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CORRESPONDENCE

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Artificial tears: Promising treatment or silent threat to public health?

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Abstract

Background and Aims: Dry Eye Disease (DED) is a multifactorial chronic inflammatory condition of the corneal surface, attributed to insufficient or low-quality production of tears, accounting for 5-50% of the cases globally. Artificial tears are the first line of treatment as they reduce ocular surface tension, and improve film stability and optical quality. EzriCare Artificial Tears are preservative-free, multi-dose, readily accessible eye drops containing carboxymethylcellulose sodium solution (10 mg in 1 ml) aiming for relief against DED. This article discusses the public health challenges faced by the use of EzriCare Artificial Tears and emphasizes the need for alternative therapies for the effective management of DED.

Methods: We searched for articles documenting the incidence of the current multi-drug resistant P. aeruginosa strain outbreak caused by the use of preservative-free artificial tears and the challenges faced through the use of artificial tears on PubMed, and Google Scholar.

Results: EzriCare and other preservative-free artificial tears have been reported to pose a serious public health risk as they have been found to be the commonly used product among the people infected with the current multi-state outbreak of the multi-drug resistant P. aeruginosa strain.

Conclusion: The current multi-state outbreak of the multi-drug resistant P. aeruginosa strain has raised concerns about the safe use of other artificial products. It is high time that further trials should be conducted on other alternative strategies and evaluate the safety and efficacy of nanotechnology in the treatment of dry eye disease.

KEYWORDS
artificial tears, drug-resistant outbreak, dry eye disease, EzriCare, preservative-free

Dry eye disease (DED) is a widely prevalent, multifactorial, chronic inflammatory disease of the ocular surface that presents with symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.[1] Any dysfunctionality in the ocular surface, Meibomian gland, lacrimal gland, or innervations between them can cause low quality or insufficient amount of tear production resulting in DED. The prevalence of DED varies from 5% to 50% of the cases worldwide, affecting approximately 16 million

people in the United States. This results in an estimated economic burden of USD 3.84 billion yearly and was projected to reach USD 6.2 billion in 2023, ranging from $687 per person for mild disease to $1267 annually for severe DED.[2,3]

Currently, both pharmacological and nonpharmacological interventions (Topical corticosteroids, Topical cyclosporine A, Tacrolimus/pimecrolimus, Tetracycline, macrolides, Eyelid hygiene, Hot compresses, eyelid warming masks or goggles, infrared heaters, and eyelid massage) are available and being used in the management of DED. Since tear insufficiency has been long presented as a core cause of DED, tear replacement therapy with artificial tears has become the mainstay of therapy as they increase film stability, reduce ocular surface stress, and improve contrast sensitivity and optical quality. Among all ocular lubricants, EzriCare Artificial Tears, preservative-free, multidose lubricant eye drops containing carboxymethylcellulose sodium solution, 10 mg in 1 mL, ½ fl oz (15 mL) bottle, formulated, designed, and imported by Aru Pharma Inc and manufactured by Global Pharma Healthcare PVT LTD, sold under the name of Ezri care artificial tears, was one the readily available product due to its multidose packaging, cost-effectiveness, and a great amount of positive and immediate results against irritation and dryness. In contrast to preservatives containing artificial tears, the preservative-free EzriCare artificial tears have been associated with better ocular surface health and tolerability, preventing exacerbation of symptoms and further irritation, thereby enhancing its effectiveness.[4,5]

However, despite being the primary therapy for DED, its management still poses significant challenges and concerns. Initially reported on January 31, 2023 by the Centers for Disease Control and Prevention (CDC), Artificial tears have been identified as the suspected agent of the current multi-state outbreak of the carbapenem-resistant strain of *Pseudomonas aeruginosa* with Verona integron-mediated metallo-β-lactamase and Guiana extended-spectrum-β-lactamase (VIM-GES-CRPA).[6] As of March 14, 2023, the VIM-GES-CRPA strain of *P. aeruginosa* has been found to infect 68 individuals from 16 states, of whom eight subjects reported vision loss, four have undergone enucleation, and three mortalities due to bloodstream infections have been reported so far. As reported, the infection has presented in a variety of ways, including keratitis, endophthalmitis, respiratory infection, urinary tract infection, and sepsis, indicating the systemic nature of the outbreak. Surprisingly, EzriCare Artificial Tears was observed to be the only common artificial tear used among the infected individuals, and laboratory testing further confirmed its contamination with the drug-resistant *P. aeruginosa* strain. This has led the FDA to issue a warning against using EzriCare Artificial Tears along with Delsam Pharma's Artificial Tears and Eye Ointment.[7] This has initiated an alarming wake-up call for the potential risk of drug-resistant *P. aeruginosa* outbreak among Artificial Tear's users, making DED a challenging disease to treat. FDA records show that lack of sterility and violation of the safety protocols, including lack of appropriate microbial testing, formulation issues, distribution of the drug in multi-use bottles, and inadequate controls concerning tamper-evident packaging during the manufacturing process have led to microbial contamination of EzriCare artificial tears, emphasizing the need for adherence to standard protocols of drug manufacturing to ensure the quality of the drug products. Moreover, EzriCare is a multi-dose, preservative-free (MDPF) Artificial tear, and MDPF eye drops are associated with an increased risk of contamination[8] as compared with single-dose eye drops if proper handling and storage practices are not followed. However, despite being the gold standard in sterility and preservative-free eye drops, increased cost burden, wastage, lack of convenience, and risk of self-contamination have hindered the use of the latter. Therefore, it is necessary to educate the masses about safe handling techniques to ensure maximum effectiveness and prevent any potential risk of contamination. In addition, the patients affected by the outbreak reported using 10 different brands of artificial tears, therefore testing the unopened bottles of EzriCare as well as other preservative-free eye artificial tears used by the affected individuals, will help determine the risk of microbial contamination during the manufacturing process. Despite the fact that the recent outbreak of the *P. aeruginosa* strain has been reported in the United States of America only, and is observed to be associated with 10 identified brands of artificial tears, it has raised concerns about the safe use of other artificial products. Would preservatives-free artificial tear products provide a ground for another outbreak in the future? All of the above data draw attention to future trials to reduce the contamination of artificial tears.

However, artificial tears are palliative in nature and are not useful to treat the underlying cause. To address this issue, it is essential to explore a newer approach of nanotechnology-based drug delivery system for the management of DED. Owing to its extreme site-specific controlled delivery and nanoscale size, it can deliver therapeutic agents directly to the affected ocular tissue, with minimal side effects and prolonged residence time on the affected site, thereby reducing the need for frequent administration. It has been reported that artificial tears used multiple times a day have increased susceptibility to microbial contamination. A study conducted on mice models demonstrated that administration of nanoparticle cyclosporine A once a week successfully eliminated inflammatory infiltrates with complete recovery of the ocular surface, leading to a significant reduction in dosage and improving the patient's compliance. However, further studies are needed to explore the complete usefulness and safety assessment of this novel approach.[9] We urge the authorities to conduct the necessary research to ensure our expectations are realized. We are optimistic that ongoing clinical trials on nanotechnology if they remain successful, could help bring a significant breakthrough by revolutionizing the treatment of DED.

AUTHOR CONTRIBUTIONS

Sanila Mughal: Conceptualization; supervision; writing—original draft; writing—review and editing. **Syeda K. Sakina**: Conceptualization; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Sanila Mughal affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Lemp MA, And GN, Foulks FACS. The definition and classification of dry eye disease. *Ocul Surf*. 2007;5(2):75-92.
2. Rouen PAPFB, White MLPFB. Dry eye disease: prevalence, assessment, and management. *Home Healthc Now*. 2018;36(2):74-83.
3. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. *Ocul Surf*. 2017;15:334-365.
4. Aragona P, Benítez-Del-castillo JM, Coroneo MT, et al. Safety and efficacy of a preservative-free artificial tear containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized, controlled, multicenter 3-month study. *Clin Ophthalmol*. 2020;14:2951-2963.
5. Moshirfar M, Pierson K, Hanamaikai K, Santiago-Caban L, Muthappan V, Passi SF. Artificial tears potpourri: a literature review. *Clin Ophthalmol*. 2014;8:1419-1433.
6. Centers of Disease Control and Prevention. Outbreak of extensively drug-resistant *Pseudomonas aeruginosa* associated with artificial tears. April 28, 2023. https://www.cdc.gov/hai/outbreaks/crpa-artificial-tears.html
7. Food and Drug Administration. FDA warns consumers not to purchase or use EzriCare Artificial Tears due to potential contamination. April 28, 2023. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-purchase-or-use-ezricare-artificial-tears-due-potential-contamination
8. Crary M. A review of the containers available for multi-dose preservative-free eye drops. *Biomed J Sci Tech Res*. 2022;45(1):36035-36044.
9. Nagai N, Otake H. Novel drug delivery systems for the management of dry eye. *Adv Drug Deliv Rev*. 2022;191:114582.