Research Article Volume 01, Issue No. 01. 2024

The International Medical Journal of Opthalmology

Efficacy and Safety of Lotilaner 0.25% Ophthalmic Solution for Treating Demodex Blepharitis: A Systematic Review

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Article History :
Received date : 2024/07/02
Revised date : 2024/08/22
Accepted date : 2024/09/10
Published date : 2024/10/07

ABSTRACT

Background: Blepharitis is a prevalent ocular disorder characterized by inflammation of the eyelid margins, with *Demodex* mite infestations being a significant contributor. Lotilaner, an FDA-approved antiparasitic from the isoxazoline class, offers a new therapeutic option by selectively targeting *Demodex* mites. **Methods**: A systematic review was conducted following PRISMA guidelines, focusing on studies published between 2014 and 2024. **Results**: Multiple studies demonstrated Lotilaner's effectiveness in reducing *Demodex* mite density and symptoms of blepharitis. Key trials showed that collarette cure rates reached 81.3% by day 43, with mite eradication in 67.9% of patients, compared to placebo groups. These findings consistently highlight Lotilaner's efficacy and favorable safety profile across diverse patient populations. **Conclusion**: Lotilaner 0.25% ophthalmic solution represents a significant advancement in treating *Demodex*-related blepharitis. While promising, further research is needed to confirm its long-term safety and comparative effectiveness against other therapies.

Keywords: blepharitis, Demodex mite, Lotilaner 0.25%

INTRODUCTION

Blepharitis is a highly prevalent ocular disorder characterized by inflammation of the eyelids, particularly affecting the lid margins.[1,2] While it can arise from various causes—including allergic reactions, bacterial infections, and seborrheic dermatitis—one of the most common and significant contributors is infestation by Demodex mites.[3] These microscopic parasites reside in the follicles and sebaceous glands near the base of the eyelashes and can extend into the meibomian glands, leading to both anterior and posterior forms of blepharitis.[4,5] Aging significantly increases susceptibility to Demodex infections, with studies showing that over 80% of individuals above 60 and nearly all individuals over 70 harbor these mites. Additionally, between 42% and 81% of blepharitis cases are associated with concurrent Demodex infestations, highlighting the mite's substantial role in the disease.[6]

Clinically, patients with Demodex blepharitis often experience itching, discomfort, crusting at the eyelid margins, abnormal discharge, and blurred vision.[7,8] Key signs of the condition include cylindrical dandruff (collarettes) at the base of the eyelashes, meibomian gland dysfunction, and eyelid margin inflammation. In severe cases, complications may arise such as recurrent chalazion, corneal vascularization, or opacification.[9] The collarettes, formed by the mites' mechanical, chemical, and bacterial activities, are pathognomonic for Demodex infestation. These lash-cuffing formations consist of undigested material, dead mites, eggs, and keratinized cells.[10]

Diagnosis typically relies on a detailed clinical history, slit-lamp examination, and microscopic confirmation of Demodex mites. However, effective treatment remains a challenge.[11] Historically, multiple treatments—such as mercury oxide ointments, camphorated oil, sulfur-based ointments, and pilocarpine gel—have been proposed, but none have been consistently effective in eradicating the mites or alleviating symptoms. The limited success of these therapies often stems from poor patient tolerance, adverse effects, and lack of long-term compliance, which are critical factors in managing this chronic condition.[12]

Lotilaner, a member of the isoxazoline class of insecticides, represents a breakthrough in the management of Demodex blepharitis. It is the only FDA-approved treatment specifically indicated for this condition. Initially developed for veterinary use in controlling mites, ticks, and fleas in animals, Lotilaner selectively inhibits glutamate- and gamma-aminobutyric acid (GABA)-gated chloride channels in mites, causing paralysis and death of the parasite without affecting mammalian systems. This high specificity makes it a promising antiparasitic agent for human use.[9,11]

In this systematic review, we aim to critically assess the tolerability and efficacy of Lotilaner in managing blepharitis caused by Demodex infestation. We will explore the available evidence on its clinical outcomes, focusing on its ability to reduce parasite load, alleviate symptoms, and improve patient quality of life. Additionally, we will address the safety profile of Lotilaner, examining its side effects and long-term usability. Through this review, we seek to determine whether Lotilaner offers a viable therapeutic solution for patients suffering from Demodex-related blepharitis, filling an unmet need in ocular healthcare.

METHODS

Protocol

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, ensuring a transparent, replicable, and methodologically sound approach. The review's primary goal was to maintain rigor throughout literature search, data extraction, and synthesis processes, minimizing bias and ensuring reliable conclusions.

Criteria for Eligibility

This review focuses on evaluating the efficacy and safety of Lotilaner 0.25% ophthalmic solution in treating *Demodex* blepharitis. It aims to consolidate findings related to treatment outcomes, tolerability, and safety. Inclusion criteria were applied to ensure high-quality, relevant data were analyzed. Eligible studies were:

1. Published between 2014 and 2024,

2. Peer-reviewed and written in English,
3. Focused on Lotilaner or other treatments for *Demodex* blepharitis, highlighting treatment efficacy, safety, and patient outcomes,
4. Included a DOI to confirm authenticity.

Studies such as reviews, editorials, case reports, or duplicate publications were excluded to ensure that only high-quality research contributed to the findings.

Search Strategy

The search strategy was tailored to identify studies relevant to *Demodex* blepharitis. Databases used included PubMed, ScienceDirect, and SagePub, employing keywords such as "Demodex blepharitis," "Lotilaner," and "ocular parasite treatment." Search strategies for each database are outlined below.

Data Retrieval

Each article was initially screened by title and abstract for relevance. Full-text articles were then thoroughly reviewed to ensure they met the inclusion criteria. Articles that did not align with the research objectives were excluded. This rigorous screening process ensured that only the most relevant and high-quality studies were considered for the final evaluation.

The factors assessed in this review included study design, authorship, publication date, geographical region, and methodology. This comprehensive assessment guaranteed that the data utilized were consistent and reliable.

Quality Assessment and Data Synthesis

To ensure robustness, the authors conducted a detailed quality assessment of each included study, focusing on methodological rigor and relevance to the research questions. Studies that passed this assessment underwent in-depth synthesis, with the results summarized and analyzed to identify trends in Lotilaner's efficacy, safety, and patient outcomes. This approach helped minimize bias and strengthen the conclusions drawn.

Table 1. Search strategy

Database	Search Strategy	Hits
PubMed	("Demodex blepharitis" OR "Lotilaner" AND "ocular treatment")	902
ScienceDirect	("Lotilaner" AND "Demodex blepharitis")	78
SagePub	("Demodex blepharitis" AND "treatment outcomes")	63

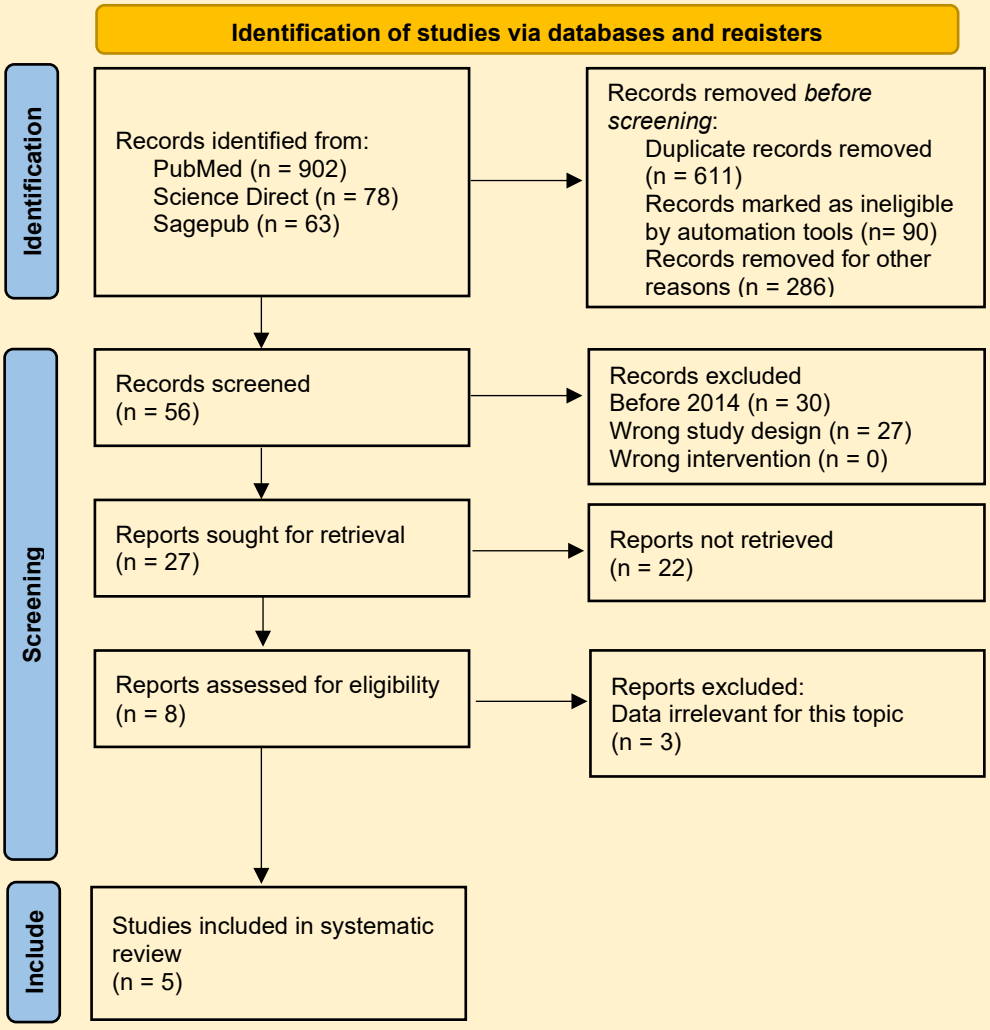

Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	Yeu et al. (2023) Satur n-1	Gonzalez -Salinas et al. (2022)	Gad die et al. (202 3) Satu rn-2	Gonzalez-Salinas et al. (2021)	Yeu et al. (2023)
1. Bias related to temporal precedence					
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation					
Was there a control group?	Yes	Yes	Yes	No	No
3. Bias related to confounding factors					
Were participants included in any comparisons similar?	Yes	Moderate	Yes	No	No
4. Bias related to administration of intervention/exposure					
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes.	Yes	Yes	No	Yes.
5. Bias related to assessment, detection, and measurement of the outcome					
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Yes	Yes	Yes	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	No	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	No	Yes
6. Bias related to participant retention					
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	No	No
7. Statistical conclusion validity					
Was appropriate statistical analysis used?	Yes	Yes	Yes	No	Yes

RESULT

We initiated the investigation by systematically gathering a significant assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected five papers that were considered very pertinent to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our study, we have included a concise summary of the evaluated information in Table 3.

Table 3. The literature included in this study

Yeu et al. (2023) Saturn-1.[12]	USA	Prospective, randomized, controlled, double-masked, phase 2b/3 clinical trial.	421 patients with Demodex blepharitis were randomly assigned.	At day 43, the study group achieved a statistically significantly higher proportion of patients with clinically meaningful collarette cure (81.3% vs. 23.0%; P < 0.0001), complete collarette cure (44.0% vs. 7.4%; P < 0.0001), mite eradication (67.9% vs. 17.6%; P < 0.0001), erythema cure (19.1% vs. 6.9%; P = 0.0001), and composite cure (13.9% vs. 1.0%; P < 0.0001) than the control group. Nearly 92.0% of patients rated the study drop as neutral to very comfortable. All ocular adverse events in the study group were mild, with the most common being instillation site pain.
Gonzalez-Salinas et al. (2022).[13]	Mexico	Phase II, randomized, controlled, double-masked clinical trial.	60 eligible participants with Demodex blepharitis.	The study group showed a statistically significant decrease in collarette grade compared to the control group beginning at Day 14 (p = 0.003) in the upper eyelid and at Day 28 (p = 0.003) in the lower eyelid. Decreases in both lids were maintained through Day 90

				(p < 0.001). At Day 28, mite eradication was achieved in 66.7% and 25.9% of eyes in the study and control group (p = 0.005); at Day 90, these proportions were 68.2% and 18.5% (p = 0.001), respectively. No serious adverse events or clinically significant changes in CDVA and IOP were observed.
Gaddie et al. (2023) Saturn-2.[14]	USA	Prospective, randomized, double-masked, vehicle-controlled, multicenter, phase 3 clinical trial.	412 participants.	At day 43, the study group achieved a statistically significant (P < 0.0001) higher proportion of patients with collarette cure (56.0% vs. 12.5%), clinically meaningful collarette reduction to 10 collarettes or fewer (89.1% vs. 33.0%), mite eradication (51.8% vs. 14.6%), erythema cure (31.1% vs. 9.0%), and composite cure (19.2% vs. 4.0%) than the control group. High compliance with the drop regimen (mean ± standard deviation, 98.7 ± 5.3%) in the study group was observed, and 90.7% of patients found the drops to be neutral to very comfortable.
Gonzalez-Salinas et al. (2021).[15]	Mexico	a single-arm, open-label, Phase 2a treatment study.	Eighteen adults with Demodex blepharitis, defined as >10 collarettes on the upper lid and/or mite density of ≥1.5 mites	Collarette elimination was achieved in 13/18 participants (72.2%) by day 42. Mean collarette grade (upper lid) declined from 3.56 ± 0.17 to 0.28 ± 0.11. Mite eradication was achieved in 14/18 participants (77.8%) by day 42. Mean mite density decreased from 2.63 ± 0.39 to 0.12 ± 0.08 mites/lash.

			per lash (upper and lower), were treated bid for 42 days with the topical lotilaner ophthalmic solution, 0.25%.	Participants reported good tolerability. Adverse events were mild and transient and did not result in treatment discontinuation.
Yeu et al. (2023).[16]	USA	Randomized, controlled, double-masked clinical trial.	54 participants were randomly assigned in a 1:1 ratio to receive either lotilaner ophthalmic solution, 0.25% (study group) or the vehicle (control group) bilaterally	The proportion of participants achieving collarette cure (80.0% vs 15.8%; $p < .001$), mite eradication (73.3% vs 21.1%, $p = .003$) and composite cure (73.3% vs 10.5%, $p < .001$) at Day 42 was statistically significantly higher in the study group than the control group.

DISCUSSION

The studies reviewed provide a comprehensive evaluation of the efficacy and safety of Lotilaner 0.25% ophthalmic solution in the treatment of *Demodex* blepharitis, demonstrating consistent, favorable results across various clinical trials.

The pivotal trial by Yeu et al. (2023), conducted in the USA, was a prospective, randomized, controlled, double-masked trial involving 421 participants. Results showed that by day 43, 81.3% of patients in the study group achieved a clinically significant collarette cure compared to 23.0% in the control

group (P < 0.0001). Additionally, mite eradication was achieved in 67.9% of the study group versus 17.6% in the control group (P < 0.0001). Importantly, the majority of patients rated the treatment as neutral to very comfortable, and adverse events were mild, with instillation site pain being the most commonly reported. This study demonstrates the substantial effectiveness of Lotilaner in reducing both *Demodex* burden and symptoms of blepharitis, while maintaining high patient comfort and safety.[12]

Gonzalez-Salinas et al. (2022), in a phase II randomized, controlled trial in Mexico with 60 participants, reinforced the earlier findings by showing significant reductions in collarette grades from as early as day 14 in the upper eyelid and day 28 in the lower eyelid. By day 90, 68.2% of the study group achieved mite eradication, compared to just 18.5% in the control group (P = 0.001). The lack of serious adverse events further supports the safety of Lotilaner in long-term use. The trial underlined the rapid onset of action and sustained efficacy of Lotilaner in managing *Demodex* blepharitis.[13]

Gaddie et al. (2023) conducted another phase 3 randomized, double-masked, vehicle-controlled trial involving 412 participants in the USA, which confirmed similar results. By day 43, the study group achieved a 56.0% collarette cure rate versus 12.5% in the control group (P < 0.0001), and mite eradication was observed in 51.8% of the study group versus 14.6% in the control group (P < 0.0001). High patient compliance (98.7%) and comfort levels further highlighted Lotilaner's tolerability, making it a viable long-term treatment option.[14]

In a smaller, single-arm, open-label study, Gonzalez-Salinas et al. (2021) demonstrated that Lotilaner achieved collarette elimination in 72.2% of participants and mite eradication in 77.8% by day 42. Though limited by its smaller sample size (n=18), this study showed substantial reductions in collarette grades and mite density, further validating Lotilaner’s efficacy in treating *Demodex* blepharitis.[15]
Lastly, the trial by Yeu et al. (2023) further confirmed that Lotilaner outperformed the vehicle control group in terms of collarette cure (80.0% vs. 15.8%, P < 0.001) and mite eradication (73.3% vs. 21.1%, P = 0.003) at day 42. The high success rates

in the study group, paired with the favorable safety profile, support the broad application of Lotilaner for the treatment of *Demodex* blepharitis.[16]

Across all studies, Lotilaner 0.25% ophthalmic solution demonstrated statistically significant improvements in *Demodex* blepharitis symptoms, collarette elimination, and mite eradication with a strong safety profile. These findings suggest that Lotilaner is an effective and well-tolerated treatment, offering promising results for patients suffering from *Demodex* blepharitis.

This systematic review has several limitations that should be considered when interpreting its findings. First, the diversity of study populations is limited. Most of the clinical trials included were conducted in specific regions, such as the USA and Mexico, which may restrict the generalizability of the results. Differences in demographic characteristics, environmental conditions, and healthcare access across other populations could impact the efficacy and safety of Lotilaner in treating *Demodex* blepharitis.

Another limitation is the small sample size in some of the studies. While larger trials such as SATURN-1 and SATURN-2 provided robust data, smaller studies like the open-label trial by Gonzalez-Salinas et al. (2021) included fewer participants. This may reduce the statistical power of these studies and make it more challenging to detect rare side effects or subtle differences in treatment outcomes. Moreover, the follow-up periods in most studies were relatively short, typically extending only up to 90 days. This limits our understanding of the long-term efficacy and safety of Lotilaner. Whether the benefits observed in the short term are sustained over a longer duration or if patients experience recurrence of *Demodex* blepharitis remains unknown.

Potential publication bias is another concern. Since the review focused on published, peer-reviewed studies, it is possible that trials with negative or non-significant results were not published, which could skew the overall conclusions toward a more favorable assessment of Lotilaner. In addition, there was a lack of direct comparison with other treatments for *Demodex* blepharitis. While this review highlights the efficacy of Lotilaner, it is difficult to position it relative to alternative therapies, as few studies directly compared it to other treatment options. However,

here was variability in the outcome measures used across studies. Different trials focused on various endpoints, such as collarette cure rates, mite eradication, and erythema reduction. This inconsistency makes it challenging to directly compare results and may introduce heterogeneity into the review's conclusions. These limitations suggest that while Lotilaner shows promise, further research is necessary to validate its long-term efficacy and safety, particularly in more diverse populations and with comparisons to other available treatments.

CONCLUSION

In conclusion, this systematic review highlights the potential efficacy and safety of Lotilaner ophthalmic solution 0.25% as a promising treatment for Demodex blepharitis. Across multiple randomized controlled trials, Lotilaner demonstrated significant reductions in collarette formation, mite eradication, and improvement in clinical symptoms compared to placebo, with favorable tolerability and minimal adverse effects. However, the review is limited by factors such as small sample sizes in some studies, short-term follow-up periods, and a lack of diverse study populations and direct comparisons with other treatment options. While the results are promising, further research is needed to confirm Lotilaner's long-term efficacy, its role in preventing recurrence, and its relative effectiveness compared to alternative therapies. Expanding future trials to include more diverse populations and longer follow-up periods will help to establish Lotilaner as a reliable, first-line treatment for Demodex blepharitis.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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