International Journal of Community Medicine and Public Health
Srivastava N et al. Int J Community Med Public Health. 2023 Jun;10(6):2285-2289
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20231718

Review Article

A review of the treatment of drug induced presbyopia

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Received: 09 April 2023
Accepted: 15 May 2023

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ABSTRACT

Presbyopia is characterized by accommodative loss that leads to negative effects on vision-targeted health-related quality of life. It occurs in people who gradually lose the ability to adapt after the age of 40. Accommodation depends on the contraction of the ciliary muscle and the iris, the change and the convergence of the lens. The parasympathetic nervous system regulates the degree of contraction of the ciliary muscle and the iris necessary to alter the shape and position of the lens, and its stimulation is effective by activating the muscarinic receptors present in both structures. The hypothesis presented here suggests that patients with emmetropic presbyopia correct accommodation with pharmacotherapy that includes a combination of cholinergic drugs and non-steroidal anti-inflammatory drugs (NSAIDs). Topical treatment deals with drug combinations to modify one or more factors involved in the accommodative process and have been proposed to be instilled either monocular/ binocularly. Result shows para-sympathomimetic stimulation of parasympathetic innervation (accommodation) and NSAID: Prolonging the effect of the para-sympathomimetic action and modulates the accommodation. The drug combination restores near vision without affecting distance vision. It is important to note that the drug form used has no inflammatory effects or other side effects. Despite the lack of a completely well understood mechanism, pharmacological control of presbyopia seems to be a possible and very attractive alternative for presbyopia patients. The studies mentioned in this review are to be considered pilot investigations as they involve either a small number of subjects or are single case series.

Keywords: Presbyopia, Medicine, Accommodation

INTRODUCTION

Presbyopia is characterized by accommodative loss that leads to negative effects on vision-targeted health-related quality of life.[1] Presbyopia is a progressive loss of accommodation that results in loss of the visual ability to focus on objects at varying distances. In humans, accommodation is achieved by contraction and convergence of the ciliary sphincter and iris muscles, and changes in shape and position of the lens.[2,3] This last action is passive, which means that the changes in the lens depend on the contraction of the ciliary muscle and the iris. Moreover, when the centres of accommodation are active, stimulating contraction of the ciliary muscles, normal binocular patients exhibit meiosis and convergence.[3,4] The iris and ciliary muscles possess muscarinic receptors which are stimulated by the parasympathetic nervous system via its cholinergic neurotransmitter acetylcholine.[5] This stimulation produces ciliary muscle contraction and changes in pupil size by altering the shape and position of the lens, resulting in accommodation associated with parasympathetic activity.[6-8] Since presbyopia has been corrected by spectacles since the 13th century and by contact lenses and surgery since the last century.[9,10] In the last few years, a number of surgical techniques aimed to compensate presbyopia have been proposed, but each one presents some limitations, thus the most recent trends prefer non-surgical solutions for this condition.[11,12] A non-invasive pharmacological treatment providing near

lenses independence would be a truly ground breaking approach in the treatment of presbyopia. A pharmacological approach to restore accommodation is presented here.

LITERATURE RESEARCH

PubMed and Google Scholar were the main resources used to investigate the medical literature. We identified and reviewed all relevant articles using the keywords "presbyopia," "presbyopia treatment," "pharmacological presbyopia treatment," and "presbyopic corrections" from 2010 to February 9, 2020. The reference lists of the articles analysed were also considered as a potential source of information. We attempted to present all publications that investigated different pharmacological presbyopia treatment methods. Studies were critically reviewed to create an overview and guidance for further research. No attempts were made to discover unpublished data.

PHARMACOLOGICAL APPROACHES BASED ON THE PINHOLE EFFECT

There are a number of new pharmaceutical agents currently being investigated for the treatment of presbyopia, and they are based on 2 main mechanisms of action. The first class of drugs is pupillary miotics, which exert a pinhole effect and increase the depth of field.[16] The parasympathetic system regulates the degree of ciliary muscle and iris contraction necessary to modify the shape and position of the lens, and its stimulation is effective through the activation of muscarinic receptors that are present in both structures.[15] Muscarinic agonists cause the ciliary muscle to contract and the lens thickness to increase, and the induced meiosis increases the depth of focus and creates pseudo accommodation. One of the main muscarinic agonists used in clinical trials is pilocarpine 1%. Pilocarpine provides both meiosis and ciliary body contraction, thus stimulating accommodation and potentially improving tear production by stimulating lacrimal gland secretion.[17] The drop affects the ciliary muscle, which causes a physiological accommodation and a dynamic pseudo-accommodation. "This means a mild and dynamic meiosis, which changes with light intensity."

HYPOTHESIS

Spastic contraction of the ciliary muscle occurs and the thickness of the lens increases, which increases the depth of field.[8,11] This condition improves near vision but reduces distance vision because the lens cannot change thickness or position.[7,13] By combining NSAIDs with parasympathetic agonists, the force of contraction of the pupil and ciliary muscle is reduced, allowing the lens to change shape and position for good vision at all distances.[13] The combination of with NSAIDs abolished the local inflammation always secondary to chronic stimulation by pilocarpine (fixation of the pupil, posterior synechiae and dispersion of the pigment).[13] In this sense, the hypothesis aimed to address the treatment of patients with emmetropic presbyopia with the drug, using parasympathetic stimulation in combination with NSAIDs as described above. A completely different approach for the pharmacological treatment of presbyopia consists in targeting the crystalline lens.

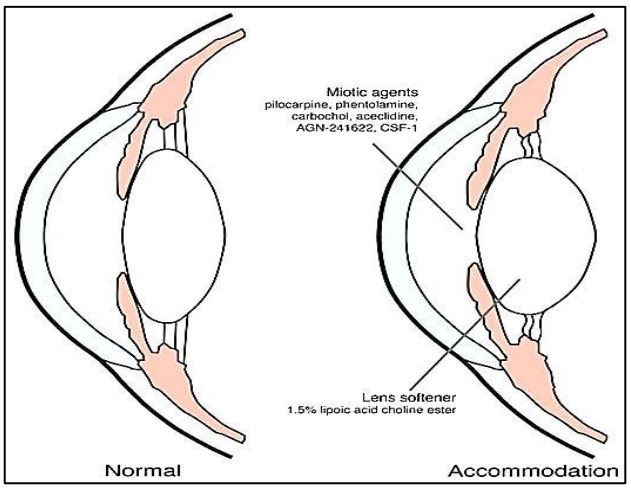

Figure 1: Pharmacological effect on presbyopia.

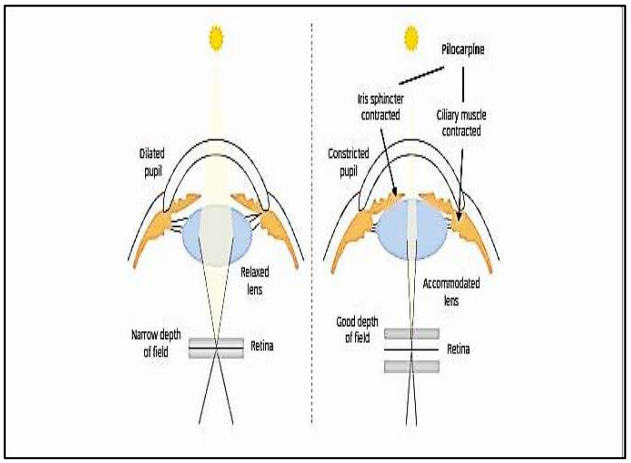

Figure 2: Pharmacological treatment-presbyopia mechanism of action.

DISCUSSION

The reviewed studies showed that there are a variety of substances being investigated for presbyopia treatment. Nevertheless, most of the studies use different combinations of different substances. Moreover, results of studies are rarely confirmed by other authors, and thus, only individual studies are available for the great majority of combinations. NSAIDs were used in combination with para-sympathomimetics. Work on muscarinic stimulation with carbachol, pilocarpine and physostigmine (anticholinesterase inhibitors) has been conducted for 10 years on a hypothetical basis. In all cases, near vision was restored with varying degrees of success, depending on

the quality and concentration of the stimulant. Loss of distance and intermediate vision was observed in all treated patients.[3,8] However, chronic stimulation with one of these agents 4044 induces an inflammatory response in the anterior choroid. When an NSAID (diclofenac) was added to the parasympathetic drug pilocarpine, the drug combination restored near vision without causing distance vision impairment or an inflammatory response. The inflammatory response can be prevented with a combination of a parasympathetic agonist and a steroidal anti-inflammatory drug (dexamethasone). Near vision was also restored, but distance and intermediate vision decreased. Thus, clinical benefit was observed in patients treated with the combination of pilocarpine and diclofen.[13,17] NSAIDs that can inhibit cyclooxygenase activity act as anti-inflammatory agents in the anterior uvea, reducing meiosis and spasmodic ciliary contraction, pigment dispersion, and posterior adhesions, because they reduce local inflammation caused by chronic infusion of parasympathetic stimulants.[14,18,19] In this sense, the combination of pilocarpine and diclofenac has proven to be the most effective formulation for long-term use in the treatment of presbyopia without the side effects of (pilocarpine 1% and 0.1% diclofenac, [1% pilocarpine Poen, Buenos Aires, Argentina Voltaren 0.1%, Novartis, Buenos Aires, Argentina] at daily intervals of 6 hours). Of the 100 treated subjects, 20 patients experienced ocular burning and discomfort immediately after installing eye drops, of which only one patient discontinued treatment for these reasons. The remaining four patients who remained on drug treatment feared chronic decline from instillation. 200 emmetropic eyes of presbyopic patients of 100 male and female patients aged 45-50 years were treated over a 5-year period. All patients had Jaeger 1 (J1) 20/20 near and 20/20 distance vision daily with eye drops 6 h apart. None had the ocular or systemic disease and 95% of patients were treated. Additionally, 1% of patients discontinued treatment due to burns and eye discomfort, while 4% opted for glasses.

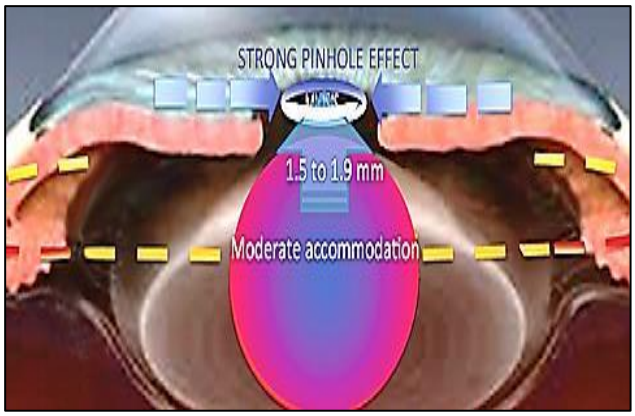

Figure 3: This image shows the results of para-sympathomimetics: Stimulation of parasympathetic innervation (accommodation) and NSAID: Prolonging effect of para-sympathomimetic action with pupil size less than 2 mm. Accommodation is modulates.

These Drugs allows for improved near and distance vision at once, without typical side effects. The pharmacological management constricts the pupil and increases depth of focus with the pinhole effect.

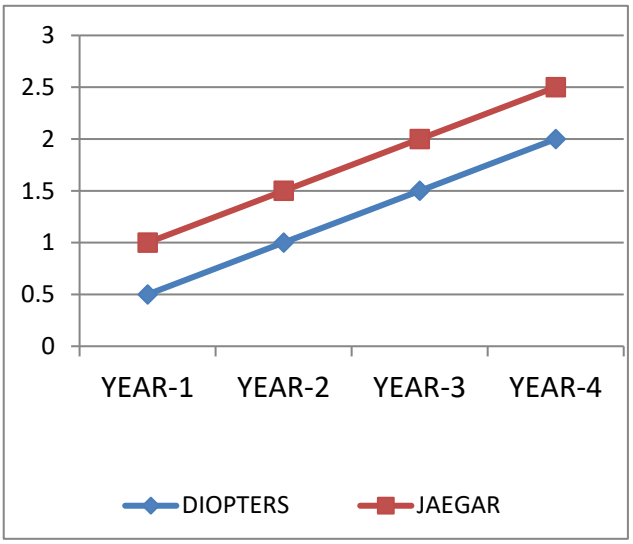

Figure 4: Near vision accommodation in patients with pharmacological treatment. Accommodation in near vision in 200 emmetropic eyes of 100 patients treated with or without or with the combination of pilocarpine and diclofenac during a 5 year period.

During the first year of treatment, had improved near vision accommodation, and these had improved vision maintained at 5 years. The distance vision remained at 20/20, unchanged over the same period. The combination of muscarinic cholinergic agonists and NSAIDs allows the long-term use of topical treatment to restore accommodation with good near and distance vision.

Most of the studies conducted in wide range of patients with presbyopia. Since presbyopia is a progressive condition in which power of accommodation is gradually lost in older patients, studies on different specific age groups, for example, patients with presbyopia whose age are between 45 and 50 years old, or more than 60 years old, might be helpful to understand the treatment efficacy in these different age groups.[23] There is still no standard on applying miotics agents as unilateral or bilateral treatment. The unilateral application requires familiarity of monovision from patients. There was still no direct comparison between the efficacies of unilateral or bilateral instillation of miotics agents. Application of miotics agents for presbyopia may also have a limitation in those aging patients who have cataract since meiosis may worsen their vision. It should be emphasized that pilocarpine which was U.S. FDA approved for treatment of presbyopia has a concentration of 1.25% which is different from pilocarpine for treatment of glaucoma which has a concentration of 2% or 4%. There was not enough data to conclude that other miotics agents, such carbachol or brimonidine, can be given to treat presbyopia with similar efficacy and safety, compared

with pilocarpine. In addition, there was still inconclusive evidence that compounds for presbyopia treatment which were made to minimize adverse effects in counteract with, or to provide additional pinhole effect to, a miotics agent were beneficial.[22]

Table 1: Overview of advantages and disadvantages of each treatment method for presbyopia.

Method	Advantage	Disadvantage
Spectacles	Easy access	-
	Very low risk of ophthalmic and systemic adverse event	Temporary effect
	Proven for long term use	Inconvenience
Contact lenses	Convenient for those who regularly use contact lens	Temporary effect
	-	Temporary effect
	-	Need daily care of contact lens
	-	High risk of ophthalmic adverse event
Pharmacologic	Easy to use	Temporary effect
	No spectacles and contact lens needed	Risk of ophthalmic and systemic adverse events
	No surgical risk	Required long term application
Surgical	Can be permanent	No proven standard procedure
	Low risk of systemic adverse event	-

CONCLUSION

Restoration of accommodation can be achieved by stimulating contraction of the ciliary muscle and parasympathetic administration of to alter the shape and position of the lens. The drug treatment studied has shown that using pilocarpine in combination with diclofenac, it is possible to restore the decline in accommodation in presbyopic patients. This possibility of drug treatment opens a new way of treatment for presbyopic patients, allowing them to achieve good regulation over time. In the future, new drug treatments may also be used to treat other refractive problems that are dependent on accommodation. The pharmacological control of presbyopia is a very attractive option for those affected by presbyopia and increasing near vision spectacle dependence. Despite the interest on this topic, there are only a few publications available, all from the recent years. As a non-invasive solution for addressing this problem, pharmacological control of presbyopia would meet all of the established criteria for the severity of presbyopia in different subjects. The pharmacological compounds analysed in this review aim to target one or more factors involved in the near vision process. Most of the topical products use pharmacological compounds, including a combination of different drugs. Therefore, it remains unclear how much each of the drug in the final combined form is involved in the outcome and contributes to it. The pharmacological control of presbyopia presents itself, on this review, as a possible and very attractive alternative for presbyopic patients. There are ongoing studies on other miotics agents, as monotherapy or in combination with other agents as treatment of presbyopia pharmacological treatment of presbyopia is, without a doubt, one of the promising fields in research in ophthalmology since all people who are more than 45 years old will have this condition eventually. The studies mentioned in this review are to be considered pilot investigations as they involve either a small number of subjects or are single case series. Moreover, reports presented at international meetings and published in scientific tabloids, are not peer-reviewed. Due to its large interest and potential general application, further and more complete studies are needed to confirm which will be the more effective pharmacological drug for presbyopia treatment despite the limitations of the papers reviewed; such preliminary results speak to the possibility of a pharmaceutical treatment for presbyopia. Patient studies are very expensive and probably limited the scope of these investigations.

Although there is no doubt that pharmacological treatment of presbyopia is an attractive form of therapy, more objective and well-designed studies are needed to evaluate its safety and effectiveness.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Srivastava N, Dwivedi PN, Chaurasia VK. A review of the treatment of drug induced presbyopia. Int J Community Med Public Health 2023;10:2285-9.