

### Pharmacological treatment of presbyopia: A systematic review

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#### Abstract

The aim of this study was to identify the efficacy of drug agents for pharmacological Treatment of Presbyopia. Published research papers were reviewed using the relevant terms in PubMed, Science direct, Google scholar, Medline, Google patent, Ovid, Cochrane Database of Systematic Reviews, Scopus. In the initial search, 2270 records were obtained. By removing duplicate articles and all articles that did not meet the inclusion criteria or were inappropriate due to indirect relevance to the subject, 44 studies were selected. It should be noted that all studies had inclusion criteria. There are a number of topical pharmacological agents available for treating presbyopia such as FOV Tears and PresbiDrop. They consist of parasympathetic agent and non-steroidal anti-inflammatory drugs (NSAIDs), to contract the ciliary and pupil muscle and restore the accommodation. Another example of topical pharmacological agent is EV06. It is a lens-softening eye drop which can affect the rigid lens in presbyopia. Currently there is no pharmacological agent available to treat presbyopia. Although there are limited number of peer-reviewed articles available, the outcome for future agents under investigation are promising.

**Key Words:** Presbyopia; supplements; herbal; pharmacological.

*Eur J Transl Myol 32 (3): 10781, 2022 doi: 10.4081/ejtm.2022.10781*

Presbyopia is an age-dependent eye disease, which is caused by the gradual loss of accommodation. It mostly emerges the 4th decade of people's life. Nearly 100% of adults after the age of 50 suffer from presbyopia, an eye condition which is widespread.<sup>1-6</sup> Eyesight inability for focusing on near objects, headache and eyestrain are well-known symptoms of the presbyopia.<sup>7</sup> Presbyopia is unavoidable, irreparable and leads to enormous economic burden globally. According to the International data base of world population by age and sex, in 2015, more than 2.5 billion people worldwide with the average age of forty or more will expose to presbyopia in the future.<sup>5,6</sup> To manage presbyopia numbers of treatments such as, wearing contact lenses and reading spectacles are available as well as series of surgical interventions, for instance cornea or intraocular surgery,<sup>8</sup> which are not usually payable on the NHS.<sup>9</sup> Improving presbyopia using surgery is one of the most common treatments that eliminates the weakness of the fibers attached to the lens of the eye and restores the power of focus and adaptation to the lens of the eye; However, the risk of rupture of the eyeball, eye erosion, infection, as well as reduced blood

supply to the eyeball are some of the problems that limit this procedure. Surgery also has limitations such as disruption of daily activities and reduced visual quality, blurred vision and ocular complications after surgery.<sup>10-13</sup> Owing to all the limitations associated with current treatment of presbyopia, the interest for finding nonsurgical interventions is still increasing,<sup>6,14</sup> and tends to develop non-invasive pharmacological approaches over the past few decades.<sup>15</sup> A novel pharmacological approach is the FOV drops in which include parasympathetic, a nonsteroidal anti-inflammatory drug, two alpha-agonists, and an anticholinesterase agent to maintain near vision.<sup>6,11,16,17</sup> These drugs are based on two main mechanisms of action: pupillary miotics, the first class of drugs, are applied pinhole effect and caused in increasing the depth of the field. Since the degree of ciliary muscle and iris contraction, which is required to adjust the position and shape of the lens, is regulated via parasympathetic intervention, the effectiveness of this system exerts through the activation of muscarinic receptors in both ciliary and iris muscles.<sup>10,18</sup> Stimulation of the muscarinic receptors of the anterior uveal tracked by parasympathomimetic drops like pilocarpine,

carbachol and physostigmine as an anti-cholinesterase inhibitor can trigger local chronic inflammation and fixed pupil stimulation, posterior synechiae and spasmodic contraction of the iris myopic shift, and pigment dispersion. For this reason, combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and miotics are used, as it has been declared that inhabitation of cyclooxygenase activity facilitates the arachidonic acid breaking down to generate prostaglandins.<sup>18</sup> NSAIDs have anti-inflammatory impact on the anterior uveal tract via miosis reduction and spasmodic ciliary contraction, posterior synechia and pigment dispersion. They can be selected from variety groups containing diclofenac, bromfenac, ketorolac, suprofen, flurbiprofen, indomethacin and bendazac.<sup>19</sup> According to Benozzi et al. (2020)<sup>11</sup> consumptions of pilocarpine 1% and diclofenac 0.1% reestablish near vision without promoting blurred far and half-distance vision or inflammatory reactions. Moreover, it was reported that combination of NSAIDs with muscarinic agents prolongs the effect of parasympathomimetic agent by inhibiting production of prostaglandin in the anterior uvea.<sup>10</sup> Thus, these combinations avoid any histological and physical changes (fibrosis and rigidity) in the Zonula-ciliary muscle complex.<sup>19,20</sup> Many drugs with different pharmacological properties are used to treat presbyopia, but each of them shows different levels of therapeutic effectiveness in patients.<sup>21-23</sup> Therefore, it is important to evaluate the effectiveness and levels of drugs effectiveness under study. Our aim is to search the literature and write a systematic review to answer the following question: Could presbyopia be treated using pharmacological agents?

Objectives are to identify keywords, construct research question, finding databases that are going to be used, conduct a search, identifying articles, screening based on inclusion and exclusion criteria and extract information from articles and write this review.

### Materials and Methods

#### Databases

Systematic review was undertaken using PubMed, Science direct, Google scholar, Medline, Google patent, Ovid, Cochrane Database of Systematic Reviews (Ovid), Scopus, Nature and the American Academy of Ophthalmology, Springer, and Wiley online library, NICE Evidence search as electronical databases in addition to NHS and Clinical trail.gov websites, as all are accepted through university library databases. Publications from 2010-2021 were used to find studies related to pharmacological treatment of presbyopia. However, in some patents the publication year is considered instead of the date of application.

#### Search strategy

Studies were reviewed systematically, and data has been extracted based on following criteria. Boolean strategy was used by joining some of the key words together such

as: presbyopia, presbyopia AND drugs, supplements AND presbyopia, herbal AND presbyopia treatment, "presbyopia treatment" and presbyopia correction.

Articles were filtered in the initial search and those with open accessed and on English language were used. Investigation of articles were based on their title, abstract and result sections, human and animal studies, no specific country or region or ethnicity or gender, for choosing the most relevant article for the research and as well as those that are peer reviewed. Duplications were removed. Full texts were screened. Full indication of this processes can be seen in the Prisma chart.

#### Inclusion and exclusion criteria

Inclusion criteria: Pharmacological agents for treatment of presbyopia which can include: Supplements, Herbal, Biologics, Drugs. All key words also used to identify relevant patent and clinical trials available for this topic.

Exclusion criteria: Most of the research available is based on LASIK, interventions include intraocular refractive surgery and also surgical devices, for correction and also surgical data, as well as glasses and contact lenses, for example using implantable lenses, light sword lens treatment, multifocal contact lenses. People under the age of 40, people from a specific country or region, gender and ethnicity were excluded, as well as patients with previous comorbidities such as dry eye, glaucoma, cataract or any retinal problem. Clinical trials are also excluded, as few have been completed and some are without results, while those with results did not meet the inclusion criteria of this project. However some were used, if published articles.

#### Screening and extracting data

The two trained authors performed search strategies and then they separately screened the titles and abstracts of the articles and selected the relevant studies based on their relevance to objectives of the review article, inclusion and exit criteria, and their quality. In the event of a discrepancy, the two researchers thoroughly reviewed the article and reached a consensus, citing reasons for including or deleting the article. In the initial search, 2270 records were obtained. At this stage, 1843 records were deleted by duplication or because they did not meet the inclusion criteria. Then, during the screening phase, cases that had an indirect relationship or an inappropriate topic were eliminated (383 records). The full review resulted in the final selection of 44 studies that met all inclusion criteria (Figure 1).

### Results

Forty-four articles met the desired criteria. In the articles that were reviewed, 17 articles were randomized clinical trial, 16 articles were retrospective clinical trial, 8 articles were visual examination, 2 articles were prospective clinical and 1 article was cross-sectional. In the present study, a study showed that 44% (21 articles) of the studies found the effectiveness of parasympathomimetic compounds with NSAIDs to be medically appropriate for

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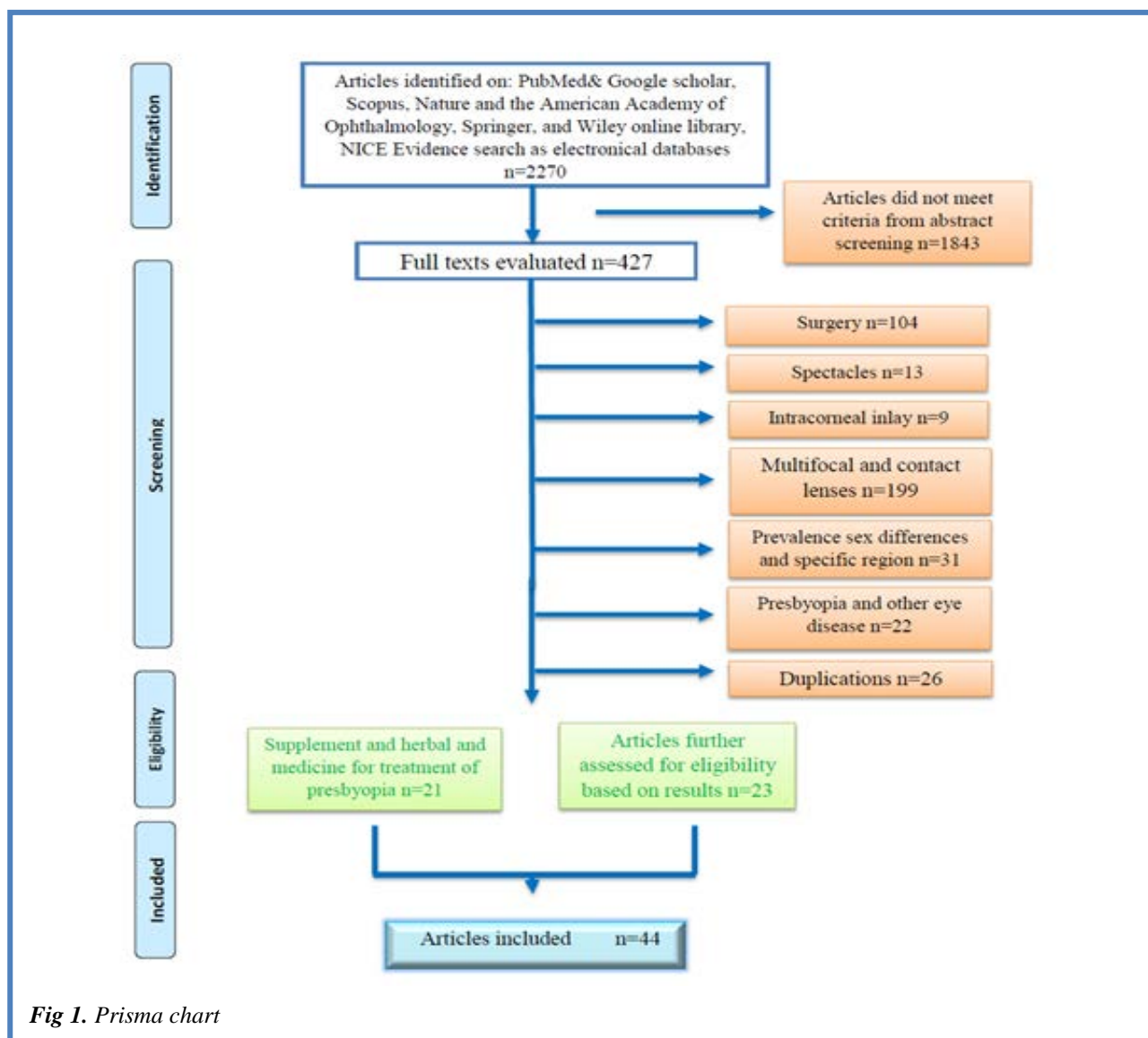


Fig 1. Prisma chart

correcting presbyopia. 10% (4 articles) of the articles showed that some agents such as FOV Tears are more promising in younger patients.

In one study, near vision enhancement with different concentration of pilocarpine and brimonidine, pilocarpine only and carbachol with and without brimonidine was examined, comparing all with the placebo (artificial tears). Pilocarpine optimal concentration was 1% and 3% for carbachol based on the authors' report. They determined that the effect of cholinergic agonists would be prolonged, therefore using carbachol and brimonidine once daily can cause achievement of an 8-hour effect. Drops were instilled for the nondominant eye to create a pharmacological pinhole effect; thus, clear but slightly dimmer eye vision was observed. The other eye with normal pupil, became blurry while looking at near objects, however distance vision was clear with no reduction in light perception. In another study, where 3% carbachol and 0.2% brimonidine, were instilled in the eyes of the subjects,

respectively and as a combination. Only 0.2% brimonidine (as a control agent), in the nondominant eye, by a crossover manner and washout period of 1-week between tests, was instilled. Statical results indicated that the effectiveness of a combined solution was significantly better compared to other solutions and again using both agents together once in a day would give an 8-hour effect.<sup>24</sup>

In a different study, subjects were allocated into 4 categories (treatment, placebo, and dividing each group based on their age range in to 2 more groups). Following up subjects for 3 months while they used 0.2% brimonidine with less carbachol concentration (2.25%) eye drops once a day and in one eye, was revealed change and considerable improvement in uncorrected near vision. Continues use of the drops, if available, was stated by all the patients. Continuing the placebo drops was not decelerated by any of the subjects.<sup>23</sup> Based on patent No. US852475B2, outcomes were stable and successful in emmetropic and hypermetropic subjects for a minimum

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of five years. However, the unsuccessfulness of this invention was due to the rigidity of the lens in which limits its shape adjustment. This innovation specifically investigated the topical use of NSAID and pilocarpine for the presbyopia treatment. Accordingly, the preferred part of the invention was, applying pilocarpine in its hydrochloride form with diclofenac sodium (an NSAID).<sup>19</sup> According to, European patent application No. EP 13745508.5: Pilocarpine 0.247%, Polyethyleneglycol 0.09%, Nepafenac 0.023%, Phenylephrine 0.78%, Naphazoline 0.003% and Pheniramine 0.034% were instilled binocularly to stimulate the ciliary muscle contraction. Whereas preserved variation in physiological pupil diameter is not allowing visual performance deterioration in dimness situation and combination of physiological image and clear focus at different distances, respectively. While the contraction of miosis and ciliary muscle can cause stimulation of accommodation, it may increase secretion of lacrimal glands and more tear production. Pheniramine, Phenylephrine and Nepafenac reduce spasm of ciliary muscle, hyperemia and vascular congestion, which is produced by pilocarpine and prevents excessive pupil contraction. Naphazoline boosts release of acetylcholine and counteracts release of norepinephrine, which enables pilocarpine to apply its relaxation effect on dilator pupillae and subsequently lower the side effects. Polyethyleneglycol's lubricant impact, provides protection against topical burning, experience with majority of above agents and increases tolerance. Near vision improvement after using eye drops, were stated by all the patients and they would prefer to use them for maintaining the observed benefits. There were no side effects associated with using this agent.<sup>5</sup>

Since, administration of the above drops could trigger an inflammatory reaction in the anterior uvea, a non-steroidal anti-inflammatory (diclofenac) was combined with the parasympathetic agonist pilocarpine, to re-establish near vision without any blurred far and half distance vision or any inflammatory responses. Furthermore, using the parasympathetic agonist and steroidal anti-inflammatory (dexamethasone) together, was showed to prevent inflammatory reactions. Although, restoration of the near vision was stated, blurry far and half distance vision was detected. As a result, clinical advantage was reported in those that had been treated with the pilocarpine and diclofenac.<sup>25</sup> According to Benozzi method,<sup>11</sup> 100 cases were treated with the combination of pilocarpine 1% and diclofenac 0.1%, at intervals of 6 hours for 24 hours a day. Following the eye drop instillation, twenty patients complained of ocular discomfort and burning, but only one patient stopped treatment for this reason. Four patients decided to abandon treatment due to anxiety they had for chronic instillation of drops. During the 5-year period, two hundred emmetropic eyes in 100 presbyopic patients from both genders, age ranged between 45 to 50 years old, were

treated. While 95% of the cases had been treated, no ocular or systematic disease were observed and only 1% of the cases discontinued treatment because of ocular burning and discomfort. Glasses were preferred by only 4% of the subjects.<sup>15</sup>

Kaufman (2012)<sup>24</sup> described new protentional approach for correcting presbyopia through monocular instillation of pilocarpine or carbachol, both known to be cholinergic agonists, with bromondine (Alphagan-P, Allergan), as an alpha agonist, in order to prolong the effect of cholinergic agonists. After administration of this topical formulation in the non-dominant eye, clear but slightly dimmer vision was seen. While normal pupil eye's vision might be blurry in near objects, further objects were clear with no reduction in light perception.<sup>26</sup>

Results of a double-masked, randomized placebo-controlled clinical trial including 48 certainly emmetropic and presbyopic cases, with the age range between 43 and 56 years were published by Abdelkader in 2015.<sup>23</sup> During the 3 months' period, the effect of daily instilled carbachol 2.25% together with brimonidine 0.2%, monocularly, was assessed. The active ingredients were selected based on stimulation effect of parasympathomimetic agent which increases depth of the focus via miosis. Moreover, alpha agonist was added to prolong accommodation, induced by the parasympathomimetic. According to results, one hour after using eye drops, Jaeger scale recorded a mean improvement of 4-line in uncorrected near vision acuity (UNVA). It was regressed gradually to 1 to 2 line after 10 hours with no deterioration of the uncorrected far visual acuity (UDVA) at any point and no adverse effect was observed. One patient (3.3%) experienced mild burning sensation and 10% of all cases noted dull headache. Additionally, during first few weeks, one patient (3.3%) reported, impermanent difficulty in low luminosity (dimness). Therefore, usage of near glasses was abandoned by all subjects in treatment group, and they reported satisfaction with near and distance vision. Twelve patients (40%) described excellent effectiveness in the first 8 hours, however it was disappeared progressively.<sup>15</sup>

Optical quality and pupil diameter evaluation were performed by Vargas et al. (2018)<sup>16</sup> in 117 cases with presbyopia, age range between 41 and 65. The therapy was based on new treatment with drops involved: polyethylene glycol 0.09%, pilocarpine 0.247%, phenylephrine 0.78%, naphazoline 0.003%, nepafenac 0.023% and pheniramine 0.034%. The follow-up time for study was very short (2 hours). 92.3% of patients had improved near vision after 2 hours, in which proved the promising effect of the therapy. Remarkably, they realized significant alteration in the pupil diameter outcomes, in different age groups. Thus, pupil diameter could change in response to different level of the lights, maintaining a dynamic pupil (dynamic pseudoaccommodation), which was not evaluated in this study. Nonetheless, it is worth mentioning that near

vision improvement, is due to ciliary muscle contraction not the constricted pupil's stenopeic effect. In this study 26% of cases suffered from dynamic pupil, describing it as reduced light perception (dimness) which was worse at night. Nevertheless, it was only reported at the start of treatment and resolved after 12 months of follow-up. Despite the discomfort, patients preferred to continue treatment as there is no need for spectacle.<sup>11</sup>

In another study, using 2.25% carbachol and 0.2% brimonidine eye drops in one dose, individually for treating presbyopia was investigated. While following up patients for 3 months, no tachyphylaxis or ocular complications were reported. In other research, higher concentration of carbachol (3%) with an alpha agonist (0.2% brimonidine) was used as in combined formulation and separately to enhance vision and the depth of focus. Near vision enhancement was higher in all of those receiving one formulation which combined carbachol 3% and brimonidine, compare to whom received each separately. Furthermore, treating presbyopia monocularly, with one drop of carbachol and brimonidine daily, creates reasonable reading vision for high population of presbyopic patients even in elderly subjects. Being non-invasive topical agent is one of the many criteria that make this compound a convenient option for treating presbyopia.<sup>27</sup>

Based on report from other study, UNR84 (formerly known as EV06) has been demonstrated promising results for near vision improvement, which is decreased in presbyopia. When administered topical UNR844 ophthalmic solution (b.i.d.), unilaterally and bilaterally, there was no safety concerns for using this agent, and it was tolerated well. The mechanism of action for UNR844, is not depended to "pinhole effect", which increases the depth of focus by reversible contraction of pupil. By contrast, UNR844 mechanism of action is based on gradual pathologic changes of the crystalline lens in an oxidizing environment. Using UNR844 for treating presbyopia, seems to change the crystalline lens durometer through decreasing disulfide bonds. In theory, there is a possibility, that if the lens becomes softer, the gross shape and curvature of lens would change.<sup>28</sup>

In an animal study, pirenoxine was used as an agent to effect on lens degeneration, which is an age-related process, and limits accommodation in presbyopic eyes. Results indicated, in rats which were given pirenoxine preparation, significant suppression of the lens hardening was observed. Since, it was suggested that administrating pirenoxine eye drop could prevent presbyopia.<sup>29</sup>

Based on results from patent No US6291466B1, a base solution including: Boric Acid 1.0%, Sodium Chloride 0.3%, Benzaliconium Chloride 0.01%, Edetate Disodium 0.1%, Sodium Hydroxide (adjusted to pH 6.4) and Water was used. In addition, pilocarpine 0.1% was added to the solution. In a 50-year-old patient with inability to read fine print, due to presbyopia, enhancement of vision was experienced, following binocular instillation of this formulation.<sup>30</sup>

Regarding to the report from Takahashi and colleagues, periocular warming, rises accommodation recovery and the blood flow to the ocular region, as well as improving parasympathetic responses in the ciliary muscle.<sup>2</sup> Yet, the data available on pharmacological treatment of presbyopia, indicates low quality of evidence. Furthermore, only few peer-reviewed studies are published and, majority of published studies are patented formulations that patent owners conducted those.<sup>10</sup> In general, according to the studies, ocular drugs did not have severe side effects. Complications studied in studies include headache and redness of the eyes, and in less cases, vision change, blurred vision, eye irritation, eye pain and tearing have been reported.

### Discussion

Our systematic study was performed to evaluate and identify the treatment of presbyopia. Our findings show that all ophthalmic drugs have some benefits that in many cases are not fully effective, but their side effects are less than those of surgery. Based on the results of the study done by Benozzi, Perez, Leiro, Facal and Orman (2020),<sup>11</sup> no related adverse effects were found using a specific pharmacological agent consisting of parasympathetic stimulation combined with NSAIDs. Combination of pilocarpine 1% and diclofenac 0.1%, known as Benozzi method, instilled two times a day, in patients with emmetropia. The patients were followed up for 8 years. Significant improvement of UNVA and UDVA was observed. Although administrating this formulation associated with few side effects like headache, dimness, eye itching and burning, there is no safety concerns for using. Currently, this research presents first available scientific evidence for treating presbyopia safely and effectively, without needing spectacles or surgeries.<sup>11</sup> Moreover, contraction of ciliary muscle can be stimulated administering parasympathetic drugs, which can rest the accommodation and makes change in the position and the shape of the lens. Based on former results from various pharmacological treatments studies, combination of the pilocarpine with diclofenac was selected among all the available parasympathetics and NSAIDs to reduce accommodation in the presbyopic eyes. Better accommodation would be achieved gradually because of this possible pharmacological approach and can leads to a new therapeutic way to treat this eye disease.<sup>31</sup> NSAIDs are normally used combined with parasympathomimetics agents, thus evaluating NSAIDs action alone is complicated. Remarkably, no reported side effects with stimulating anterior uveal tract were observed even in the trials which NSAIDs were not used. Hence, there is no clear clinical justification regarding their usage.<sup>10</sup> Interestingly, due to the difference in NSAIDs drugs used in each study, Vargas et al. (2018)<sup>16</sup> found significant changes in pupil diameter outcomes, depending on age group, which were not observed in the Benozzi method.<sup>11</sup>

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**Table 1.** The commercial and non-commercial drops used or tested for treating presbyopia.<sup>31</sup>

Name of the preparation	Content	Action
No name	Pilocarpine 1% Diclofenac 0.1%	Miosis CM contraction Inflammation reduction
No name	Pilocarpine 1% Dexamethasone	Miosis CM contraction Inflammation reduction
No name	Pilocarpine 1% Brimonidine 0.2%	Miosis CM contraction
Vejarano drops	Pilocarpine 0.247% Phenylephrine 0.78% Polyethylene glycol 0.09% Nepafenac 0.023% Pheniramine 0.034% Naphazoline 0.003%	Miosis CM contraction, mydriasis CM relaxation Lubrication Inflammation reduction and parasympathomimetic adverse effects
PresbiDrops	Unknown exact active ingredients, combination of parasympathomimetic and NSAID	Miosis Inflammation reduction
No name	Pilocarpine 1% Bromfenac 0.0018%	Miosis CM contraction Inflammation reduction
PresbyPlus	Two parasympathomimetic One parasympatholytic	Miosis CM contraction Reduction in parasympathomimetic adverse effects
Presbyeye drops	Unknown exact active ingredients, combination of parasympathomimetic and NSAID	Miosis Inflammation reduction
PresbV drops	Pilocarpine (unknown strength) Phenylephrine (unknown strength)	Miosis CM contraction Mydriasis CM relaxation Vasoconstriction
PRX-100	Aceclidine Tropicamide	Miosis with no accommodation stimulation
AGN-190584 and AGN- 199201	Presumed to be oxymetazoline and the unknown agent	Miosis Mydriasis Reducing in adverse effects
EV06	Choline ester of the lipid acid	Lens softening
Liquid vision	Aceclidine Tropicamide (a cycloplegic)	Miosis CM contraction Cycloplegia for moderating accommodation

Many studies have been performed to identify the degree of involvement of each factor to the accommodative process. Currently, few topical agents for presbyopia treatment are under investigation, which effect various aspects in the accommodative process, such as working on monovision, parasympathetic-mediated miosis and stimulating ciliary muscle or softening the lens to re-established shape-changing ability of the lens. However,

several disadvantages are associated with each of these approaches, for instance purely treating with parasympathetics can result in slightly smaller pupil diameter and a myopic shift, conceding far distance vision. Additionally, stimulating ciliary muscle and pupil sphincter can lead to some well-known side effects. Although lens-softening agents seem to be safe treatment options, their effectiveness are less as altering the lens's

mechanical properties appears to be less important in initiating and progression of presbyopia compared to altering lens geometry.<sup>6</sup>

Opposed to binocular treatment, in the decreased light conditions, monovision treatment can reduce vision. Most of the studies regarding the treatment of presbyopia used this approach.<sup>6</sup>

In few embodiments, applying an ophthalmic formulation may be sufficient for enhancing the patient's near distance visual acuity without any other treatment methods. For instance, focusing on objects at the same distance as the normal reading distance, is the advantage of using a topical parasympathomimetic drug and one or more C.1 (alpha1) adrenergic agonists or antagonists with no need to use corrective eye surgery or lenses. However, these agents seem to be more beneficial for treating presbyopia if have been used in the early stages.<sup>25</sup>

Based on a pilot study by Renna et al. (2016)<sup>6</sup> administering pharmacological [Vejarano (patent pending)] eye drops binocularly, improve reading vision in presbyopic eyes. Additionally, being noninvasive beneficial therapeutic method makes these agents ideal treatment for presbyopia. Despite the limitations associated with this study, such as the heterogeneity and small sample group of the patients, the suggested outcomes are promising compared to other studies.<sup>4</sup>

To sum up, there is no a pharmacological treatment available for treating presbyopia, though the possibility that UNR844 become the first-in-class modifying pharmacological agent for treating presbyopia is high. Nevertheless, the need to find safe and accessible topical ocular therapeutic drug to treat presbyopia, is vital.<sup>32</sup>

Table 1 summarizes commercial and non-commercial drops in trial or used for managing presbyopia.

On the other hand, reduction of pupil size is associated with side effects. Very small pupil sizes may reduce overall vision quality and cause myopic shift in distance vision. One way to decrease this adverse effect is through monocular instillation of eye drops. Using a single miotic agent, monocularly, provides appropriate reading vision for majority of presbyopes, even in elderly patients.<sup>31</sup> Further limitations of pharmacological agents, for instance, are related to the fact that the majority of the reviews are based on current treatments, mostly non-pharmacological, and most of the pharmacological interventions for treatment are still under clinical trials. Another limitation was using database platforms like Micromedex, which could be used as it was included relevant articles, however it is not accepted by most university library databases. Finally, difficulty to find only human studies in presbyopia treatment, leads to using both human and animal studies in this project.

### Conclusion

The combination of parasympathomimetic with the NSAIDs is the most used approach for correcting presbyopia pharmacologically. However, some agents

such as FOV Tears are more promising in younger patients. To answer the project question, currently none of the available drugs are promising to pharmacologically treat presbyopia. However, lens softening agents has the higher possibility to become first pharmacological agents to correct presbyopia in the future. Though, this topic seems to be attractive, there are only limited number of reviews available. In order to overcome the above limitations in the future, broad studies with substantial number of subjects are needed. In conclusion, there are number of agents under investigation for pharmacological treatment of presbyopia, none of them are consider as the definite treatment for presbyopia. Thus, there is an increasing need for verifying the safety and efficacy of the agents.

### List of acronyms

EV06 - other name for UNR844

FOV Tears: Field of view

LASIK - Laser-Assisted In-Situ Keratomileusis

NHS - National health service in United Kingdom

NICE - National Institute Health Care Excellence

NSAIDs - non-steroidal anti-inflammatory drugs

Prisma - Preferred reporting items for systematic reviews and meta-analyses

UDVA - uncorrected far visual acuity

UNR844 - ophthalmic solution for topical oral administration

UNVA - uncorrected near vision acuity

### Contributions of Authors

NH, RA: Study conception and design; Data analysis and interpretation; Critical revision of the article. All authors have read and approved the final edited typescript.

**Acknowledgments** None

**Funding** None

### Conflict of Interest

The authors declare no conflict of interests.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Submission: August 05, 2022

Revision received: August 08, 2022

Accepted for publication: August 09, 2022