PRESBYOPIA TREATMENTS

PRIORITY

[001] This application claims the benefit of priority from U.S. Provisional Patent Application serial no. 62/662,144, filed April 24, 2018, U.S. Provisional Patent Application serial no. 62/780,117, filed December 14, 2018, and U.S. Provisional Patent Application serial no. 62/790,957, filed January 10, 2019, the disclosures of which are hereby incorporated in their entireties herein by reference.

BACKGROUND

[002] Presbyopia and other visual disorders have long been treated primarily with optical lenses and other such mechanical devices. As discussed in further detail herein, it would be advantageous to provide an alternative treatment that would avoid the use of such devices and the various disadvantages that these entail.

[003] Cholinergic agonists, such as pilocarpine, have been used to lower intraocular pressure ("IOP") so as to treat primary open angle glaucoma. Such cholinergic agonists were a mainstay for treatments that sought to lower IOP until the introduction of timolol in 1978. In the subsequent decades, and with the introduction of topical carbonic anhydrase inhibitors, alpha agonists, and prostaglandin agonists, pilocarpine became prescribed less often since the newer drugs had a much lower incidence of side effects such as reduced visual acuity and ocular discomfort (Allingham *et al*., Shields' Textbook of Glaucoma, 5th edition, Lippincott Williams & Wilkins (Philadelphia), 2005, pp. 501-503).

BRIEF SUMMARY

[004] Described herein are compositions and methods for improving vision using pilocarpine.

[004a] In one aspect, the present disclosure provides a use of a composition in the manufacture of a medicament for treating presbyopia, wherein the composition is pharmaceutically acceptable and comprises pilocarpine hydrochloride at a concentration of 1.25% w/v, wherein pilocarpine hydrochloride is the sole active ingredient, and wherein the composition further comprises boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water.

[004b] In another aspect, the present disclosure provides a use of a composition in the manufacture of a medicament for improving at least one vision parameter in a patient with presbyopia, wherein the composition is pharmaceutically acceptable, and wherein the composition comprises 1.25% w/v pilocarpine hydrochloride, boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water, and wherein the at least one vision parameter is selected from the group consisting of near vision acuity, distance vision acuity, night vision, day vision, glare, and light scattering, wherein pilocarpine hydrochloride is the sole active ingredient.

[004c] In yet another aspect, the present disclosure provides a use of a composition in the manufacture of a medicament for improving near vision in a patient with presbyopia, the composition comprising 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, 0.0075% w/v benzalkonium chloride, and water, with a pH of 3.0-5.5, wherein pilocarpine hydrochloride is the sole active ingredient.

[005] In some examples, there is provided a method of treating an ocular condition in a patient comprising administering to the patient an ophthalmic composition comprising pilocarpine hydrochloride.

[006] In one preferred example, there is provided a method of treating an ocular condition in a patient in need thereof, comprising administering to the patient a pharmaceutically acceptable ophthalmic composition comprising pilocarpine hydrochloride at a concentration

from 1.0 to 1.5% w/v, wherein the formulation is administered topically to at least one eye of the patient, and wherein the ocular condition is selected from the group consisting of presbyopia, hyperopia, mydriasis, anisocoria, accommodative esotropia, myopia, and astigmatism.

[007] In another preferred example, there is provided a method of improving at least one vision parameter in a patient in need thereof, comprising administering to the patient a pharmaceutically acceptable ophthalmic composition comprising pilocarpine hydrochloride at a concentration from 1.0 to 1.5% w/v, wherein the formulation is administered topically to at least one eye of the patient, and wherein the at least one vision parameter is selected from the group consisting of near vision acuity, intermediate vision acuity, distance vision acuity, night vision, day vision, glare, and light scattering.

[008] In a further preferred example, there is provided a method for improvement of near vision in a patient with presbyopia in need thereof, comprising administering to an eye of the patient a pharmaceutically acceptable ophthalmic composition comprising pilocarpine hydrochloride at a concentration from 1.0 to 1.5% w/v.

[009] In some examples, the ocular condition is presbyopia. In some examples, the ocular condition is hyperopia. In some examples, the ocular condition is mydriasis. In some examples, the vision parameter is near vision acuity. In some examples, the vision parameter is intermediate vision acuity. In some examples, the vision parameter is distance vision acuity. In some examples, the vision parameter is night vision. Additional examples provide for the method resulting in an at least 3-line improvement from baseline under the condition of mesopic, high contrast UNVA. In some examples, the method results in an at least 2-line improvement from baseline under the condition of mesopic, high contrast UNVA. In some examples, the method results in an increase in the average letter change from baseline under the condition of mesopic, high contrast UNVA. In some examples, the method results in an at least 2-line improvement from baseline under the condition of photopic, high contrast UNVA. In some examples, the method results in an at least 2-line improvement from baseline under the condition of photopic, high contrast UDVA. In some examples, the method results in an at least 3-line improvement from baseline under the condition of mesopic, high contrast DCNVA. The method may result in an at least 3-line improvement from baseline under the condition of photopic, high contrast DCNVA. In some examples, the method results in an at least 3-line improvement from baseline under the

condition of mesopic, high contrast DCIVA. The method may result in an at least 3-line improvement from baseline under the condition of photopic, high contrast DCIVA. In some examples, the method results in an improvement of at least one line in at least one selected from the group consisting of UNVA, UDVA, DCNVA, and DCIVA.

[0010] Further examples provide for the pharmaceutically acceptable ophthalmic composition to comprise pilocarpine hydrochloride at a concentration that is greater than or equal to 1% and less than 1.5% w/v. The pharmaceutically acceptable ophthalmic composition may comprise pilocarpine hydrochloride at a concentration of 1.25% w/v. Some examples provide for pilocarpine hydrochloride being the sole active ingredient in the pharmaceutically acceptable ophthalmic composition. In some examples, the pharmaceutically acceptable ophthalmic composition does not comprise a polymer. Administration of the pharmaceutically acceptable ophthalmic composition may in some examples result in a lower incidence of at least one of ocular blurring, ocular discomfort, eye pain, brow ache, blurry vision, light sensitivity, stinging, and itching, compared to administration of a second ophthalmic composition comprising pilocarpine and a polymer. In some examples, the pharmaceutically acceptable ophthalmic composition further comprises boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water. The pharmaceutically acceptable ophthalmic composition may be administered once daily. The pharmaceutically acceptable ophthalmic composition may be administered twice daily. The pharmaceutically acceptable ophthalmic composition may be administered to both eyes of the patient. The pharmaceutically acceptable ophthalmic composition may be administered to one eye of the patient. The pharmaceutically acceptable ophthalmic composition may be administered to the nondominant eye of the patient. The pharmaceutically acceptable ophthalmic composition may be administered to the dominant eye of the patient.

[0011] An additional preferred example provides for a composition for the treatment of an ocular condition, wherein the composition is pharmaceutically acceptable and comprises pilocarpine hydrochloride at a concentration from 1.0 to 1.5% w/v, and wherein the ocular condition is selected from the group consisting of presbyopia, hyperopia, mydriasis, anisocoria, accommodative esotropia, myopia, and astigmatism.

[0012] In some examples, the composition comprises 1.25% w/v pilocarpine hydrochloride, and the ocular condition is presbyopia. In some examples, the composition

comprises 1.25% w/v pilocarpine hydrochloride, boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water. In further examples, the composition is applied once daily. The composition may be applied twice daily. The composition may be administered to both eyes of a patient. The composition may be administered to a nondominant eye of a patient. The composition may be administered to a dominant eye of a patient. In some examples, pilocarpine hydrochloride is the sole active ingredient. Some examples, may further comprise a preservative. The preservative may be benzalkonium chloride. In certain examples, the composition comprises about 1.25% w/v pilocarpine hydrochloride, about 1.0% w/v boric acid, about 0.015% w/v sodium citrate dihydrate, about 0.08% w/v sodium chloride, and about 0.0075% w/v benzalkonium chloride. The composition may consist essentially of 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, and 0.0075% w/v benzalkonium chloride, with a pH of 5.0. The composition in some examples reduces the incidence of at least one adverse event selected from the group consisting of ocular blurring, ocular discomfort, eye pain, brow ache, blurry vision, light sensitivity, ocular stinging, and ocular itching, compared to administration of a second ophthalmic composition comprising pilocarpine and a polymer. The second composition may comprise 1% w/v pilocarpine and the polymer may be hydroxy propyl methyl cellulose.

[0013] In yet another preferred example, there is provided a composition for improving at least one vision parameter, wherein the composition is pharmaceutically acceptable and comprises pilocarpine hydrochloride at a concentration from 1.0 to 1.5% w/v, and wherein the at least one vision parameter is selected from the group consisting of near vision acuity, distance vision acuity, night vision, day vision, glare, and light scattering.

[0014] In some examples, the composition comprises 1.25% w/v pilocarpine hydrochloride, and the vision parameter is near vision acuity. The composition may comprise 1.25% w/v pilocarpine hydrochloride, and the vision parameter may be distance vision acuity. The composition may comprise 1.25% w/v pilocarpine hydrochloride, boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water. The composition may be applied once daily. The composition may be applied twice daily. In some examples, the composition is administered to both eyes of a patient. The composition may be administered to a nondominant eye of a patient. In some examples, the composition may

be administered to a dominant eye of a patient. In some examples, pilocarpine hydrochloride is the sole active ingredient. The composition may further comprise a preservative. The preservative may be benzalkonium chloride. In some examples, the composition comprises about 1.25% w/v pilocarpine hydrochloride, about 1.0% w/v boric acid, about 0.015% w/v sodium citrate dihydrate, about 0.08% w/v sodium chloride, and about 0.0075% w/v benzalkonium chloride. In some examples, the composition consists essentially of 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, and 0.0075% w/v benzalkonium chloride, with a pH of 5.0.

[0015] In another preferred example, there is provided a composition for the improvement of near vision in a patient with presbyopia, wherein the composition is pharmaceutically acceptable and comprises pilocarpine hydrochloride at a concentration from 1.0 to 1.5% w/v.

[0016] In some examples, the composition comprises 1.25% w/v pilocarpine hydrochloride, and the ocular condition is presbyopia. In some examples, the composition comprises 1.25% w/v pilocarpine hydrochloride, boric acid, sodium citrate dihydrate, sodium chloride, hydrochloric acid and/or sodium hydroxide, and water. The composition may be administered once daily. In some examples, pilocarpine hydrochloride is the sole active ingredient. The composition may further comprise a preservative. The preservative may be benzalkonium chloride. In another example, the composition comprises about 1.25% w/v pilocarpine hydrochloride, about 1.0% w/v boric acid, about 0.015% w/v sodium citrate dihydrate, about 0.08% w/v sodium chloride, and about 0.0075% w/v benzalkonium chloride. In yet another example, the composition consists essentially of 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, and 0.0075% w/v benzalkonium chloride, with a pH of 5.0.

[0017] In a preferred example, there is provided a composition for the improvement of near vision in a patient with presbyopia, the composition comprising 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, 0.0075% w/v benzalkonium chloride, and water, with a pH of 3.0-5.5.

[0018] In some examples, the composition consists of 1.25% w/v pilocarpine hydrochloride, 1.0% w/v boric acid, 0.015% w/v sodium citrate dihydrate, 0.08% w/v sodium chloride, 0.0075% w/v benzalkonium chloride, and water, with a pH of 5.0. In some examples, the composition is topically administered to the patient once daily.

[0019] In yet another preferred example, a method for the improvement of near vision in a patient with presbyopia comprises administering to at least one eye of the patient a pharmaceutically acceptable ophthalmic composition comprising pilocarpine as the sole active ingredient, wherein said composition does not contain any viscosity-enhancing polymers.

[0020] In some examples, the composition comprises pilocarpine hydrochloride. The composition may comprise 1.25% w/v pilocarpine hydrochloride. In some examples, the composition comprises pilocarpine nitrate. In further examples, the composition comprises 1.25% w/v pilocarpine hydrochloride or a molar equivalent pilocarpine salt. The composition may be administered once daily. The composition may be administered twice daily. In some examples, the composition is administered to a nondominant eye of the patient. In some examples, the composition is administered to a dominant eye of the patient. The composition may also be administered to both eyes of the patient. In some examples, the composition does not contain hydroxy propyl methyl cellulose. In further examples, administration of the pharmaceutically acceptable composition reduces the incidence of one or more adverse events compared to the administration of a pilocarpine composition comprising one or more viscosity-enhancing polymers. The one or more adverse events may be selected from the group consisting of ocular blurring, ocular discomfort, eye pain, brow ache, blurry vision, light sensitivity, ocular stinging, and ocular itching.

[0021] In a further preferred example, there is provided a method comprising administering to at least one eye of a patient with presbyopia a pharmaceutically acceptable ophthalmic composition comprising a first amount of pilocarpine hydrochloride as the sole active ingredient, wherein such administration is made without previously administering a second amount of pilocarpine hydrochloride and/or subsequently administering a third amount of pilocarpine hydrochloride; wherein the second amount is lower than the first amount, and wherein the third amount is higher than the first amount.

[0022] In some examples, the first amount of pilocarpine hydrochloride is 1.25% w/v. The pharmaceutically acceptable ophthalmic composition may be administered to both eyes of the patient. The pharmaceutically acceptable ophthalmic composition may be administered once daily, or twice daily.