U.S. Application No. 2010/0016395 A1 reports being able to increase the dose of pilocarpine to 1% to 2% by adding the non-steroidal anti-inflammatory agent diclofenac, but at a concentration that was five times more concentrated than that approved by the FDA. Congdon *et al.* reported that diclofenac is associated with serious side effects such as persistent epithelial defects, corneal melting, and corneal perforation. (Congdon *et al.*, 2001, Corneal complications associated with topical ophthalmic use of nonsteroidal anti-inflammatory drugs, *Ophthalmology*, 27:622-631)

WO 2009/077736 discloses a combination of pilocarpine and dapiprazole (or thymoxamine) and pilocarpine and brimonidine (or iopidine) to treat defects of visual acuity, presbyopia, myopia, hypermetropia, low night vision, and astigmatism. The combinations listed are pilocarpine and dapiprazole (or thymoxamine), and pilocarpine and brimonidine (or iopidine). The combination of pilocarpine and dapiprazole produced red and irritated eyes (WO 2009/077736) and topical administration of brimonidine is known to those in the art to produce lightheadedness, dizziness, dry mouth, tachycardia, and stomach upset, among other side effects, which limits its usage even among patients using it for a severe eye condition such as glaucoma.

Although more than 75 molecules have been disclosed for the medical treatment of presbyopia, no clinically effective preparations suitable for use by the general public without unreasonable side effects have been found.

Summary of the ~~Invention~~Disclosure

Compositions and methods for treating ocular conditions, including presbyopia and mild hyperopia, up to about 4.00 diopters, or more in very young patients, irregular astigmatism, hyperopic accommodative esotropia, and glaucoma, are disclosed. The compositions of the present ~~invention~~ disclosure include a cholinergic agent, such as a muscarinic acetylcholine receptor M_3 agonist, and an alpha-stimulant agonist having an imidazoline group or a non-steroidal anti-inflammatory agent (NSAID) having COX-2 selectivity. Examples of muscarinic acetylcholine receptor M_3 agonists include pilocarpine, acetylcholine, pilocarpidine, bethanechol, carbachol, and oxotremorine. Examples of alpha-stimulant agonists having an imidazoline group include oxymethazoline, naphazoline, tetrahydrozoline, and xylometazoline. Examples of NSAIDs with COX-2 selectivity include meloxicam,

celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, nimesulide, etodolac and nabumetone.

The compositions of the present ~~invention~~ disclosure were surprisingly and unexpectedly found to potentiate the action of and decrease the side effects of a cholinergic agent, such as pilocarpine, such that a cholinergic agent can be effectively used in combination with an alpha-stimulant agonist having an imidazoline group or a non-steroidal anti-inflammatory agent (NSAID) having COX-2 selectivity to contract the ciliary and pupillary sphincter muscles for treating ocular conditions, such as presbyopia, mild hyperopia, and irregular astigmatism, hyperopic accommodative esotropia and glaucoma ,without the patient experiencing the undesirable side effects normally associated with pilocarpine therapy. The present ~~invention~~ disclosure can also be used to potentiate or to enhance interventions that retard, reverse or modify the aging process of the crystalline lens and its surrounding tissues. Unlike previous compositions disclosed in the prior art, it is believed that the compositions of the present ~~invention~~ disclosure can safely be used by patients for treatment of ocular conditions, including presbyopia, mild hyperopia, irregular astigmatism, hyperopic accommodative esotropia, and glaucoma, on a chronic basis.

In one aspect, there is provided the use of a therapeutically effective amount of a composition comprising pilocarpine and oxymetazoline in the manufacture of a medicament for treating an ocular condition in a subject; wherein the ocular condition is selected from the group consisting of presbyopia, mild hyperopia, irregular astigmatism, and hyperopic accommodative esotropia; and wherein the medicament is to be administered to the subject.

Brief Description of the Figures

Figure 1 shows the effect of a composition comprising pilocarpine and oxymetazoline on near vision (Jaeger Equivalent) over time.

Figure 2 shows the effect of a composition comprising pilocarpine and oxymetazoline on distance vision (LogMAR Equivalent) over time.

Figure 3 shows a comparison of the effect of a composition comprising pilocarpine and oxymetazoline and a composition comprising pilocarpine alone on near vision (Jaeger Equivalent) over time.

Figure 4 shows a comparison of the effect of a composition comprising pilocarpine and oxymetazoline and a composition comprising pilocarpine alone on distance vision (LogMAR Equivalent) over time.

Figure 5 shows the effect of a composition comprising pilocarpine and meloxicam on near vision (Jaeger Equivalent) over time.

Figure 6 shows the effect of a composition comprising pilocarpine and meloxicam on distance vision (LogMAR Equivalent) over time.

CLAIMS

1. Use of a therapeutically effective amount of a composition comprising pilocarpine and oxymetazoline in the manufacture of a medicament for treating an ocular condition in a subject; wherein the ocular condition is selected from the group consisting of presbyopia, mild hyperopia, irregular astigmatism, and hyperopic accommodative esotropia~~, and glaucoma~~; and wherein the medicament is to be administered to the subject.

2. The use of claim 1, wherein administering comprises administering the composition to an eye of the subject.

3. The use of claim 1, wherein the medicament is to be administered to only one eye of the subject.

4. The use of claim 1, wherein the medicament increases refractive power of an eye of the subject by up to about 4.0 diopters.

5. The use of claim 1, wherein the ocular condition could alternatively be corrected with eye glasses having about +0.5D to about +1.0D lenses and wherein the therapeutically effective amount comprises from about 0.3% to about 1.0% pilocarpine.

6. The use of claim 1, wherein the ocular condition could alternatively be corrected with eye glasses having about +1.0D to about +1.5D lenses and wherein the therapeutically effective amount comprises from about 0.8% to about 1.6% pilocarpine.

7. The use of claim 1, wherein the ocular condition could alternatively be corrected with eye glasses having about +1.5D to about +2.0D lenses and wherein the therapeutically effective amount comprises from about 1.4 % to about 2.2% pilocarpine.

8. The use of claim 1, wherein the medicament comprises from about 0.01% to about 10% w/w pilocarpine and from about 0.01% to about 0.5% w/w oxymetazoline.

9. The use of claim 1, wherein the medicament comprises from about 0.5% to about 2% w/w pilocarpine and from about 0.02% to about 0.125% w/w oxymetazoline.

10. The use of claim 1, wherein administering the medicament to a subject treats the ocular condition for at least four hours.

11. The use of claim 1, wherein administering the medicament to a subject treats the ocular condition for at least six hours.

12. The use of claim 1, wherein the ocular condition is presbyopia.

13. The use of claim 1, wherein the ocular condition is mild hyperopia.

14. The use of claim 1, wherein the ocular condition is irregular astigmatism.

15. The use of claim 1, wherein the ocular condition is hyperopic accommodative esotropia.

~~16. The use of claim 1, wherein the ocular condition is glaucoma.~~