Pharmacological Pinhole in Presbyopia Treatment: A Brief History from Pilocarpine to Aceclidine

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Dear Editor,

In recent years, the pharmacological treatment of presbyopia has gained attention as a safe, reversible, and non-invasive alternative to glasses and surgery. The recent U.S. Food and Drug Administration (FDA) approval of VIZZ™, the first aceclidine-based eye drop, is an important milestone in this area and is expected to impact daily practice.[1]

The use of eye drops for the treatment of presbyopia has mainly been based on efforts to manipulate pupillary physiology. The approach is to improve near visual acuity by increasing focal depth, because studies to address the pathophysiology of presbyopia by increasing the elasticity of the crystalline lens have not yet yielded the desired effect.[2]

When examined historically, the first eye drops used in the treatment of presbyopia were myotic agents that increase the depth of focus by inducing myosis, thereby creating the pinhole effect. Pilocarpine stimulates the ciliary muscle and iris sphincter, causing both accommodative spasm and myosis. Initially used to treat glaucoma, pilocarpine was also observed to temporarily improve near vision.[3] However, pilocarpine has often been associated with side effects such as headache, poor low-light vision, and myopic shift. These adverse effects occur as a result of pilocarpine stimulating the ciliary muscle as well as the iris sphincter. Therefore, it did not offer an acceptable solution for daily use in the treatment of presbyopia.

From the mid-20th century, lower-concentration formulas or combinations with other agents that promote the myotic effect and reduce the adverse effects of pilocarpine have been investigated. Although these approaches have managed to slightly improve the side effect profile, a fully "pupil-selective" effect has not been achieved. In the literature, frequent emphasis has been placed on the search for an ideal molecule that targets only pupillary myosis while minimizing the effect on the ciliary muscle.[4]

In the early 21st century, advances in pharmaceutical technology enabled the development of a new generation of eye drops. The new formulations aimed to provide a longer-lasting effect and reduce side effects. The most important development of this revival period in terms of pharmacological treatment of presbyopia was the FDA's approval of the first presbyopia eye drop containing 1.25% pilocarpine HCl (Vuity™, Allergan) in 2021.[5] Vuity™ was able to achieve the desired effect with a lower concentration of pilocarpine by using an optimized pH and formulation, thereby minimizing side effects. As a result of low-dose efficacy studies, Qlosi™ (Orasi), an unpreserved eye drop containing pilocarpine 0.4%, is another formulation approved by the FDA in 2023. Although there are studies in the literature involving the use of pilocarpine in different doses or in combination, these formulations have not received FDA approval.

Most recently, the FDA approved eye drops containing 1.44% aceclidine (VIZZ™, LENZ) for the treatment of presbyopia.[5] Aceclidine (in the VIZZ™ formulation) differs mechanistically from pilocarpine. It has a more pupil-selective effect, providing a stable pupil constricting to below 2 mm, thus increasing the

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depth of field without causing myopic shift. Efficacy lasting up to 10 hours and a good safety profile have been reported in phase 3 studies.[5]

Pharmacological treatment of presbyopia is of great interest for both presbyopic individuals and the pharmaceutical industry. As a result, pharmacological treatments for presbyopia are evolving from experimental approaches to clinically validated options. The approval of aceclidine and the accumulated evidence on pilocarpine indicate that these treatments will have an important place in the management of presbyopia. However, it is important that the pharmacological treatment used is effective, reliable, and reversible and that its long-term side effect profile is known.

Declarations

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