Review Article

A Systematic Review and Meta-Analysis on the Efficacy and Safety of Topical Pilocarpine 1.25% in Presbyopia Treatment

Mamta Singh[1], Bibhuti Prassan Sinha[2], Siddhartha Dutta[3], Kunal Khanderao Deokar[4], Deepak Mishra[5], Khyati Goswami[1]

[1]Department of Ophthalmology, All India Institute of Medical Sciences, Rajkot, Gujarat, India, [2]Department of Ophthalmology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, [3]Department of Pharmacology, All India Institute of Medical Sciences, Rajkot, Gujarat, India, [4]Department of Pulmonary Medicine, All India Institute of Medical Sciences, Rajkot, Gujarat, India, [5]Department of Ophthalmology, Regional Institute of Ophthalmology, IMS/BHU, Varanasi, Uttar Pradesh, India

Abstract

Purpose: To do a qualitative and quantitative assessment of the existing literature on the effectiveness and safety of pilocarpine 1.25% eye drops in presbyopia management.

Methods: Relevant articles were extracted from the online database using keywords – "pilocarpine and presbyopia", "AGN-190584 and presbyopia", and "Vuity and presbyopia". The primary outcome measure considered was an improvement in distance-corrected near visual acuity (DCNVA) and secondary outcome measures were improvement in distance-corrected intermediate visual acuity (DCIVA) and adverse events (AEs). Risk of bias (ROB) assessment was done using the ROB2 tool and R software was used for quantitative analysis.

Results: The 3 included randomized control trials (RCTs) had a total of 980 participants between 40–55 years of age. They were randomized into 2 groups – 489 in the pilocarpine group and 491 in the vehicle group. In the pilocarpine group, 1.25% of pilocarpine was used either once (in the Gemini 1 and 2 trials) or twice daily (Virgo trial). A significantly higher proportion of patients reported improvement of DCIVA and gain of ≥ 3 lines in binocular DCNVA in the pilocarpine group than the vehicle group ($P < 0.01$). Headache was the most commonly reported AE (13.49% of participants). Three case reports published on pilocarpine use for presbyopia management have reported vitreomacular traction in 1 and retinal detachment in 5 eyes.

Conclusions: The available evidence documents significant improvement in near and intermediate vision in presbyopia participants with pilocarpine 1.25% drop. However, more RCTs, involving a wider age group, larger refractive error, longer follow-up, and clinical testing in a real-world scenario are required to conclusively prove its role in presbyopia management.

Keywords: Near vision, Pharmacotherapy, Pilocarpine, Presbyopia

Address for correspondence: Mamta Singh, All India Institute of Medical Sciences, Rajkot, Gujarat, India.
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Introduction

Presbyopia is an age-related insufficiency of accommodation leading to the inability to focus clearly on near objects. With a projected 21% of the world's population expected to be 60 years or above by 2050, the aging trend can make presbyopia a significant visual issue of the 21st century. The number of people affected by presbyopia is estimated to reach 1.8 billion worldwide by 2050.[1] The reported prevalence of uncorrected presbyopia in India is 33% and has been reported to cause a 2-fold increase in the difficulty of tasks requiring near eyesight, and a >8-fold more difficulty in executing very demanding near-vision-related tasks.[2,3] The physiological changes leading to this age-related decrease in amplitude of accommodation are decreasing efficiency of ciliary muscles, sclerosis of the crystalline lens fibers, and capsular changes

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leading to decreased spontaneous curvature adjustments with ciliary muscle contraction.[4] The increased thickness of the lens with age leads to the spread of vector force of zonules to a wider area of the equator, making it less effective. These changes lead to the receding of near points of accommodation beyond the reading distance, causing functional restriction in seeing near objects.[5] The present available options for presbyopia correction involve optical correction in the form of glasses, contact lenses, and cornea and lens-based surgical procedures. None of these methods ensures satisfactory long-term correction without their inherent adverse effects. A nonsurgical method, restoring or strengthening the physiological accommodation, and providing a clear vision at all focal distances would be an ideal presbyopia correction modality. Pharmacotherapy for correcting presbyopia operates on two fundamental principles. The first involves the use of parasympathomimetic agents such as pilocarpine and carbachol, which work by assisting accommodation and being miotics, they induce a pinhole effect to improve the depth of focus. The second principle involves the application of lens softeners, such as lipoic acid choline ester, which reduce disulfide bonds in the lens protein, thereby enhancing the lens's elasticity. Various pharmacological agents such as "Fundacio´n Oftalmologica Vejarano (combination of pilocarpine [0.247%], nepafenac [0.023%], phenylephrine [0.78%], pheniramine [0.034%], naphazoline [0.003%], and polyethylene glycol [0.09%]) vision" have been tried in different combination to achieve the physiological state of accommodation without depending on optical devices or surgeries.[6] The most evaluated and tested pharmacological agent for presbyopia correction is pilocarpine. At present, pilocarpine 1.25% eye drop or AGN-190584 is the only Food and Drug Administrative (FDA)-approved drug for presbyopia management. It received FDA approval in once daily dose in October 2021 and in twice daily dose in March 2023. It is a re-engineered pilocarpine formulation developed to address presbyopia while ensuring safety and tolerability.[7,8] We aimed to do a qualitative and quantitative assessment of the existing literature regarding the effectiveness and safety of using pilocarpine 1.25% eye drops in presbyopia management and to draw attention to the gaps if any in the evidence that currently exists regarding its use for this purpose.

Methods

Protocol registration

This systematic review and meta-analysis protocol is registered with PROSPERO under the review title "Systematic review and meta-analysis on the efficacy and safety of pilocarpine (1.25%) in presbyopia treatment" with registration number CRD42023418875.

Search strategy and study selection

An electronic database search was conducted up to April 12, 2023, by querying databases such as PubMed, the Cochrane Central Register of Controlled Trials, the International Standard Randomized Controlled Trial Number registry, the US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. The relevant articles published in English or having English translation till April 2023 were extracted using keywords: "pilocarpine and presbyopia", "AGN-190584 and presbyopia", and "Vuity and presbyopia". The same keywords were used for the electronic search engine - Google Scholar to find out any missing articles and references. Clinical studies including randomized control trials (RCTs), observational and interventional studies, and case series and case reports were included in this review. This review excluded any clinical studies that used topical pilocarpine at a concentration other than 1.25%. The references cited in articles identified were also reviewed. Two authors (MS and BPS) were involved in the literature search independently and any conflicts were resolved by a third author. The terms "AGN-190584" and "Pilocarpine 1.25% ophthalmic solution" have been used interchangeably in this review.

Data extraction

Data were extracted on standardized data extraction form. For quantitative assessment, results reported on clinical trial registry systems were taken into consideration if published reports were not available.

Eligibility criteria for inclusion and study outcomes

Studies evaluating the efficacy of pilocarpine 1.25% topical drop in presbyopia patients (age more than 40 years) were included in this review. The primary outcome measure considered in this review was an improvement in mesopic (lighting 3.2–3.5 candelas per square meter [10–11 lux] measured at the target) binocular distance-corrected near visual acuity (DCNVA) measured at 40 cm, from baseline (day 1) to hour 3 on day 14 and on day 30. The proportion of participants who reported improvements in their DCNVA by ≥3 lines without losing >5 letters of high contrast and binocular corrected distance visual acuity by with the same refractive correction was taken into account.

The secondary outcome measures considered here were improvement in high-contrast, binocular distance-corrected intermediate visual acuity (DCIVA) measured at 66 cm, and adverse events (AEs) associated with this drop.

These AEs were grouped as serious and nonserious AEs. The total AE (TAE) included a summation of both serious and nonserious AEs. The AEs were recognized using the standard nomenclature from the Medical Dictionary for Regulatory Activities (MedDRA) version v20.1.[9] The ocular AEs included a summation of all the AEs linked with the eye disorders listed as per the MedDRA classification.

Quality assessment of studies

Risk of bias (ROB) assessment: Using the Cochrane Collaboration ROB 2 instrument and independently, two authors (MS and BPS) evaluated the methodological quality of the studies.[10,11]

The Robvis (visualization tool) program was used to create the figure plots for the bias risk.[12]

Data synthesis and summary measures

For quantitative analysis of data, R software was used.[13] The data were analyzed using a random effect model.

The consistency of the size and direction of impacts were examined in the forest plot. The dichotomous variables were summarized as odds ratio (OR) and risk ratio (RR) along with their 95% confidence intervals (CI). The continuous outcomes were measured in mean difference (MD).

The evaluation of the heterogeneity of RCTs was based on I^2 value with its CI. I^2 from 30% to 60%: might be taken as moderate heterogeneity, 50% to 90% for substantial heterogeneity, and 75% to 100% for considerable heterogeneity. However, the magnitude and direction of effects and *P* value (Chi-square test) or CI for I^2 were considered for significant heterogeneity.[14-16]

Results

Literature search and study characteristics

Online database search with the keywords "pilocarpine and presbyopia", "AGN-190584" and "Vuity and presbyopia", yielded 151 titles, including 75 clinical trials. On removal of 86 duplicate records and 5 records not relevant to this review, full-text articles of 60 reports were sought for retrieval. Ongoing clinical trials ($n = 11$) with no available results and trials which have been withdrawn ($n = 1$), were not included in this review. Inclusion and exclusion criteria were applied on the remaining 48 reports and 42 reports were further excluded (review article [$n = 7$], animal studies [$n = 5$], correspondence [$n = 1$], not meeting other inclusion criteria [$n = 29$, 8 studies evaluating different outcome measure, 1 *in vitro* study, 8 pilocarpines with other drugs used for presbyopia pharmacotherapy, 12 pilocarpine concentration other than 1.25% used]). Ultimately, 6 articles were included in this review, 3 RCTs, and 3 case reports.[17-22] The summary of the study selection process is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart [Figure 1].

All the 3 RCTs included in this review were phase 3, multicenter, double-masked, randomized, vehicle-controlled,

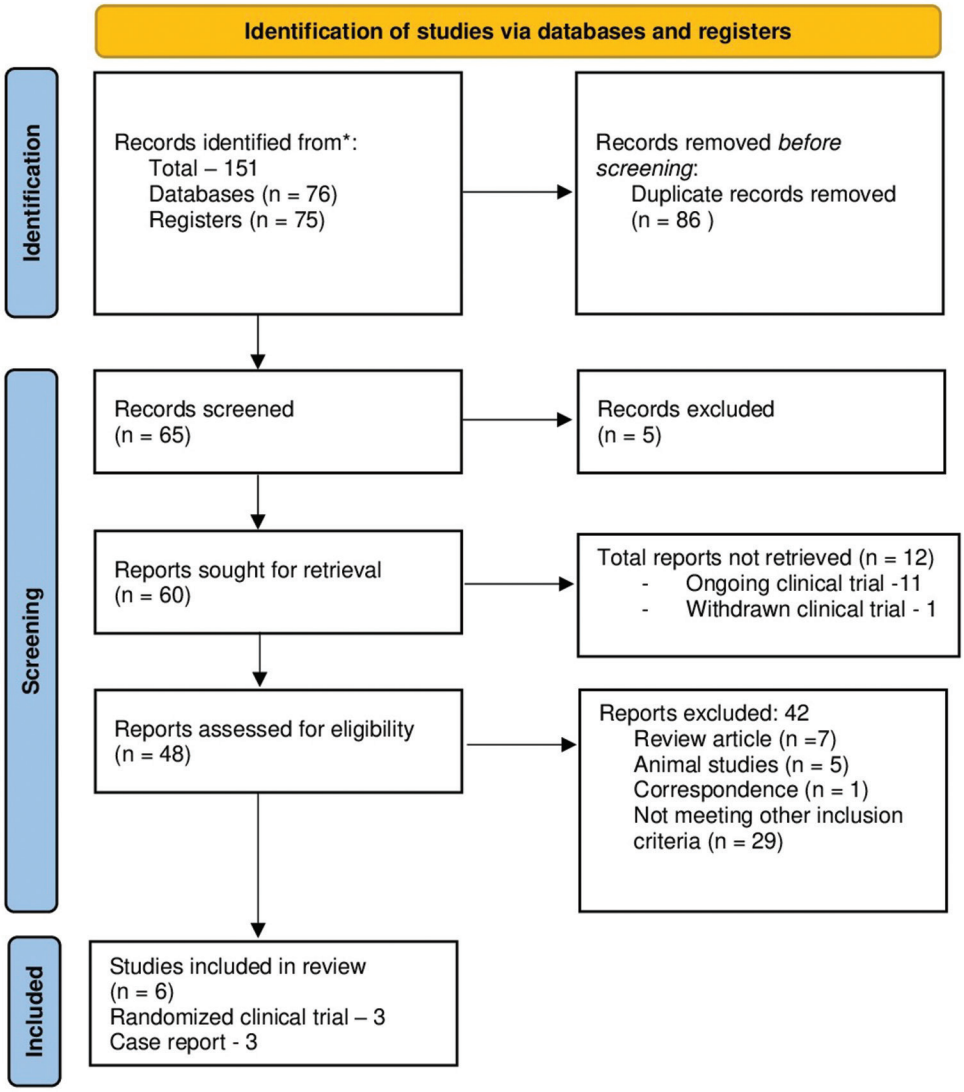

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

parallel-group study conducted for evaluating the safety and efficacy of pilocarpine 1.25% eye drop in subjects of presbyopia [Figure 1].[17-19] The quantitative assessment was performed with the published results of the Gemini 1 trial by Waring *et al*.[17] and with the available results of the Gemini 2 and Virgo trials on ClinicalTrials.gov database, as their results are yet to be published.[18,19] The Virgo trial data were not included in quantitative analysis because the primary outcome measure, improvement in DCNVA, was evaluated here on day 14, unlike the Gemini 1 and 2, where the assessment took place on day 30. In the quantitative analysis of the efficacy of pilocarpine, the Virgo trial was not included as the primary outcome measure, improvement in DCNVA, was assessed here on day 14 as compared to day 30 in the Gemini 1 and 2.[17-19] For the quantitative analysis of the safety of pilocarpine in presbyopia patients, data of all the 3 RCTs were considered. Table 1 provides a summary of the characteristics of the included studies.

Study group

The study group was homogenous, involving subjects between 40 and 55 years of age with subjective and objective evidence of presbyopia. The DCNVA of the study group was between 20/40 and 20/100 and best distance correction was between −4.00 to +1.00 diopter (D) sphere and cylinder ≤±2.00 D. Any patient with severe dry eye, punctum occlusion, corneal pathologies in either eye, narrow anterior chamber angles (Shaffer grade ≤2), history of ocular hypertension, glaucoma, iridotomy, cataract surgery, phakic intraocular lens surgery, corneal inlay surgery, radial keratotomy, or any history of ocular surgery except photorefractive keratectomy (PRK) or laser-assisted *in situ* keratomileusis (LASIK), and anisocoria more than 1 mm under mesopic conditions were excluded from the study.

Of a total of 980 participants, 68.07% were female and 31.93% were male. About 84.69% of the study's participants were white and the mean age of the study population was 49.8 ± 3.58 years. Table 2 summarizes the demographic profile of the study group.

The participants were randomly assigned in a 1:1 ratio to either the pilocarpine group (489 participants) or the vehicle group (491 participants). The subgroup analysis was done on the basis of age (≤50 years or >50 years), baseline binocular DCNVA (≥20/60 or <20/60), iris color (brown or nonbrown), and refractive status (emmetropes with a range of −0.50 D to +0.75 D and/or a cylinder <0.75 D, or nonemmetropes).

Intervention

Out of 3 RCTs, in the Gemini 1[17] and the Gemini 2,[18] the experimental group received pilocarpine 1.25% in each eye, once daily, for 30 days. In clinical trial identifier NCT04983589 also known as the Virgo trial, the experimental group received pilocarpine 1.25% in each eye, twice daily, with a gap of 6 h between both doses, for 14 days.[19] The comparator group in all three trials received a placebo (only vehicle).

Efficacy outcomes

Improvement in near visual acuity

Improvement in DCNVA was assessed on day 14 at 3 h after the second dose of pilocarpine only in the Virgo trial.[19] In this trial, 35.1% of participants in the pilocarpine group reported gain of ≥3 lines in binocular DCNVA ($P < 0.0001$, 95% CI, 17.3%–37.4%) compared to 7.8% of participants in the vehicle group.[19]

Improvement of DCNVA was evaluated on day 30, h 3 in the Gemini 1 and 2 trials.[17,18] The quantitative pooled analysis of these two RCTs (Gemini 1 and 2 trials) for DCNVA showed that pilocarpine led to a significant proportion of patients (28.1% vs. 9.6% in pilocarpine vs. placebo, respectively) to experience a clinically meaningful 3 or more lines in mesopic, high-contrast, binocular DCNVA at day 30 as compared to placebo (OR = 3.68 [2.16–6.28], I^2 = 37%, $P < 0.01$) [Figure 2].

Improvement in intermediate visual acuity

Assessment of improvement in photopic intermediate visual acuity on day 30, h 3 was conducted in the Gemini 1 and 2 trials. The results of these two studies have been summarized in Table 3. The quantitative pooled analysis of two RCTs (Gemini 1 and 2 trials) revealed a significant improvement in mean DCIVA from baseline with pilocarpine as compared to the placebo (MD = 3.50 [95% CI = 2.72–4.28], I^2 = 37%, $P < 0.01$) [Figure 3].

Safety outcomes

The safety profile of pilocarpine was evaluated including 3 RCTs with a total of 980 participants (489 in the pilocarpine group and 491 in the placebo group). It was evaluated on the basis of AEs occurring in participants during the treatment (Virgo trial-average 15 days)[19] and within a month after completion (up to 60 days) of the trial (Gemini 1 and 2) [Table 4].[17,18]

Total adverse event

Pooled analysis of TAE from the three studies showed a significantly increased risk of TAE with pilocarpine as compared to placebo (RR = 1.97 [95% CI = 1.32–2.96], I^2 = 51%, $P < 0.01$) [Figure 4].

Headache

Headache was the most common AE seen in the pilocarpine group, reported in 13.49% of participants (vs. 6.12% in the vehicle group).[17-19] Eighty-seven percent of participants with headaches in the Gemini 1 trial had mild headaches (transient and easily tolerated by the subject) that did not require treatment.[17] On pooled analysis of data from three RCTs, a significantly increased risk of headache with pilocarpine was observed as compared to placebo (RR = 2.17 [95% CI = 1.29–3.65], I^2 = 20%, $P < 0.01$) [Figure 5].

Ocular adverse events

The pooled results of three trials showed a significantly increased risk of ocular AEs with pilocarpine as compared to placebo (RR = 2.19 [95% CI = 1.34–3.59], I^2 = 45%, $P < 0.01$) [Figure 6].

Conjunctival hyperemia, blurring of vision, and eye pain were reported by 5.06%, 4.53%, and 4.26% of the pooled the

Table 1: Study characteristics

Study identifier	Type of study	Study group	Sample size - intervention/ control	Intervention/ comparator	Outcome measure
Gemini 1[17]	RCT	Presbyopia 40–55 years	323-163/160	Pilocarpine hydrochloride ophthalmic solution 1.25% in each eye, once daily, for up to 30 days/vehicle	Participants gaining ≥3 in mesopic, high-contrast, binocular DCNVA at day 30, hour 0.25, 3, 6, 8, 10 Change from baseline mesopic, binocular DCNVA letters at day 30, hour 0.25 and 0.5 Proportion of participants achieving ≥20/40 in photopic, binocular, DCNVA at day 30, hour 1 and 3 Change from baseline photopic, high contrast, binocular DCIVA letters at day 30, hour 3 Mean change in mesopic NVPTQ satisfaction score, PICQ coping score, PICQ impact score, mesopic NVPTQ performance score, from baseline at day 30, hour 3
Gemini 2[18]	RCT	Presbyopia 40–55 years	427-212/215	Pilocarpine hydrochloride ophthalmic solution 1.25% in each eye, once daily, for up to 30 days/vehicle	Participants gaining ≥3 lines in mesopic, binocular DCNVA, without losing >5 letters of binocular CDVA with the same refractive correction at day 30, hour 3 Participants gaining ≥3 lines in mesopic, binocular DCNVA at day 30, hour 6, 8, 10 Change from baseline mesopic, high contrast, binocular DCNVA letters at day 30, hours 0.25 and 0.5 Participants achieving 20/40 or better in photopic, binocular, DCNVA at day 30, hours 1 and 3 Change from baseline photopic, binocular DCIVA letters at day 30, hour 3 Mean change in mesopic NVPTQ satisfaction score, PICQ coping score, PICQ impact score, mesopic NVPTQ performance score, from baseline at day 30, hour 3
Virgo[19]	RCT	Presbyopia 40–55 years	230-114/116	Pilocarpine hydrochloride ophthalmic solution 1.25%, one drop bilaterally (in each eye), twice daily, with a gap of 6 h between both doses, for up to 14 days	Proportion of subjects gaining ≥3 lines in mesopic, binocular DCNVA with no >5- letter loss in mesopic CDVA with the same refractive correction at day 14, hour 9 (3 h after the second dose) Participants gaining ≥3 lines in photopic, binocular DCNVA with no >5-letter loss in photopic CDVA with the same refractive correction Participants gaining ≥2 lines in mesopic, binocular DCNVA with no >5-letter loss in mesopic CDVA with the same refractive correction Participants achieving ≥20/40 or mesopic, binocular DCNVA with no >5-letter loss in mesopic CDVA with the same refractive correction
Al-Khersan *et al*.[20]	Case report	Presbyopia patients	2 patients	Pilocarpine 1.25% eye drop - once daily	Reported RD
Amarikwa *et al*.[21]	Case report	Presbyopia patients	1 patient	Pilocarpine 1.25% eye drop - once daily	Reported vitreofoveal traction
Eton *et al*.[22]	Case report	Presbyopia patients	2 patients	Pilocarpine 1.25% eye drop - once daily	Reported RD

DCNVA: Distance-corrected near visual acuity, DCIVA: Distance-corrected intermediate visual acuity, CDVA: Corrected distance visual acuity, NVPTQ: Near Vision Presbyopia Task-Based Questionnaire, PICQ: Presbyopia Impact and Coping Questionnaire, RCT: Randomized control trial, RD: Retinal detachment

Gemini 1 and 2 trial participants, respectively, in the pilocarpine group (compared to 4.01%, 0.80%, and 1.6% in the vehicle group).[17,19] Ocular irritation was reported by 6.14% of Virgo trial participants (compared to 0% in the vehicle group)[19] and 2.5% of the Gemini 1 trial participants in the pilocarpine group (compared to 0.6% in the vehicle group).[17] No mortality was reported in either of the treatment groups in the included three trials. Likewise, there were no life- or vision-threatening serious AEs reported among the participants in the pilocarpine group.

The three case reports published on the adverse effects of using pilocarpine 1.25% topical drop included 5 patients. Among them, one patient was in their 70s, two were in their 60s, and two were in their 40s.[20-22] Eton *et al*. reported, two myopic pseudophakic patients with a history of refractive surgery (radial keratotomy and LASIK) who developed unilateral retinal detachment (RD) within 10 days of starting pilocarpine 1.25% eye drop for presbyopia management. One of them had a history of RD surgery.[22] In Al-Khersan's report, one of the patients who developed bilateral RD was emmetrope, with no prior retinal degeneration, had unilateral pseudophakia, and reported onset of flashes and floaters 3 days after starting pilocarpine 1.25% eye drop. The other patient was myopic with prior cobblestone

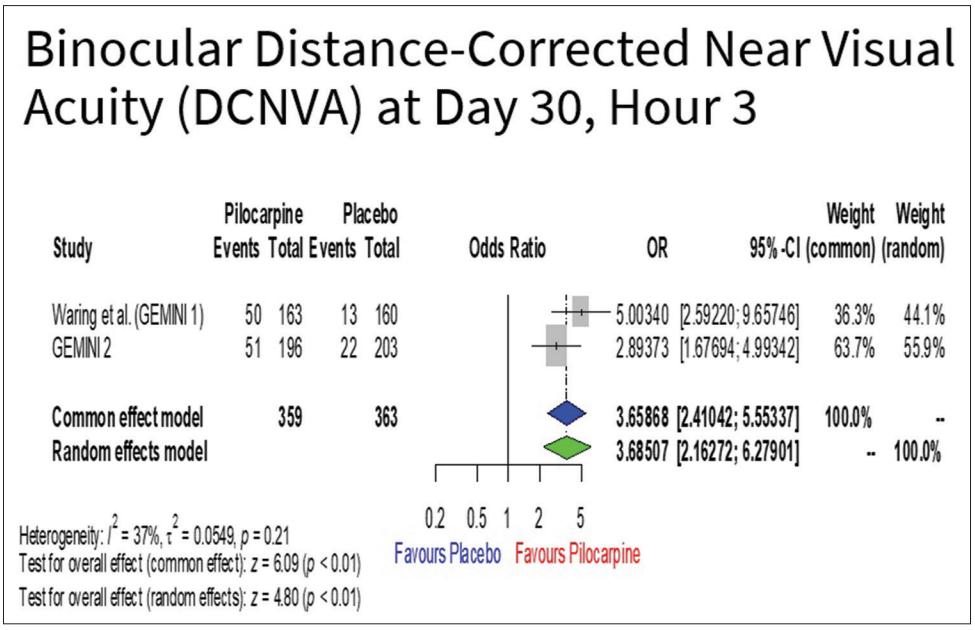

Figure 2: Forest plot for distance-corrected near visual acuity

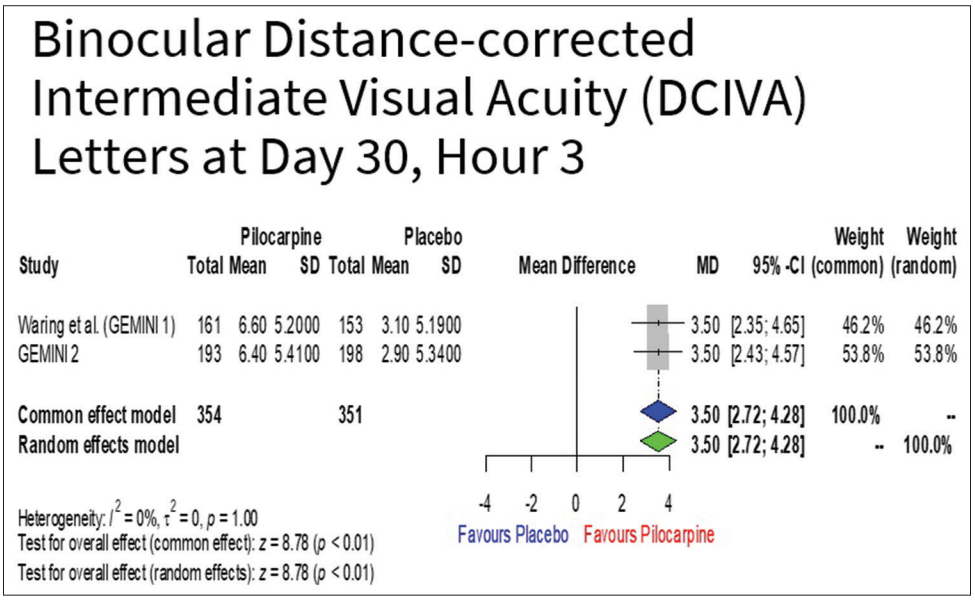

Figure 3: Forest plot for distance-corrected intermediate visual acuity

Table 2: Demographic profile of study group

Demographic parameters	Number (%)
Total number	980–489 in pilocarpine group, 491 in vehicle group
Mean age (years)	49.8±3.5
Male, *n* (%)	313 (31.93)
Female, *n* (%)	667 (68.07)
White race, *n* (%)	830 (84.69)
Nonwhite race, *n* (%)	150 (15.31)

retinal degeneration and presented with RD after 5 weeks of starting pilocarpine 1.25% drops.[20] Amarikwa *et al*. reported the development of vitreomacular traction immediately following the first administration of pilocarpine 1.25% drop.[21]

Quality assessment

Quality assessment of RCTs was done with the Cochrane ROB tool version 2 and all the three RCTs included in this review presented low ROB [Figure 7].

Discussion

Topical muscarinic agents such as pilocarpine, carbachol, and physostigmine help in the treatment of presbyopia by enhancing accommodation and depth of focus by contracting the ciliary and iris sphincter muscles. Pilocarpine causes mild ciliary

Table 3: Improvement in distance-corrected near/intermediate visual acuity

Clinical trial	Gemini 1			Gemini 2			Virgo		
	Pilocarpine 1.25%	Vehicle	*P*	Pilocarpine 1.25%	Vehicle	*P*	Pilocarpine 1.25%	Vehicle	*P*
Gain ≥3 line in mesopic DCNVA at day 14 - hours 3 after 2nd dose	Not applicable			Not applicable			35.1, *n*=116	7.8, *n*=114	<0.0001
Gain ≥3 line in mesopic DCNVA at day 30 - hours 3	30.7, *n*=163	8.1, *n*=160	<0.0001	26, *n*=196	10.8, *n*=203	<0.0001	Not applicable		
Change from baseline photopic, high contrast, binocular DCIVA letters at day 30, hour 3 - least squares mean±SE - numbers read correctly, *n*	6.6±0.41, *n*=161	3.1±0.42, *n*=153	0.011	6.4±0.39, *n*=193	2.9±0.38, *n*=198	<0.0001	Not applicable		

DCNVA: Distance-corrected near visual acuity, DCIVA: Distance-corrected intermediate visual acuity, n: Number of participants, SE: Standard error

Table 4: Adverse events

RCT	Gemini 1		Gemini 2		Virgo	
	Pilocarpine 1.25% group - 163, *n* (%)	Vehicle group - 159, *n* (%)	Pilocarpine 1.25% group - 212, *n* (%)	Vehicle group - 215, *n* (%)	Pilocarpine 1.25% group - 114, *n* (%)	Vehicle group - 116, *n* (%)
Headache	23 (14.11)	15 (9.43)	33 (15.57)	11 (5.12)	10 (8.77)	4 (3.45)
Blurring of vision	4 (2.5)	1 (0.6)	13 (6.13)	1 (0.47)		
Conjunctival hyperemia	4 (2.5)	4 (2.5)	15 (7.08)	11 (5.12)		
Eye irritation	4 (2.5)	1 (0.6)			114 (6.14)	0
Eye pain	4 (2.5)	1 (0.6)	12 (5.66)	3 (1.40)		

RCT: Randomized control trial

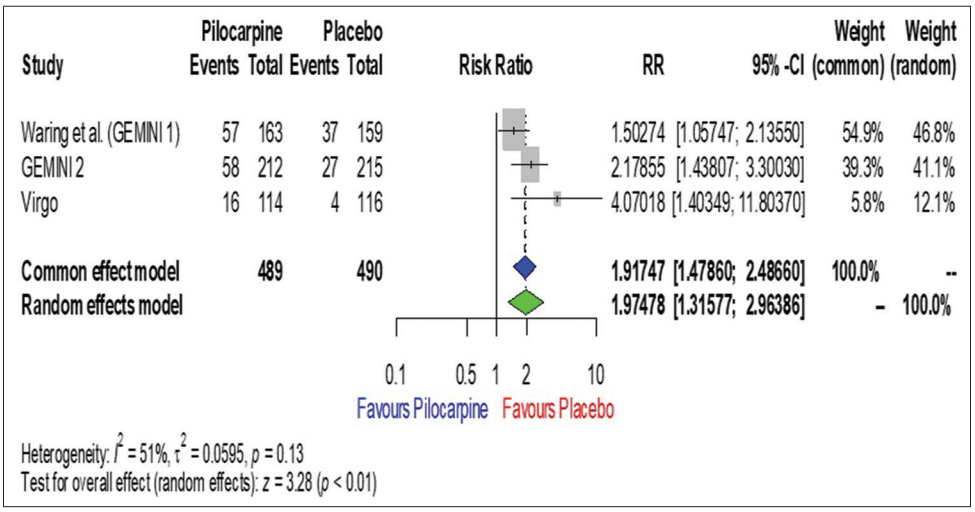

Figure 4: Forest plot for total adverse event

muscle contraction and dynamic pupil modulation, which together improve near vision without significantly impairing distance vision.[23] It is one of the most widely experimented pharmacotherapies for presbyopia correction. Different concentrations and combinations of topical pilocarpine have been evaluated in *in vitro* and *in vivo* studies to achieve its therapeutic benefit in treating presbyopia while avoiding AE associated with its use.[24-27] The concentration of 1.25% of pilocarpine for presbyopia treatment has come up on the basis of efficacy and safety of results of Phase I and II clinical trials using it in concentrations of 0.5%, 1%, and 1.5%.[23,28] A polynomial regression model based on the dose–response curve determined that the optimal concentration range for pilocarpine would fall between 1.16% and 1.32%. Based on efficacy, ocular adverse effects, and the properties of dedicated and optimized vehicles, a concentration of pilocarpine 1.25% has been found suitable for presbyopia treatment, and at present, it is the only FDA-approved topical drop for presbyopia correction.[7]

Improvement in distance-corrected near visual acuity

In each of the 3 RCTs, the use of pilocarpine leads to gain of 3 or more lines of DCNVA in about one-third

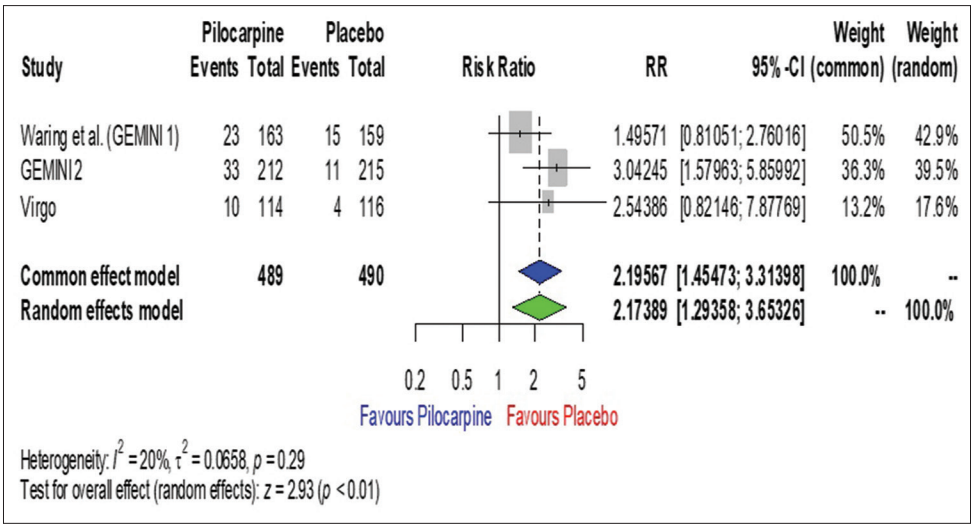

Figure 5: Forest plot for headache

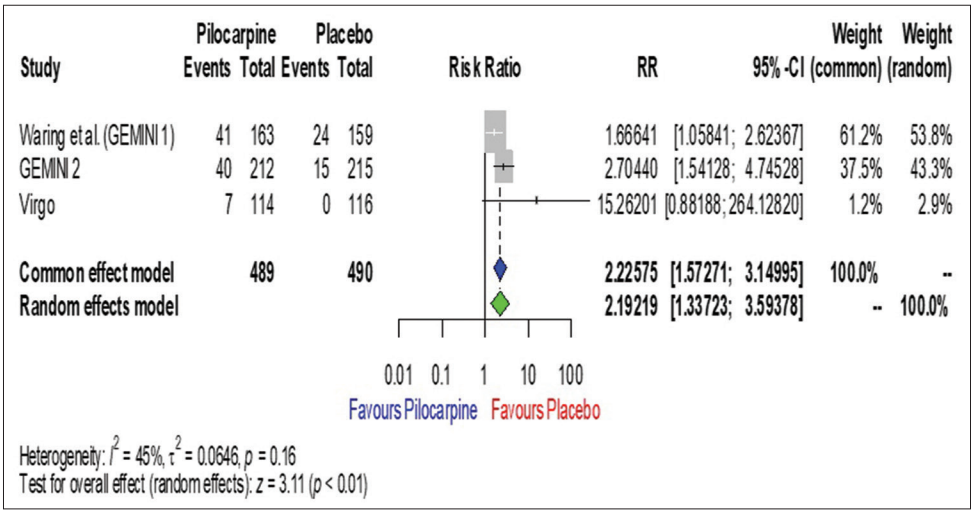

Figure 6: Forest plot for ocular adverse event

of the included participants. It was significantly high in comparison to the control group.[17-19] The improvement in DCNVA was measured on day 30 at different time durations after using pilocarpine 1.25% eye drop in the Gemini 1 and 2 trials. A significant proportion of participants in the pilocarpine group reported improvement in DCNVA 15 min after drop application, showing an early onset of action ($P < 0.011$ in the Gemini 1 trial and $P < 0.0001$ in the Gemini 2).[17,18] In the Gemini 1 trial, the peak efficacy of pilocarpine was seen at 1 h after application.[17] In a pooled data analysis of the Gemini 1 and 2 trial, the percentage of participants reporting ≥ 3-line of DCNVA was significantly greater in pilocarpine 1.25% users at 0.25 h ($P \leq 0.0018$), 0.5 h ($P < 0.0001$), 1 h ($P < 0.0001$), 3 h ($P < 0.0001$), and 6 h ($P \leq 0.0018$) as compared to placebo.[1] At h 8 and beyond, the difference between the two groups was not significant. The subjective assessment of the efficacy of pilocarpine drop in presbyopia patients was also a part of the Gemini 1 and 2 trials. The mesopic Near Vision Presbyopia Task-based Questionnaire performance score and Presbyopia Impact and Coping Questionnaire Coping Score were used to assess the subjective response of participants to treatment and it was significantly in favor of the pilocarpine group at hour 3 on day 30. These questionnaires were based on difficulty and the related coping mechanism in performing near work.[17,18] As compared to participants who received a vehicle, this demonstrates improved near-vision reading ability and satisfaction, as well as a clinically significant decrease in the usage of presbyopia coping mechanisms.

Improvement in distance-corrected intermediate visual acuity

The pooled data analysis of the Gemini 1 and 2 revealed significantly better results in the pilocarpine group than the vehicle group at various hours on day 30 in terms of least squares mean change from baseline in photopic DCIVA (h 1 [$P < 0.0001$], h 3 [$P < 0.0001$], h 6 [$P < 0.0001$], h 8 [$P = 0.0001$], and h 10 [$P < 0.0001$]).[29]

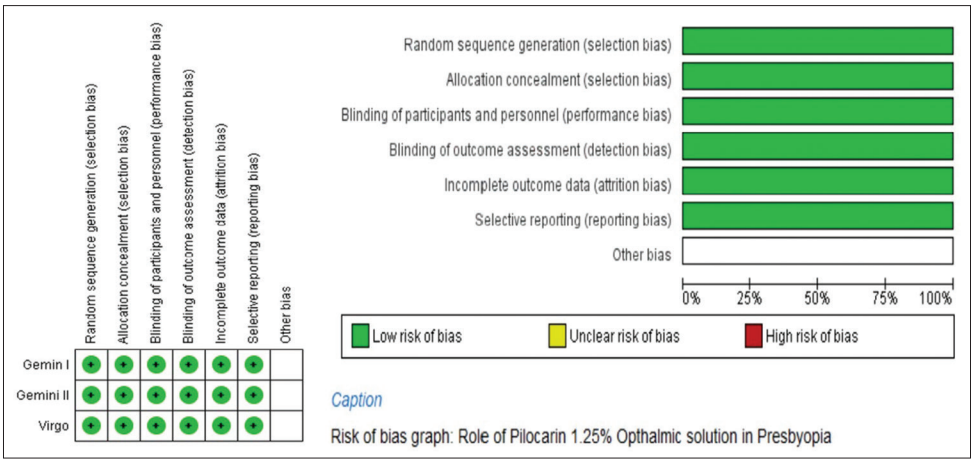

Figure 7: Risk of bias assessment

Adverse events

Patients on topical pilocarpine can have AEs such as blurring of vision, visual field constriction, night vision loss, RD, headache, and brow ache.[30,31] Headache is one the known AE of topical pilocarpine.[32,33] With commercially available 2% pilocarpine preparation, the incidence of headache has been reported as high as 24%.[34] With the use of pilocarpine 1.25% also, the most common AE was headache (13.49%), which was mild in nature and none of the patients discontinued the treatment due to it.[17] In the study by Hartenbaum *et al*., conjunctival hyperemia, blurring of vision, ocular irritation, and eye pain were complaints of 13.2%, 14.2%, 11.2%, and 7.1% of pilocarpine 2% drop users, respectively.[35] The initial *in vitro* study and pilot study have reported lesser ocular discomfort, visual blurring, and AEs with the optimized formulation of pilocarpine as compared to the generic pilocarpine preparation.[28] This better tolerability may be attributed to lesser dosing and dedicated proprietary vehicle that reaches the ocular surface pH within 1 min, increasing the ionized portion of pilocarpine on the ocular surface, thereby increasing membrane transmissibility, drug bioavailability, enhanced duration of action, and improved aqueous dynamics.[36] If we compare these AEs of pilocarpine 1.25% with another patented pharmacotherapy for presbyopia, (Benozzi Method; US 8.524.758 B2-EP1.938.839 B1), which is a combination of pilocarpine 1% and diclofenac 0.1%, 26% of participants reported dimness of vision, followed by 12.9% headaches, and 9.3% sensations of ocular surface burning with this combination. The purpose of adding diclofenac with pilocarpine was to primarily enhance visual performance across various distances by decreasing the intensity of the contraction of the pupil and the ciliary muscle, allowing the lens to change shape and position, and to get the benefit of anti-inflammatory properties of diclofenac.[37]

There are several case reports on the association between pilocarpine and retinal complications, and in a questionnaire-based survey, 58.4% of 101 retinal specialists agreed that RD and the use of miotics are associated.[31] The ciliary body contracting and pulling the posterior lens surface and vitreous base forward causing traction at localized sites of firm vitreoretinal attachment or aggravate preexisting foci of vitreoretinal traction is the suggested mechanism for the development of retinal complication. For every diopter of accommodation, the ora serrata and underlying choroid move forward with contraction of the ciliary body muscles by around 0.05 mm.[38] Pape and Forbes reported a case series of RD in 34 eyes of 31 patients on topical miotics. Although they did not attribute a specific causal role to any particular miotic in individual cases, they advised thorough retinal evaluation before their application.[39] In case reports of our review, where RD was documented in 5 eyes of 4 pilocarpine 1.25% users, 3 of the eyes had myopia, 3 had pseudophakia, and 2 had undergone refractive surgery.[20-22] Similar to the report by Amarikwa *et al*. where vitreomacular traction developed immediately after the first administration of pilocarpine 1.25% drop, Walker and Alvarez reported acute-onset vitreofoveal traction with a single drop of 2% pilocarpine when it was used for dilatation reversal in a patient with no preexisting retinal pathology.[21,40] Available literature shows miotic treatment-related posterior-segment complications can manifest anytime between the first drop use to 2 months of treatment.[38] None of the patients in the 3 RCTs of this review developed any retinal complications. The study population of these RCTs did not include any participants who had myopia >4 D (77% participants of the Gemini 1 trial were emmetropes)[17], had undergone cataract or any other intraocular surgery, or were older than 55 years. Participants who had undergone LASIK or PRK surgery were included and pilocarpine was superior to vehicle in this group of patients also.[17-19,41]

Gap in the available evidence

One of the most important limitations of the currently available literature on the role of pilocarpine 1.25% eye drop in presbyopia treatment is the lack of an adequate number of RCTs. At the time of FDA approval of once daily dose of pilocarpine 1.25% for presbyopia treatment, results of only 2 RCTs (Gemini 1 and 2) were available.[17,18] The FDA approval

of twice daily dose of pilocarpine 1.25% for presbyopia is based on the results of the Virgo trial.[8,19] In each of the three currently available RCTs, participants who had an enhanced risk of developing AEs due to pilocarpine 1.25% were not a part of this study.[17-19] The study group did not include any participants who had undergone cataract surgery or any intraocular surgery in the past. Any participants with severe dry eye, glaucoma/ocular hypertension, narrow iridocorneal angles, cornea/iris abnormality, lens opacity, using any other topical ophthalmic medications, or any other uncontrolled systemic disease were not a part of the study group. The study group did not have participants more than 55 years of age. As the general presbyope population differs from the research group in many aspects, future trials are required having a broader inclusion criterion in terms of age and associated comorbidities. Subjects of presbyopia age group are prone to develop many concurrent ocular disorders such as dry eye and glaucoma and require treatment for them. Efficacy of pilocarpine drop for presbyopia correction needs to be evaluated with concurrent use of other topical medications. With declining accommodation in aging individuals, the response to a fixed dosing schedule may vary in different age groups. In the Gemini 1 and 2, the pilocarpine 1.25% drop was used once daily and significant improvement of ≥3 lines (FDA accepted significant clinical improvement)[42] was reported for the next 6 h. Hence, the once daily dose was not sufficient to have clinically significant improvement of vision throughout the day.[17,18] Available literature has evidence of plethora of complications, including RD with pilocarpine use, in different concentrations, in different formulations,[43] and at different durations. The FDA label of pilocarpine 1.25% drop does talk about rare cases of RD with miotics in predisposed individuals and those with retinal diseases. It also mentions risks of vitreous detachment, vitreomacular traction, and retinal tear.[44] It advises patients to go for urgent ophthalmic consultation in cases of acute vision loss. This makes it mandatory to do a thorough posterior segment evaluation before starting this drop.[45] As at present, we have the follow-up data of maximum of 60 days with pilocarpine 1.25%, we need RCTs with longer follow-up duration. The FDA label also advises patients to be cautious during night driving and during other activities in dim illumination because miotics may result in accommodative spasms.[45] Hence, the effect of pilocarpine 1.25% needs to be evaluated during nighttime in personnel involved in active driving. Although a clinical trial is underway to assess the same, the results are not yet available.[46] Likewise, it is necessary to determine the impact on pupil size and the resultant alterations in contrast sensitivity of the optical system before considering its broad clinical application. The efficacy of pilocarpine 1.25% eye drop needs to be compared with conventional presbyopia correction methods such as glasses in terms of clarity of vision and comfort.

Based on the available evidence, the use of topical pilocarpine 1.25% for presbyopia correction has been shown to be significantly effective in improving the vision of presbyopic patients, with minimal reported AEs. However, the use of pilocarpine in patients having a wider range of refractive errors, patients undergone cataract surgery, and other comorbidities needs to be explored along with adequate dosing, and effectiveness and safety in the geriatric population. A clear word of caution for individuals who are more prone to develop these posterior segment complications can help in creating awareness toward possible AEs. The choice would be made simpler for patients and medical professionals by conducting comparative studies on pilocarpine topical drops and alternative presbyopia correction techniques such as spectacles and contact lenses, with outcome measures such as visual acuity, contrast sensitivity, and patient satisfaction.

The result of the current review is based on three initial RCTs on the novel use of pilocarpine for presbyopia management which has established a reference point for future studies with larger sample sizes, diverse presbyopic age groups, and associated comorbidities and extended follow-up periods.

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Conflicts of interest
There are no conflicts of interest.

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