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An Interprofessional Study of the Effects of Topical Pilocarpine on Oral and Visual Function

Len V. Hua OD, PhD *College of Optometry, Pacific University*

Pam T. Kawasaki RDH, MBA *School of Dental Health Science, Pacific University*

Vedavalli N. Pokala MS, PhD *School of Pharmacy, Pacific University*

John R. Hayes, PhD *College of Optometry, Pacific University*

Abstract

INTRODUCTION In light of expanding use of pilocarpine for numerous systemic disorders over the past decades, it is important to understand its effects on visual and oral function.

OBJECTIVE To study the adverse effects of topical pilocarpine on visual and oral function in healthy volunteers via interprofessional collaboration.

METHODS Thirty-six subjects, 21 years and older, were enrolled for the study. The study was designed to have each subject undergo tests for oral and visual function before and 20 minutes after a topical dose (2% ophthalmic solution), so the subjects served as their own controls.

RESULTS The sample included 24 females and 11 males with a mean of 22 years. The pupil diameter was significantly reduced post treatment with pilocarpine. The effect was larger in dim light than in bright light. Distance and near visual acuity were significantly reduced by pilocarpine treatment. Distance visual acuity under low contrast illumination and automated perimetry were significantly reduced with pilocarpine. Remarkably, salivary volume was significantly increased.

CONCLUSION In young normal subjects, pilocarpine adversely affects the visual acuity, contrast sensitivity, visual field and thus the overall visual function, but it positively increases salivary volume.

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Implications for Interprofessional Practice

- Topical pilocarpine can induce headache as a side effect in young patients.
- Topical pilocarpine can significantly reduce visual acuity, especially in natural (low contrast) environment.
- Oral pilocarpine causes miosis and can also reduce visual acuity.
- Clinicians who prescribe pilocarpine or other miotic drugs need to pay closer attention to the ocular side effects of this class of drug because they can significantly affect the daily tasks that require clear vision.
- Over the years, there has been an expanding use of miotics in medicine, so miosis-induced visual impairment affects an increasing number of patients, especially the elderly.

Introduction

Pilocarpine is a natural alkaloid derived from the leaves of a plant, *pilocarpus jaborandi*, indigenous to South America (Vivino et al., 1999). Pilocarpine hydrochloride is known as a direct-acting cholinergic agonist that activates muscarinic receptors [M1-M5] nonspecifically resulting in a broad spectrum of pharmacological effects. It stimulates exocrine secretions from sweat, salivary, and lacrimal glands (Brown & Taylor, 2006). It is indicated for the treatment of inadequate salivary flow secondary to radiation therapy for cancers of the head and neck. It is also commonly used in patients with Sjogren's syndrome, which is a chronic autoimmune disease that gradually damages the moisture-producing glands, causing significant dryness in the mouth and eyes (Bruce, 2003).

In eye care, pilocarpine has been one of the earliest drugs used in the treatment of glaucoma (Grierson et al., 1978). Although it is no longer the first line of drug prescribed for treatment of glaucoma, pilocarpine is still being used widely to treat acute angle closure and to prepare the iris for laser peripheral iridotomy. Moreover, it is still a glaucoma drug of choice for many patients in third world countries because of its affordability (Wu et al., 2011).

Muscarinic receptors are found on the secretory exo-

crine gland, on smooth and cardiac muscles, and distributed throughout the central nervous system including the eyes (Eglen, 2006). Pilocarpine acts unselectively on multiple subtypes of muscarinic receptors therefore it can cause various parasymphomimetic effects. Stimulation of peripheral muscarinic receptors produces salivation, lacrimation, sweating, rhinorrhea, bronchospasm, urinary frequency, diarrhea, bradycardia, and miosis. It is generally known that miosis induced by topical pilocarpine can adversely affect visual field, and ciliary spasm can cause reduction in accommodation and visual acuity (McCluskey et al., 1986; Gilmartin, Amer, & Ignleby, 1995). Although there have been a number of studies over the past few decades on the effects of topical pilocarpine on high-contrast visual acuity and visual field with respect to glaucoma treatment, little has been done to investigate the potential effect of topical pilocarpine on low-contrast visual acuity which is encountered in many daily environmental settings. Furthermore, the effects of topical pilocarpine on oral function are not well-documented.

In light of expanding use of pilocarpine for numerous systemic disorders over the past decades, it is important to understand its adverse effects on visual and oral function. Therefore, we designed an interprofessional study to look at the effects of topical pilocarpine on visual function including low-contrast sensitivity; and its effects on oral function in healthy volunteers.

Materials and methods

Thirty-five subjects, between 21 and 38 years of age, were enrolled for the study. All subjects were required to fill out informed consent forms, medical intake forms, and questionnaires related to ocular and dental health. The study was designed to have each subject undergo tests for oral and visual function before and 20 minutes after a topical dose (2 percent ophthalmic solution), so the subjects served as their own controls. Pilocarpine hydrochloride ophthalmic solution 2 percent (Bausch + Lomb, FL, USA) was used for the study. The study was reviewed and approved by Pacific University Institutional Review Board before initiation.

The study location was the Pacific University Eye and Dental Clinics. Investigation oral hydration was performed using Saliva-Check BUFFER kit (GC Corporation, Tokyo, Japan). Prior to the dental visit, subjects were instructed not to smoke, consume food or drink, brush teeth, or use a mouth wash for at least one hour before the scheduled appointment time. The lower lip was blotted dry with a small piece of gauze and the examiner observed the mouth skin under good illumination. Level of hydration was inspected by measuring how long it took for saliva to form inside the lower lip. The volume of saliva was collected and measured by having subjects chew on a piece of wax to stimulate salivary flow and spat intermittently into the cup over a period of five minutes. The thickness of the saliva was examined for salivary consistency by observation. The pH of the saliva was tested with a pH test strip. Buffering capacity of the saliva was done via a simple chemical test supplied with the kit.

Visual function was assessed by visual acuity (VA), contrast sensitivity and visual field. The size of pupil was also measured under bright and dim light. Distance VA was measured at 20 feet using LogMAR optotypes via Pro Video System (Innova System Inc, IL, USA). Near VA was taken at 16 inches using pocket-sized near vision card with Sloan letters (Good-Lite, IL, USA). Contrast sensitivity testing was measured using 5 percent chart in LogMAR sizes at 10 feet (Good-Lite, IL, USA). Visual field was tested via N-30-5 FDT screening on Humphrey Matrix (Carl Zeiss Meditec Inc, CA, USA). Pupil sizes were measured in bright and dim illumination using pupil gauge on pocket-sized near vision card. In addition, pictures of pupil size were taken using Handycam HDR-CX550V with infrared feature (Sony

Corporation, Tokyo, Japan).

Statistical analysis

Descriptive statistics provided the basic findings. OD and OS measures were averaged to provide a single value. Before and after treatment values were compared with a paired t-test.

Results

Sample and Survey

The sample included 24 females and 11 males with ages ranging from 22 to 38 with a mean of 22 years. Ten (10) reported no dry eye complaints, nine rarely had dry eye, 15 reported sometimes, and one always. Seventeen had no night time vision complaints and nine rarely had complaints, while nine sometimes had problems, three usually, and one always. Four people complained of dry mouth. Table 1 (following page) summarizes the numeric variables collected.

Visual Function

Table 2 (following page) summarizes the change scores for different visual tests. The pupil diameter was significantly reduced post treatment with pilocarpine. The effect was larger in dim light than in bright light. Representative photographs of pupils before and after pilocarpine treatment are shown in Figures 1a and 1b (page 5). Both distance and near visual acuity (VA) were significantly reduced by pilocarpine treatment with larger effects on distance VA. Distance visual acuity under low-contrast illumination was significantly reduced with pilocarpine. Automated perimetry was also significantly affected by pilocarpine. Representative printouts of VF results are presented in Figure 2 (page 6).

Salivary Function

Salivary consistency, buffering capacity, and pH of the saliva were not significantly affected by topical pilocarpine, but the salivary volume was significantly increased (see Table 2) .

Discussion

Pilocarpine, a direct acting cholinergic agonist, has been proven to be effective in the treatment of radia-

Table 1*Numeric variables collected*

N = 35	Minimum	Maximum	Mean	Std. Deviation
Saliva Volume Before	4.0	16.0	8.314	3.2315
Saliva Volume After	5.0	17.0	9.757	2.9812
Pupil Size Dim Before	4.0	8.0	5.586	1.0743
Pupil Size Light Before	2.0	7.5	3.786	1.1394
Pupil Size After	1.5	4.0	2.814	.6869
VA Distance Before	1.5	4.5	2.614	.7484
VA Near Before	1.50	4.25	2.7143	.65626
VA Distance After	11	31	17.14	3.719
VA Near After	10	25	16.09	2.934
Contrast Sensitivity Before	11.5	25.5	16.614	2.8622
Contrast Sensitivity After	16	30	20.34	2.169
Stinging Rate	16	25	20.06	1.371
Visual Field Before	16.0	25.0	20.200	1.5913
Visual Field After	13	200	52.91	53.559
Headache Rate	15	399	66.00	78.714
Eyestrain Rate	16.0	299.0	59.457	64.3590

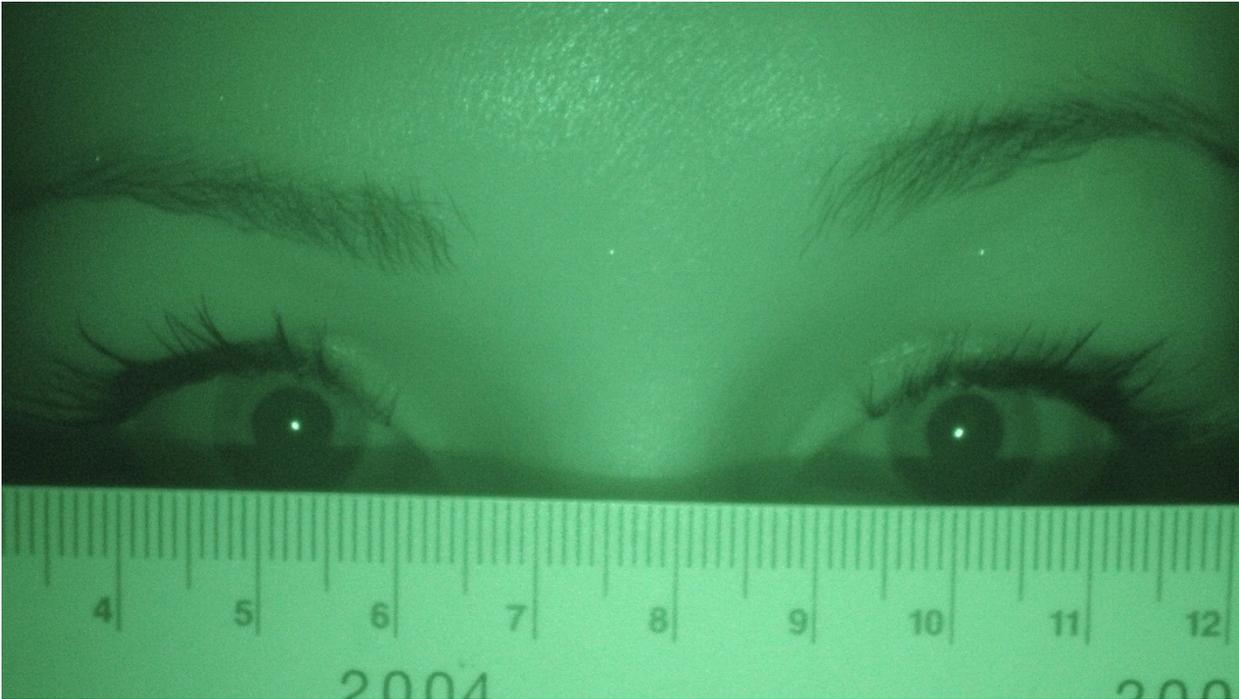
Table 2*Change scores (post-application – pre-application) for numeric variables (left and right eyes averaged)*

After – Before	Mean Difference	Std. Deviation	Paired t (df=35)	p
Saliva Volume	1.4429	1.9470	4.384	.000
Pupil Size Dim	-2.7714	1.1653	-14.070	.000
Pupil Size Light	-1.1714	1.1628	-5.960	.000
VA Distance	36.3000	53.8179	3.990	.000
VA Near	12.8000	25.1160	3.015	.005
Contrast Sensitivity	54.2429	50.0747	6.409	.000
Visual Fields	3.029	5.199	3.446	.002

Note: The variables in Table 2 were examined for association with dry eye, night vision complaints, and dry mouth (non-parametric median tests). There were no significant relationships.

Figure 1a

Photograph of pupil diameter of a representative subject in dim light before treatment

**Figure 1b**

Photograph of pupil diameter of the subject in dim light after treatment



Figure 2a

N-30-5 FDT Screening of another representative subject before pilocarpine treatment

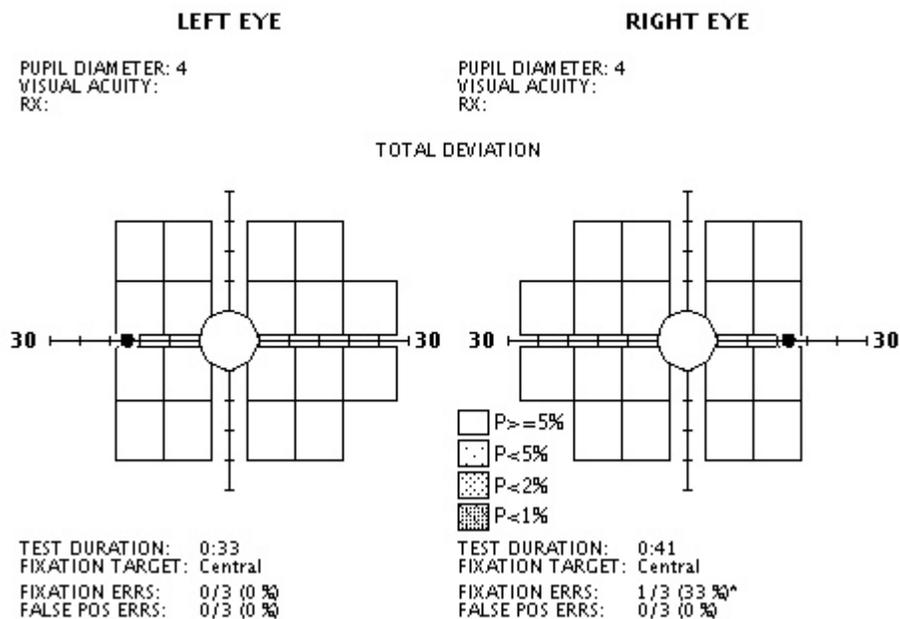
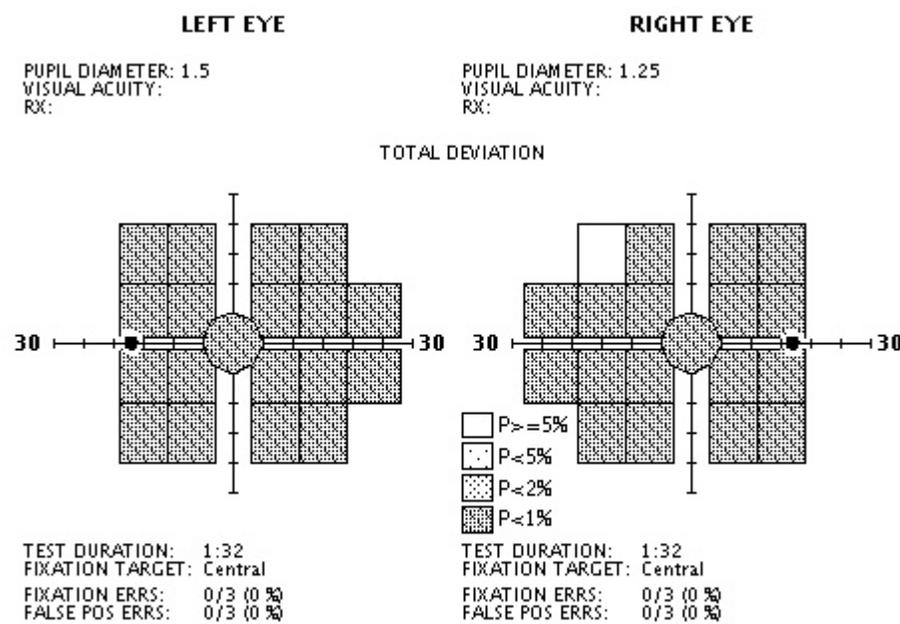


Figure 2b

N-30-5 FDT Screening of the subject after pilocarpine treatment



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tion-induced xerostomia (Greenspan & Daniels, 1995). It was also found to increase salivary flow in patients with Sjogren's syndrome (Vivino et al., 1999; Fox et al., 1991). Therefore, pilocarpine (Salagen) tablets are commonly prescribed both for the treatment of dry mouth as a result of radiation therapy for cancers of the head and neck; and for dry mouth and dry eyes secondary to Sjogren's syndrome. Moreover, a number of studies over the years had shown that pilocarpine was also effective in relieving inadequate salivary flow caused by opioid psychoactive medications, with antimuscarinic and anticholinergic properties, leading to the increasing usage of pilocarpine (Sebastiano, 1998; Gotrick et al., 2004; Masters, 2005).

While oral pilocarpine has been prescribed more frequently over the last decade, the use of topical pilocarpine has declined and replaced by newer and more effective glaucoma medications. Nevertheless, topical pilocarpine is still being used widely in third world countries for treatment of glaucoma because of its affordability. Furthermore, it is still being utilized to relieve intraocular spike in acute angle closure and to prepare pupil for laser peripheral iridotomy. Altogether, topical pilocarpine still remains an important drug in glaucoma management hence it is important to investigate its effects on visual function. This study aims to study the effects of topical pilocarpine on visual function and also examine its potential effects on oral function in healthy volunteers. In addition, the study may provide useful data for future study on the effects of oral pilocarpine.

Topical pilocarpine has been known for decades to cause miosis via stimulation of muscarinic receptors present on constrictor muscles of the iris. Miosis is a physiological response regulating the amount of light reaching the retina for optimal vision. Pharmacological miosis, however, is unnatural because the pupil is fixed and unresponsive to light and excessive miosis can induce diffraction which interferes with vision.

The data from the study confirmed that a single instillation of pilocarpine significantly reduced the pupil diameters in normal subjects. The effect was larger in dim than in bright illumination. Both distance and near visual acuity were significantly reduced by pilocarpine treatment with larger effects on distance VA. Contrast sensitivity (CS) testing further assesses visual function beyond visual acuity because VA test only measures

at one high-contrast level, daily activities, however, consist of different low contrast environments. Some patients can have normal visual acuity, but have difficulty in doing daily tasks because of reduced CS at lower spatial frequencies. Therefore, it is important to test VA with low contrast optotype to better represent natural environment. The distance visual acuity under low-contrast illumination was decreased most significantly by topical pilocarpine. This finding is similar to what was found in previous study by Edgar et al. (Edgar et al., 1999). On the contrary, another study conducted by Sloane et al. on the effect of senile miosis ($n=11$, M age=73) on contrast sensitivity comparing to young adults ($n=13$, M age=24) found that older adults' miotic pupils actually improved contrast sensitivity (Sloane, Owsley, Alvarez, 1988). The difference found in our study may be accounted for by the fact that pupil sizes induced by pilocarpine was significantly smaller as compared to senile miosis and thus diffraction could be an important factor affecting the vision in the young cohorts.

Automated perimetry is an additional method to assess a person's visual function. It permits a thorough assessment of both the central and peripheral visual field. Topical pilocarpine significantly reduced the field of vision affecting more of the peripheral field than central field. The effects of pilocarpine on automated perimetry was consistent with previous studies (McCluskey et al, 1986; Webster et al, 1993).

Cumulatively, the significant effects of topical pilocarpine on multiple visual tests and overall visual function could be attributed by the miotic effects of pilocarpine. Excessive miosis can decrease vision in two ways: decreased retinal illumination and the presence of diffraction (Campbell & Green, 1965). Optimal visual resolution is achieved when the pupil sizes are neither too large nor too small. Large pupils are more prone to optical aberrations, whereas small pupils are subjected to diffractions (Campbell & Gubisch, 1966). The pupil size for best axial resolution in the human was found to be about $4.30\text{mm} \pm 1.90\text{mm}$ in a recent study (Donnelly & Roorda, 2003). According to Weber's law, the differential light threshold remains unchanged when the pupil size is altered, however the law only holds when the pupils are ranging approximately 3.0 mm to 7.0 mm under mesopic illumination levels (Edgar et al., 1999; Herse, 1992). In our study, a substantial number of subjects had pupil diameters below 3.0 mm, at which

significant reduction in retinal illumination and diffraction could occur and break Weber's law as a possible explanation for significant worsening of visual function.

In addition to the effects of pilocarpine on visual function, other side effects were noted by the majority of subjects including severe stinging upon instillation and supraorbital headache. Since our subjects were relatively young, ciliary spasm and over accommodation caused by cholinergic stimulation can account for the headache symptom. On the other hand, a number of subjects appreciated a relief of dry eyes with pilocarpine. However, this benefit was outweighed by the discomfort of headache and blurry vision. Thus, the subjects would not choose to use it to treat dry eye (based on survey questionnaire). Moreover, miotic agents have been found occasionally to cause retinal detachment and macular hole (Walker, 2007).

Salivary function

Saliva lubricates, cleans, and protects the oral tissues from infectious microorganisms. It also facilitates chewing, digesting, tasting, and swallowing of food (Atkinson, 2005). Xerostomia is a symptom of dryness in the mouth associated with salivary hypofunction due to various etiologies including autoimmune disease (Sjogren's), systemic disease (diabetes mellitus), anticholinergic effects of many drugs and aging (Narhi, 1999). Chronic xerostomia can significantly affect the quality of life because of the increased risk of dental cavities, oral ulcers and mucosal infection (Perno Goldie, 2007). The drug of choice for stimulating salivary flow in the treatment of xerostomia is either pilocarpine or cevimeline (Fox & Michelson, 2000; Porter, Scully & Hegarty, 2004). Pilocarpine (Salagen®) is available in both tablet formulation (5 mg) and 1 and 2 percent solutions (Bruce, 2003). Although oral pilocarpine has been known for decades to effectively increase the salivary volume, the effects of topical pilocarpine (2 percent) on salivary volume has not been measured. While we studied the effects of topical pilocarpine on visual function, we also wanted to know whether it might affect oral function. Remarkably, the data indicated that there was a significant effect of topical pilocarpine on salivary volume. The significant effects of topical pilocarpine on oral function suggested that there was residual pilocarpine reaching the salivary glands via the nasal lacrimal ducts from the eyes. Further study is needed to exam-

ine whether the increased in salivary volume by topical pilocarpine is clinically beneficial.

Chronic use of pilocarpine (12 weeks or more) has been shown to cause diaphoresis, increased urinary frequency and facial flushing (Nieuw Amerongen & Veerman, 2003). Serious pilocarpine toxicity is rare, but has been reported in a case of idiosyncratic reaction to the drug. The patient's heart rate was slowed to 38 beats per minutes and the blood pressure was decreased to 102/42 mm Hg. Intravenous atropine (0.5 mg) over two minutes was used successfully as an antidote (Hendrickson, Marocco & Greenberg, 2003). Therefore, it is important to educate patients on potential symptoms of pilocarpine toxicity.

This study provides further support to previous studies on the effects of topical pilocarpine on visual function including contrast sensitivity. Interestingly, topical pilocarpine can significantly stimulate salivary volume and may relieve dry mouth symptom in patients who happens to take the drop topically for glaucoma. One difference in this study is that it focused more on visual function in general, whereas most previous studies concentrated on the effects of topical pilocarpine on visual field with respect to glaucoma treatments. The study also looked at the possible effects of topical pilocarpine on oral function which was rarely known. The limitations in this study include a young study cohort and one dose-response point. On the other hand, the strength of the study is the subjects served as their own controls before and after treatment, and the study is interprofessional including both visual and oral functional tests. The findings from this study serve as a good starting point for future studies on the effects of miotics on oral and visual functions of patients.

Generally, the effect of pilocarpine as a miotic can be inferred for other drugs that could constrict pupils and affect visual function such as opioids and antipsychotics. Unfortunately, there are no alternative cholinergic agonists such as pilocarpine that is not a mitotic, because cholinergic receptors are abundant in the iris sphincter muscle, so knowing its potential visual and oral effects would ensure closer monitoring of the side effects of the miotics and adjusting the dosage appropriately.

Conclusions

This is the first study to investigate the effects of a miotic drug via interprofessional collaborations between optometry, pharmacy, and dental health science. The authors have better appreciation of other health profession and establish a good foundation for future collaboration.

In young normal subjects, pilocarpine adversely affects the visual acuity, contrast sensitivity, visual field, and thus the overall visual function, but it positively increases salivary volume. Future study of the side effects of oral pilocarpine is necessary to better understand the full impact of oral miotics on visual and oral function.

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Corresponding Author

Len Hua, OD, PhD
Assistant Professor

College of Optometry
Pacific University
Forest Grove, OR 97116

lenhua@pacificu.edu