Original Article

Efficacy and safety of pilocarpine as a secretagogue versus artificial tears in the management of dry eye disease

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ABSTRACT

Background: Dry eye disease (DED) is a common multifactorial ocular surface disorder that substantially impairs quality of life and remains among the leading reasons for ophthalmic consultations worldwide. We aimed to compare the efficacy and safety of oral pilocarpine versus artificial tears (AT) in the treatment of DED.

Methods: This randomized clinical trial study enrolled patients with DED, randomly allocated to a pilocarpine group receiving 5 mg pilocarpine hydrochloride tablets four times daily (20 mg/day) or an AT group receiving 0.2% sodium hyaluronate eye drops four times daily, for eight weeks. Primary outcomes were changes in Dry Eye Quality of Life Score (DEQS), tear film breakup time (TBUT), and Schirmer's test after treatment. Secondary outcomes were incidence of adverse events like brow ache, sweating, nausea, headache, diarrhea, and allergic conjunctivitis (AC).

Results: Enrolment comprised 120 patients, randomly assigned to the Pilocarpine group (n = 60) or the AT group (n = 60), with comparable mean age and sex distribution between groups (both $P > 0.05$). Both groups demonstrated significant post-treatment improvements in DEQS, TBUT, and Schirmer's test as opposed to baseline (all $P < 0.001$). The AT group showed a significantly diminished mean (standard deviation [SD]) DEQS (12.1 [2.7] vs. 21.9 [8.4]; $P < 0.001$) and longer mean (SD) TBUT (11.8 [1.4] s vs. 9.8 [1.8] s; $P < 0.05$) than the pilocarpine group, while Schirmer's test results were comparable ($P > 0.05$). Adverse events were significantly more frequent in the pilocarpine group, with sweating (n = 38, 63%), brow ache (n = 17, 28%), and nausea (n = 15, 25%) occurring exclusively in pilocarpine-treated patients (all $P < 0.05$); conversely, AC was reported only in the AT group (n = 8, 13%) but did not differ significantly between groups ($P > 0.05$).

Conclusions: Both pilocarpine and AT produced significant improvements in DED symptoms and objective clinical parameters. However, AT demonstrated superior efficacy in enhancing tear film stability and reducing symptom scores, with a better safety profile. Pilocarpine may still have a role in severe or refractory cases requiring enhanced tear secretion but should be prescribed cautiously due to its systemic cholinergic adverse events.

KEYWORDS

secretogogue, pilocarpine hydrochloride, artificial tear, lubricant eye drop, dry eye disease, intervention study, clinical trial

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INTRODUCTION

Dry eye disease (DED) is a common and multifactorial disorder of the ocular surface that exerts a profound influence on patients' quality of life (QoL) and represents one of the most common causes of ophthalmic consultations [1, 2]. It manifests through symptoms like ocular dryness, foreign body sensation, burning, pain, and blurred vision, leading to considerable discomfort and functional impairment in daily activities [3]. Epidemiological studies report that DED affects approximately 5–35% of the general population, with a higher prevalence among females and a peak incidence around age 60, when rates may reach up to 70% [4]. Beyond the general population, elderly individuals and those with autoimmune conditions, particularly Sjogren's syndrome, are disproportionately affected due to impaired lacrimal gland function and reduced tear secretion [5].

The tear film, essential for maintaining ocular surface homeostasis and visual clarity, comprises three integral layers—mucin, aqueous, and lipid. Disruption in any of these layers or in the glands responsible for their secretion contributes to DED pathogenesis [6]. Reliable diagnosis of DED depends on both subjective and objective evaluations. The ocular surface disease index provides a validated measure of symptom burden and its effect on daily life [7], while diagnostic parameters like tear film break-up time (TBUT) and tear osmolarity remain critical. A TBUT < 10 s reflects tear film instability, whereas osmolarity ≥ 308 mOsm/L or an interocular difference ≥ 8 mOsm/L indicates the presence of DED [8].

Artificial tears (AT) are widely recognized as the first-line treatment for DED, yet their therapeutic benefit may be insufficient in moderate-to-severe cases [9]. Secretagogues like pilocarpine, which enhance lacrimal secretion through muscarinic receptor stimulation, have emerged as potential alternatives or adjuncts [10, 11]. Owing to its capacity to increase tear production, pilocarpine may offer advantages for patients unresponsive to AT alone, particularly those with Sjogren's syndrome [12, 13]. Nonetheless, data comparing the efficacy and safety of pilocarpine and AT in DED remain limited [14-17].

This randomized clinical trial was undertaken to compare the efficacy and safety of pilocarpine versus AT in patients with DED. We hypothesized that pilocarpine would yield greater improvements in tear secretion and symptom relief than AT, albeit with a higher incidence of adverse events [17]. Primary endpoints were changes in Dry Eye QoL Score (DEQS), TBUT, and Schirmer's test, with treatment-emergent adverse events assessed as secondary outcomes. By directly comparing a pharmacologic secretagogue with conventional tear supplementation, this study addresses an important gap in current DED management and provides evidence to inform individualized treatment strategies for patients with moderate-to-severe DED who have failed to respond adequately to standard therapy.

METHODS

This prospective, randomized, controlled clinical trial was conducted across multiple tertiary ophthalmology centers in Egypt, including Benha University, Al-Azhar University (Cairo and Damietta), and Aswan University. Recruitment and data collection were carried out between January and May 2025. A total of 120 participants, aged 40 to 70 years, who met the predefined diagnostic criteria for DED were enrolled. Approval for the research protocol was obtained from the Institutional Review Board of the Faculty of Medicine, Al-Azhar University, Damietta (Approval Code: DFM-IRB 00012367-24-12-005). All procedures conformed with the ethical principles stated in the Declaration of Helsinki. The study was retrospectively registered at ClinicalTrials.gov (Identifier: NCT06752278). Written informed consent was secured from every participant prior to inclusion. Personal identifiers were removed from all records to maintain confidentiality, and data were stored securely on password-protected digital systems accessible only to authorized personnel. Participants were fully informed of their right to withdraw from participation at any stage without any consequences for their clinical care. Any adverse or unexpected events were promptly documented and reported to the ethics committee in accordance with institutional guidelines.

Inclusion criteria required a DEQS > 12, a TBUT ≤ 10 s, and a Schirmer test result ≤ 10 mm, confirming decreased tear secretion. Exclusion criteria were Sjogren's syndrome, ocular surgery within the preceding six months, active ocular infection, significant ocular surface pathology such as keratitis or pterygium, recent use of topical or systemic anti-inflammatory agents that could affect tear production, known hypersensitivity to pilocarpine or sodium hyaluronate, and refusal to participate.

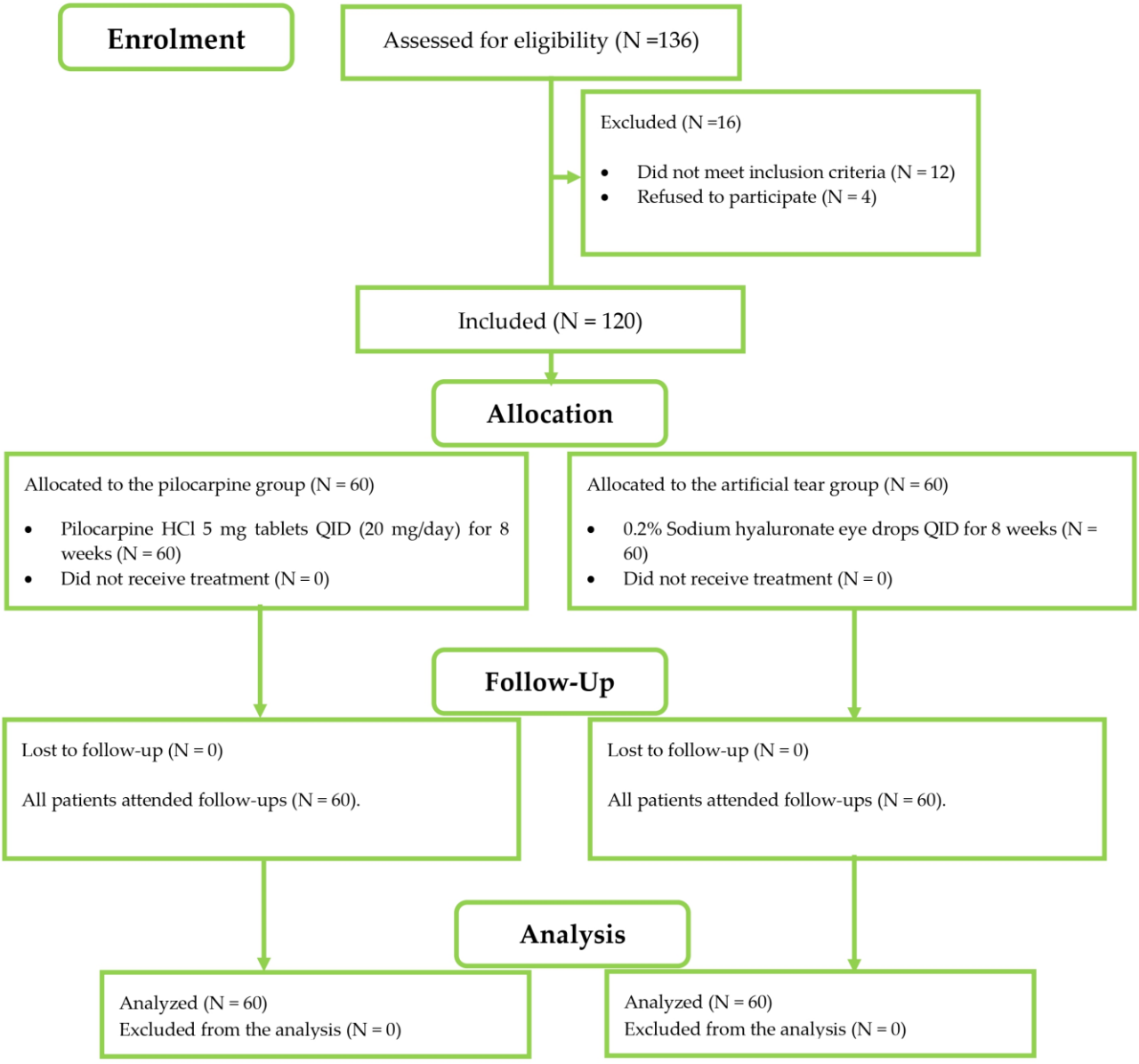

Figure 1. CONSORT flow diagram for study participants' allocation to the pilocarpine or artificial tears treatment group. Abbreviations: Pilocarpine HCl, pilocarpine hydrochloride; mg, milligrams; QID, four times daily; N, number of patients.

Eligible participants were randomly allocated in a 1:1 ratio to either the pilocarpine group (n = 60) or the AT group (n = 60) using a computer-generated randomization sequence to minimize allocation bias. At baseline, all participants underwent comprehensive ophthalmic examination, including slit-lamp biomicroscopy (Carl Zeiss Meditec AG, Jena, Germany), to confirm eligibility and establish pre-treatment values.

The pilocarpine group received oral pilocarpine hydrochloride tablets (Salagen®, Novartis, Basel, Switzerland), 5 mg four times daily (total daily dose: 20 mg) [18], for eight consecutive weeks. The AT group was instructed to instill 0.2% sodium hyaluronate ophthalmic solution containing benzalkonium chloride (Hyfresh, Jamjoom Pharma, Jeddah, Saudi Arabia) four times daily (QID) over the same period. Adherence to treatment and occurrence of adverse events were closely monitored. Follow-up assessments through the DEQS, TBUT, and Schirmer test were conducted at baseline and at the 8-week visit by experienced ophthalmologists who remained blinded to treatment allocation to ensure objectivity. Symptom scores and clinical findings were recorded using validated instruments and calibrated devices. All collected data were managed within a secure electronic database restricted to authorized personnel, thereby ensuring confidentiality and integrity throughout the research process.

Outcome measures: Primary endpoints were changes in subjective discomfort, tear film stability, and tear production, assessed through the DEQS, TBUT, and Schirmer test, respectively. These evaluations were performed at baseline and after eight weeks of treatment. The DEQS questionnaire provided a standardized measure of symptom intensity and its impact on QoL [19]. TBUT was assessed by applying fluorescein dye and measuring the time interval between a complete blink and the first appearance of a dry spot on the cornea [20]. The Schirmer test was conducted without anesthesia, and the wetted length of the filter paper strip was measured after five minutes to quantify aqueous tear secretion [20].

Safety Assessment: Secondary endpoints focused on frequency and nature of adverse events documented during the treatment phase. Safety assessments were performed throughout the study period to ensure continuous monitoring of treatment-related adverse events. In addition to the scheduled evaluation at the 8-week visit, interim safety monitoring was conducted at weeks 2 and 4 through direct clinical assessment and structured patient interviews. Participants were also instructed to report any new or worsening symptoms at any time between visits via direct contact with the study team. All adverse events were recorded at each scheduled and unscheduled contact point and were evaluated in terms of onset, severity, duration, and potential relationship to the study medication.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean (standard deviation [SD]), and categorical variables as frequencies and percentages. Normality of continuous data was assessed using the Shapiro-Wilk test, together with visual inspection of histograms and Q–Q plots. Homogeneity of variance was evaluated using Levene's test prior to the independent-samples Student's *t*-test. Between-group comparisons of continuous outcomes were performed using independent-samples *t*-tests. Given the randomized design and comparable baseline values between groups, this approach was considered appropriate. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed, and a P-value < 0.05 was considered statistically significant. Analyses were conducted according to the intention-to-treat (ITT) principle, including all randomized participants. As no missing outcome data were observed, no imputation procedures were required.

RESULTS

A total of 136 patients were screened for eligibility; 12 did not meet the inclusion criteria and 4 declined participations. Consequently, 120 patients were enrolled and randomly allocated to either the pilocarpine group (n = 60) or the AT group (n = 60). All participants adhered to the study protocol, with no losses to follow-up reported. The final analysis thus included all randomized subjects according to the ITT principle (Figure 1).

Baseline demographic characteristics were comparable between groups, with no significant differences in age or sex distribution (both $P > 0.05$) (Table 1). Mean (SD) age was 54.4 (6.3) years in the pilocarpine group and 51.6 (6.1) years in the AT group. The pilocarpine group comprised 21 males (35%) and 39 females (65%), the AT group 18 males (30%) and 42 females (70%).

Regarding the primary outcomes, within-group analyses demonstrated significant improvements in DEQS, TBUT, and Schirmer's test from baseline to week 8 in both treatment groups (all $P < 0.001$) (Table 2). Baseline values for all three parameters were comparable between groups (all $P > 0.05$). At week 8, the AT group showed significantly greater improvement in symptom burden and tear film stability than the pilocarpine group, as reflected by lower mean (SD) DEQS scores (12.1 [2.7] vs. 21.9 [8.4]; P < 0.001) and longer TBUT (11.8 [1.4] s vs. 9.8 [1.8] s; P < 0.05). In contrast, Schirmer's test values remained comparable between groups at baseline and at week 8 (both $P > 0.05$), despite significant within-group increases following treatment in both groups (both $P < 0.001$).

Regarding secondary outcomes, adverse events were more frequent in the pilocarpine group overall, except for allergic conjunctivitis (Table 3). The incidence of allergic conjunctivitis and headache did not differ significantly between groups, with allergic conjunctivitis reported only in the AT group (8 [13%] vs. 0; $P > 0.05$) and headache occurring in 18 patients (30%) receiving pilocarpine versus 7 (12%) receiving AT ($P > 0.05$). In contrast, brow ache, sweating, and nausea were significantly more frequent with pilocarpine (all $P < 0.05$). Although diarrhea occurred only in the pilocarpine group (11 [18%] vs. 0), the between-group difference was not statistically significant ($P > 0.05$) (Table 3). All adverse events were mild and transient, resolving spontaneously without treatment discontinuation or additional medical intervention.

Table 1. Demographics of study groups

Variable	Pilocarpine Group (n = 60)	Artificial Tears Group (n = 60)	*P*-value
Age (y), Mean ± SD (Range)	54.4 ± 6.3 (43 to 67)	51.6 ± 6.1 (41 to 66)	0.117
Sex (Male/ Female), n (%)	21 (35) / 39 (65)	18 (30) / 42 (70)	0.523

Abbreviations: n, number of participants; %, percentage; y, years; SD, standard deviation.

Table 2. Primary outcomes of study groups

Outcome	Time point	Pilocarpine Group (n = 60)	Artificial Tears Group (n = 60)	*P*-value
DEQS (score), Mean ± SD	**Before treatment**	66.8 ± 27.5	64.1 ± 25.1	0.731
	After treatment	21.9 ± 8.4	12.1 ± 2.7	**< 0.001**
***P*-value vs. baseline**		**< 0.001**	**< 0.001**	
TBUT (s), Mean ± SD	**Before treatment**	4.4 ± 1.5	4.4 ± 1.5	0.958
	After treatment	9.8 ± 1.8	11.8 ± 1.4	**0.003**
***P*-value vs. baseline**		**< 0.001***	**< 0.001**	
Schirmer's test (mm), Mean ± SD	**Before treatment**	4.2 ± 1.1	4.6 ± 1.2	0.259
	After treatment	14.5 ± 1.6	15.2 ± 1.8	0.164
***P*-value vs. baseline**		**< 0.001**	**< 0.001**	

Abbreviations: n, number of participants; DEQS, dry eye quality of life score; SD, standard deviation; TBUT, tear film break-up time; s, seconds; mm, millimeters. Note: *P*-values < 0.05 are shown in bold.

Table 3. Adverse effects of study groups

Adverse Effect, n (%)	Pilocarpine Group (n = 60)	Artificial Tears Group (n = 60)	*P*-value
Allergic Conjunctivitis	0 (0)	8 (13)	0.214
Headache	18 (30)	7 (12)	0.226
Brow Ache	17 (28)	0 (0)	**0.018**
Sweating	38 (63)	0 (0)	**< 0.001**
Nausea	15 (25)	0 (0)	**0.043**
Diarrhea	11 (18)	0 (0)	0.094

Abbreviations: n, number of participants; %, percentage. Note: *P*-values < 0.05 are shown in bold.

DISCUSSION

We investigated the effectiveness and safety of oral pilocarpine as opposed to AT in treating DED, a multifactorial condition that markedly affects patient QoL [1, 2]. Given the complex pathophysiology of DED, optimizing management strategies remains challenging [21, 22]. Pilocarpine, a cholinergic secretagogue that stimulates lacrimal gland activity [10, 11], was compared with AT, which primarily hydrate and stabilize the ocular surface. The main outcomes assessed were DEQS, TBUT, and Schirmer's test, while secondary outcomes involved treatment-related adverse events.

Both treatments produced significant improvements in DEQS, TBUT, and Schirmer's test after eight weeks. However, AT achieved greater enhancement in DEQS and TBUT, reflecting superior symptomatic relief and tear film stabilization compared with pilocarpine. A more pronounced reduction in DEQS score was observed in the AT group, indicating more effective symptom control through restoration of ocular surface hydration and mimicry of natural tear properties [23]. TBUT, serving as a key measure of tear film stability [24], increased significantly in both groups, yet the increase was greater in the AT group, aligning with previous studies confirming AT benefit in both evaporative and aqueous-deficient DED [25, 26].

Schirmer's test values improved significantly from baseline in both groups but remained comparable between groups at baseline and at the end of treatment, indicating that although pilocarpine enhances tear secretion, its effect is not superior to that achieved with AT [27].

Adverse events were more frequent with oral pilocarpine, including sweating (63%), brow ache (28%), and nausea (25%), while these were absent in the AT group. These systemic adverse effects reflect cholinergic overstimulation of exocrine glands [28]. Conversely, allergic conjunctivitis occurred in nine patients (15%) using AT, likely due to preservative sensitivity, particularly to benzalkonium chloride [29].

The superior outcomes of AT in DEQS and TBUT improvement are consistent with Srinivasan et al. [30], who found that polyethylene glycol-based AT enhanced tear film stability and symptom control in aqueous-deficient DED. AT provide rapid relief and minimal systemic involvement, whereas benefits of pilocarpine are constrained by dose-dependent cholinergic adverse events [18, 28]. Similarly, Felberg et al. [31] observed that systemic pilocarpine improved Schirmer's test scores in Sjogren's syndrome but was limited by tolerability issues. Pharmacologically, pilocarpine's muscarinic receptor activation stimulates lacrimal secretion [32], which explains the improved Schirmer scores observed vs. baseline in this study [31, 33]. However, recent meta-analytic evidence questions its Schirmer-enhancing efficacy [34]. The dose-dependent nature of pilocarpine's side effects, particularly sweating, is consistent with Rieke et al. [35], who reported sweating in 29% of patients treated with 5 mg t.i.d. and 68% with 10 mg t.i.d. [28, 35]. This emphasizes the importance of individualized dosing, especially in elderly or systemically vulnerable patients.

Though not statistically significant, the occurrence of AC in the AT group raises concerns about long-term use of preservative-containing formulations. Kahook et al. [36] emphasized that preservatives, particularly benzalkonium chloride, may exacerbate ocular surface damage and should be considered in patients prone to allergies or with chronic DED [36, 37]. Overall, AT remain the first-line treatment for DED, particularly for mild-to-moderate symptoms [38, 39], providing symptom relief with minimal side effects. Pilocarpine may be reserved for refractory cases or severe aqueous deficiency, like in Sjogren's syndrome [40], but careful patient selection and monitoring are warranted due to cholinergic side effects.

Our findings differ from those reported by Tsifetaki et al. [17], who evaluated oral pilocarpine in patients with primary Sjogren's syndrome; they demonstrated superior subjective symptomatic improvement plus greater objective improvement, as measured by the rose bengal test with combined pilocarpine and AT compared with AT only, without significant enhancement in Schirmer's test [17]. In contrast, the present study in non-Sjogren DED showed that although pilocarpine significantly improved DEQS, TBUT, and Schirmer's test from baseline, AT achieved significantly greater improvement in DEQS and TBUT while Schirmer's test remained comparable between groups. Several factors may explain this discrepancy. First, Sjogren's syndrome is characterized by autoimmune lacrimal gland dysfunction with residual secretory tissue potentially responsive to systemic muscarinic stimulation, rendering secretagogues more mechanistically beneficial in this population [18, 41, 42] than in non-Sjogren DED, where evaporative mechanisms and tear-film instability often predominate [43, 44]. Second, participants in the Sjogren trial received a lower pilocarpine dose (10 mg/day) over 12 weeks and concomitant AT [17], whereas our study administered pilocarpine monotherapy at 20 mg/day for eight weeks, potentially altering both efficacy and tolerability profiles. Third, outcome assessment differed substantially between studies; Tsifetaki et al. [17] primarily relied on subjective visual analogue symptom scoring and rose bengal staining, whereas our trial employed DEQS and TBUT, which may differ in capturing tear-film stability and patient-reported functional impairment. These findings suggest that while systemic pilocarpine may confer therapeutic benefit in autoimmune aqueous-deficient DED [17, 18], its relative efficacy appears attenuated in broader non-Sjogren DED populations, in whom conventional tear supplementation may provide superior symptomatic and tear-film stabilization benefits with better tolerability.

Strengths of this study are its randomized controlled design, ITT framework, and comprehensive outcome assessment. Limitations are the modest sample size and relatively short follow-up duration (eight weeks), which may restrict the robustness and generalizability of the findings. Additionally, the multicenter design may introduce inter-center variability in patient recruitment and data collection. The use of preservative-containing AT might also have influenced frequency of adverse events, highlighting the importance of future evaluations using preservative-free formulations. Larger, multicenter, and longer-term trials are warranted to validate these findings. Combining pilocarpine with preservative-free AT may provide synergistic therapeutic benefit while minimizing adverse effects. Individualized dose titration may further optimize pilocarpine tolerability and improve pilocarpine's safety profile. Additional comparative studies between preservative-free AT and pilocarpine in chronic or high-risk DED populations are needed.

CONCLUSIONS

AT demonstrated greater efficacy than pilocarpine in improving DEQS and TBUT in non-Sjogren DED, with fewer adverse events. Pilocarpine remains valuable for enhancing tear secretion in severe or refractory DED but is limited by systemic cholinergic adverse events. These findings support AT as the preferred first-line therapy for mild-to-moderate non-Sjogren DED, whereas pilocarpine may be selectively used in advanced cases. Further studies should focus on optimizing pilocarpine use through individualized dosing and combination regimens to maximize efficacy and minimize adverse events.

ETHICAL DECLARATIONS

Ethical approval: Approval for the research protocol was obtained from the Institutional Review Board of the Faculty of Medicine, Al-Azhar University, Damietta (Approval Code: DFM-IRB 00012367-24-12-005). All procedures conformed with the ethical principles stated in the Declaration of Helsinki. The study was retrospectively registered at ClinicalTrials.gov (Identifier: NCT06752278). Written informed consent was secured from every participant prior to inclusion. Personal identifiers were removed from all records to maintain confidentiality, and data were stored securely on password-protected digital systems accessible only to authorized personnel. Participants were fully informed of their right to withdraw from participation at any stage without any consequences for their clinical care. Any adverse or unexpected events were promptly documented and reported to the ethics committee in accordance with institutional guidelines.

Conflict of interest: None.

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