. The UNVA and UDVA, objective scatter index (OSI), and pupil diameter under photopic and scotopic conditions before and after instillation were assessed. The results showed a change in UNVA from before to 2 h after the instillation, from 0.35 LogMAR to 0.16 LogMAR. In addition, 9 patients showed no UNVA improvement, and none of the patients showed a loss of lines. According to age, Group 1 gained more lines than Group 2. Evaluation of light scattering using the double-pass technique revealed no significant alteration in the OSI before and after eye drop instillation. However, a comparison between the groups showed a significant difference after the instillation of the eye drops. A significant reduction in mean pupil size under photopic and scotopic conditions was detected at 2 h after treatment. Both groups showed a statistically significant change under both light conditions; however, the change in pupil size between photopic and scotopic conditions was not significant [43]. Table 2 summarizes studies which evaluated the efficacy and security of pharmacological treatment for presbyopia by restoring accommodation.

Restoring the Crystalline Lens

Presbyopia is thought to be due to loss of elasticity of the crystalline lens, through cumulative protein sulfhydryl group oxidation, protein cross-links form, and the lens fibers harden, causing accommodative amplitude reduction and blurred near vision. A quite different approach is proposed for presbyopia correction with eye drops. Novartis is investigating an ophthalmic solution EV06 (lipoic acid choline ester or LACE, 1.5%), an antioxidant that chemically cuts lens disulfide bonds, leads to greater cytosol displacement during accommodation, and subsequently amplifies dynamic crystalline lens refractive power [33]. According to Novartis, "This prodrug is designed to penetrate the cornea and then break down into lipoic acid and choline, 2 naturally occurring substances" and lens fiber cells enzymes chemically reduce lipoic acid into active-form dihydrolipoic acid (DHLA), which reduces disulfide bonds between lens proteins, restoring lens microfluidics [58].

In a phase I-II study, 50 subjects received 1 drop of EV06, and 25 subjects received a placebo twice a day for 90 days. The mean distance CNVA of the group that received EV06 was improved. The drug was well tolerated with no treatment-related dropout and no significant changes in CDVA, pupil size, or intraocular pressure. On day 91, 82% of the treatment group had 20/40 CNVA or better, compared with 48% in the placebo group, with baseline values of 30% and 28%, respectively. Comparably, 60% of EV06 patients had 20/32 distance CNVA or better, compared with only 24% in placebo, while the baseline value was 8% in both groups. In addition, 36% of EV06 patients had 20/20 and 20/25 distance CNVA compared with 16% in placebo, while the baseline value was 0% in both groups. Novartis expected EV06 to be a bilateral therapy. Moreover, this drug or a similar preparation might also benefit from slow or even avoid nuclear sclerosis, which is considered to arise from the same chemical process for presbyopia [59].

DISCUSSION

Collectively, our society is currently experiencing demographic shifts due to the aging of population in conjunction with the increase in life expectancy and the acquisition of new dynamic habits [60]. These habit changes in an older population are, in some way, supported by the use of new technologies such as cellphones, computers, and platforms and demand solutions to their physiological impairments. Nowadays, turning 40, 50, or 60 is not the same as in the past century because of the extended active life [61]. At the beginning of this century, 23% of the world population was affected by presbyopia; in 2015, 25%, which is 1.8 billion people and the prediction for 2030 is approximately 2.1 billion people [62]. The etymologically, presbyopia is an ocular affection in the elderly, which is in contrast to the vision of people of their selves in their forties and on. The classical solution of presbyopia is the prescription of glasses or contact lenses, while new surgical possibilities have emerged as PresbyLASYK, intracorneal inlays, and IOLs [9].

The newest improvement in the treatment of presbyopia is topical pharmacological treatment [26-28], which presents some remarkable advantages when compared to surgical methods in that it is non-invasive, reversible, and shows no significant adverse effects. Three pharmacological treatment approaches are in progress, with different states of development, practical implementation, practice, and results.

The first is based on the induction of miosis with the enhancement of the depth-of-focus [44]. This pinhole

effect is achieved by using a parasympathetic agonist (carbachol, pilocarpine, aceclidine) to produce miosis in combination with other substances (oxymetazoline, tropicamide, brimonidine). The instillation of eye drops is unilateral in the non-dominant eye. All the revised studies were performed on emmetropic patients who obtained 20/20 of UDVA, also performed for short periods, which did not allow the ability to know of the detriment of UDVA over time. This strategy prioritizes the near vision, sacrificing the distance vision [34-40, 47-51, 53-55].

The second approach is based on the restoration of accommodation, which is the ability to change the diopter power of the eye to focus by changing the distance of the object. Benozzi's method uses eye drops with components of pilocarpine and diclofenac, while FOV uses a parasympathomimetic and NSAID and the addition of phenylephrine, pheniramine, naphazoline, and polyethyleneglycol [5, 32]. Both developments, Benozzi's method, and FOV tears stimulate the ciliary body and allow physiological variations in the position and shape of the crystalline lens. The binocular treatment prevents deterioration of visual acuity and allows the image to merge with a clear focus at all distances [5, 42, 43]. However, Benozzi's method is the only treatment of all those reported in this review, which showed that it is a safe and effective option in a study of more than 900 patients over 8 years [5].

The third line of presbyopia treatment is based on the assumption that crystalline lens stiffness and loss of flexibility are the leading causes of presbyopia. The ophthalmic solution EV06 is an antioxidant, restoring lens microfluidics [59].

Pharmacological treatment of presbyopia is a very interesting option for emmetropic patients, especially for those who have just started presbyopia. On the 1 hand, it integrates with the joviality and vitality of a 45-year-old individual in our society; on the other hand, it allows total independence from glasses and their restrictions. It is expected that with the course and experience in the implementation of pharmacological treatment, patients with other refractive errors can be treated successfully.

This review summarizes the results of three lines of investigation of pharmacological treatment for presbyopia, namely, producing miosis to take advantage of a pharmacologically induced pinhole effect, restoring accommodation, and attempting to rehabilitate the lost elasticity of the crystalline lens. However, despite its strengths, this study has the following limitations. Although the authors aimed to review the literature on pharmacological treatments for presbyopia, there is a possibility that we did not include all relevant treatment options, which may raise bias in the conclusions. Studies on pharmacological treatments for presbyopia have opened up a new field of research, and further investigations may pave the way for its use in routine clinical practice. Future perspectives on the pharmacological approach for treating presbyopia and its outcome measures will improve our understanding of this treatment method. In addition, clinical trials are essential to investigate safety and efficacy before generalizing these treatment modalities.

CONCLUSIONS

To date, there is no validated methodology for the objective measurement of accommodation that can evaluate whether drugs or formulations provide the best improvement in presbyopic patients. All of these formulations ameliorated presbyopia without relevant adverse effects. None of these treatments are prescribed globally, but patients with a restoring accommodation strategy can adhere locally where they are sold as master prescriptions. To date, Benozzi's method has successfully treated 910 patients successfully. However, many of these developments are currently in registered clinical trials, so it is to be expected that in the coming years, we will have much news about these treatments and their implementation. None of the 3 discussed strategies of pharmacological treatment for presbyopia, prescribed globally, but patients of restoring accommodation strategy can adhere locally, where they are sold as master prescriptions.

ETHICAL DECLARATIONS

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