OSI

Ocular Surface Insight

Issue 20

TFOS lifestyle: Impact of societal challenges on the ocular surface (Conclusion)

B12 deficiency: Corneal sensation

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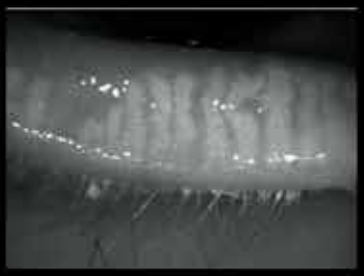

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Ocular Surface Insight

"Opportunities are like sunrises. If you wait too long, you miss them."

William Arthur Ward

Welcome to the milestone 20th issue of OSI Magazine!

As we celebrate this significant milestone, we are thrilled to present the concluding chapters of the TFOS Lifestyle series, featuring Parts 5-9.
This international collaboration delves deeper into the intricacies of ocular surface health, providing invaluable insights and practical knowledge for our readers.

In this edition, we shine a spotlight on the "Benefits of Systane Artificial Tears in Dry Eye Disease Management," through comprehensive analysis and expert perspectives.

Additionally, Mr. Jyotin Pandit enlightens us with his research on "B12 deficiency: Corneal sensation," exploring the correlation between B12 deficiency and corneal health. His findings offer valuable insights into the multifaceted nature of ocular health, highlighting the importance of holistic approaches in patient care.

As we eagerly anticipate the upcoming OSI Dry Eye Masterclass & Symposium on April 18th and 19th, we extend a warm invitation to all our readers.
Join us for two days of immersive learning and engaging discussions with leading experts in the field.
This event promises to be a cornerstone in advancing our understanding of ocular surface health and shaping the future of patient care. We look forward to welcoming you to this enlightening experience!

Finally, we express our gratitude for your continued support and engagement with OSI Magazine.
The feedback from all our readers and contributors drives us to continually strive for excellence, in delivering informative and inspiring content. As we embark on the next chapter of our journey, let us continue to explore, learn, and grow together in our shared pursuit of ocular surface health.

Samer Hamada

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We stand with Ukraine!

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Diya Baker joining OSI Editorial Board

Diya is an ophthalmology registrar in the West Midlands deanery. He began his undergraduate training at the University of Birmingham and subsequently completed post graduate qualifications at the University of Cambridge in both Education and Research. Diya continues to take an active role in research, academia and education and has experience in organising national courses and international symposiums.

As a keen educator, Diya takes great pride in writing and has authored a postgraduate qualification textbook as well novel publications. Diya is thrilled to be the new Trainee Editor for OSI; he has long enjoyed the outstanding content from prior editions and is both honoured and excited to be selected for this role and contribute to future editions of the publication.

Editorial Panel:

Contents

What's in the news?

Tranforming eyecare with AI at 100% optical

"We are drowning in people we need to see in hospital eye services, and some people are going blind as a result. We are looking at nearly 10m hospital appointments for ophthalmology a year, with an approximately 33% increase over the past five years. Since 2017 the busiest of specialties in the NHS has been for eyes. AI may help to allay these challenges," said Professor Pearse Keane, speaking on the Optical Suppliers Association stand at 100% Optical in London this week.

"Our new Moorfields Eye Hospital – due to be complete by 2027/8 at Kings Cross - is designed to take advantage of new care pathways, to help work with community optometry and to upskill people, and to give patients the ability to play a greater role in their own care," he said.

As Professor of Artificial Medical intelligence at UCL, and Medical Retinal Consultant at Moorfields, he is well placed to highlight the UK's role as a world leader in this emerging field of healthcare.

"I am proud that ophthalmology is at the forefront of AI in medicine, as an exemplar for other healthcare sectors, but we are still at the super early stages.

"We have the largest ophthalmic imaging resource in the world at Moorfields – larger than the combination of the top five US providers combined – plus we have Gold Standard governance for engagement and privacy."

The unrivalled foundation of data provided by the NHS for machine learning to aid AI is very evident. The launch of RETFound – a collaboration between UCL and Moorfields – utilises 1.6m retinal images to assist the early research phase of progressing to a functioning algorithm. As an opensource tool this can be used as a building block for others to develop, he explained.

"As a world leader in medical AI the UK has the advantage of NHS data sets and some of the best universities in the world. This has implications, particularly, for rarer or less common diseases as we could find a pathway."

Pearse said that since the 2016 Press reports of Rapid Access Macular Clinics there had been much hype but that bringing this care into the community and general ophthalmologists is not yet real.

"These AI systems are good at giving better measurements for intra or sub-retinal fluids to help guide treatments. But how do we integrate this into pathways and what is the business model?

"The most important application in the short term is, perhaps not in direct patient care, but in clinical trial planning. We can help to overcome the challenges of recruitment by sending an algorithm to clinics to identify segment pathology to find patients suitable to be approached to participate. This helps us in writing the protocol for trials, such as the size of drusen or atrophy. This does not require regulatory approval but could still bring immense benefit."

With more than 500 medical AI systems in the FDA approval system, the appetite for progress in this field is evident, but insurance and payment systems will be a major aspect to compute –

"No one has yet figured out the right business model for the use of medical AI: The infrastructure for data aggregation, and expertise in formatting governance are still in the melting pot."

Professor Keane spoke of the wider implications particularly the Alzheimer Eye Study, linked to the NHS database and impatient admissions. Using retinal scan data as a window to track patients over 40 for early signs of systemic disease with subtle changes, is progressing. Changes in the retina of patients with schizophrenia and looking at neuropathy and changes in the ganglion cell and inner nuclear layer of patients who may go on to develop Parkinsons, perhaps seven years before other symptoms appear, were also highlighted.

"With Parkinsons we have shown on average that there are subtle changes, but this is not a predictive test. Also, for cardiovascular disease – this could have big effects for the eye-care community and could have profound public health benefits, including conditions such as diabetes and high blood pressure."

Prof Keane spoke about emerging abilities starting in healthcare, with medical question answered by the potential of Chat GPT and Foundation Models which are accelerating AI development -

"A large model, trained on a large amount of data and fine-tuned for downstream tasks: This can be for any type of data as demonstrated by the 2023 Canadian study, led by Fares Antaki, which provided accurate clinical performance of 75% vs human performance of 72%.

"We are already seeing AI surpassing human performance, with so much more to come, and the potential of SORA from Open-AI is bringing text-to-video which has enormous potential. Many people around the world are looking to see how this can become a reality in healthcare."

By Janice English
28.2.24. Janice@janiceenglish.com

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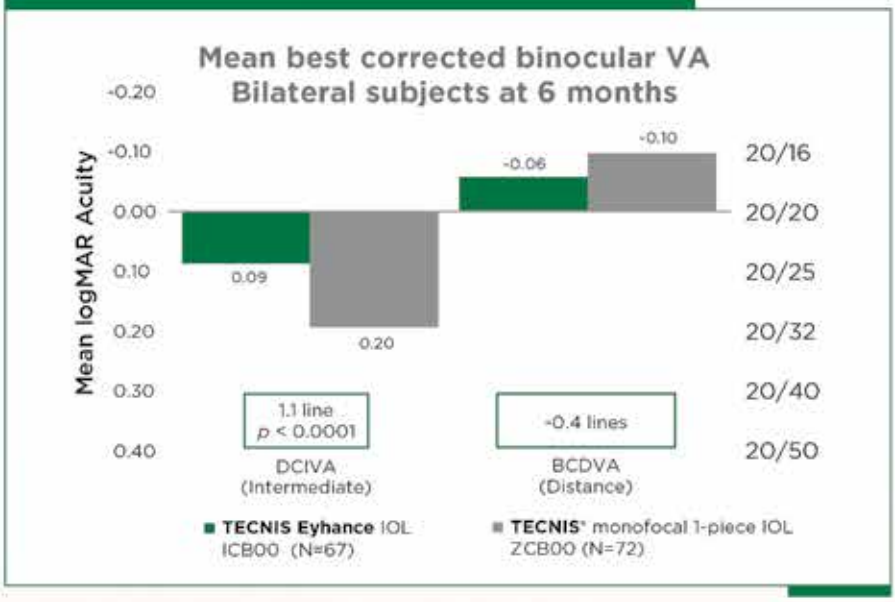

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1. Data on File. Johnson & Johnson Surgical Vision, Inc. Sep 2018. DOF2018CT4015.

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What's in the news?

Quality of vision and tear film osmolarity

The authors set out to evaluate the relationship between tear film osmolarity measurements and quality of vision in patients presenting for routine eye clinic appointments. They found that the hyperosmolar group (>316 mOsm/L) had a worse quality-of-vision score than the normal osmolarity group, with glare being the most problematic symptom.

Quality of vision is a perception and measure of real-world vision, which is not measured routinely in a clinical setting. This study aimed to evaluate the relationship between tear film osmolarity measurements and quality of vision in patients presenting for routine eye clinic appointments.

This was an observational non-randomised study. The participants were placed in groups based on tear film osmolarity (normal, ≤316 mOsm/L; hyperosmolar, >316 mOsm/L; or a difference of >8 mOsm/L between each eye). Thirty-three participants were enrolled in the study, of whom 22 were deemed to have a hyperosmolar tear film. A 30-item questionnaire including 10 symptoms rated on scales of frequency, severity, and bothersomeness was administered to participants in both groups. The quality-of-vision score ranged from 25 to 100 points, with lower scores indicating better quality of vision.

The hyperosmolar group had a significantly worse quality-of-vision score than the normal osmolarity group across all three scales; mean differences for frequency, severity, and bothersomeness were 12.66 ± 9.75 (p=0.003), 9.44 ± 7.45 (p=0.003), and 11.90 ± 11.14 (p=0.008), respectively. Of the 10 symptoms that were included in the questionnaire, glare was the most problematic in the hyperosmolar group.

In this study, the team demonstrated a significant relationship between tear film hyperosmolarity and quality of vision, as patients with hyperosmolar tear films had worse quality of vision.

Authors: David Gallagher, Daire J Hurley, Brian O'Tuama, Emily Hughes, Tim Fulcher
Publication: Optom Vis Sci. 2024 Jan 1;101(1):71-77.doi: 10.1097/OPX.0000000000002095

Ocular surface changes following computer use in post-LASIK patients

The purpose of this study was to assess the impact of computer use on the ocular surface of individuals after laser in situ keratomileusis (LASIK).

The dry eye symptoms and ocular surface of 18 post-LASIK young individuals and 18 controls were evaluated before and after performing a 30-min task on a computer without (Visit 1) and with (Visit 2) initial instillation of artificial tears. Symptoms were assessed using the Ocular Surface Disease Index (OSDI), Symptom Assessment in Dry Eye questionnaire version two (SANDE II) and Computer Vision Syndrome Questionnaire (CVS-Q). The ocular surface was assessed by measuring corneal higher order aberrations, tear meniscus height (TMH), conjunctival redness, blink rate and incomplete blinking, lipid layer thickness (LLT) and non-invasive keratograph break-up time (NIKBUT).

SANDE II scores were >0 after the computer task in both groups ($p \leq 0.01$). SANDE II and CVS-Q scores did not differ between LASIK and controls ($p \geq 0.43$). Greater bulbar-temporal conjunctival redness, TMH and LLT and shorter NIKBUT were found after computer use in the LASIK group ($p \leq 0.04$), whereas no changes were observed in the controls ($p \geq 0.20$). Lower SANDE II and CVS-Q scores were reported at Visit 2 compared with Visit 1 in both groups ($p \leq 0.01$). Likewise, no worsening of dry eye signs was observed at Visit 2 ($p \geq 0.11$).

Ocular symptoms reported during computer use were comparable between the groups. However, a worsening of dry eye signs was mostly observed in post-LASIK individuals. The instillation of artificial tears was effective in preventing the effects of computer use on the ocular surface in post-LASIK patients.

Authors: Cristian Talens-Estarelles, Clara Talens-Estarelles, Santiago García-Lázaro
Publication: Ophthalmic Physiol Opt. 2024 Feb 22.doi: 10.1111/opo.13297

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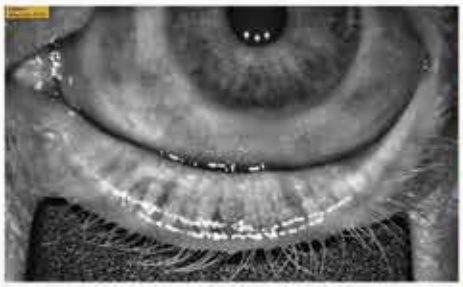
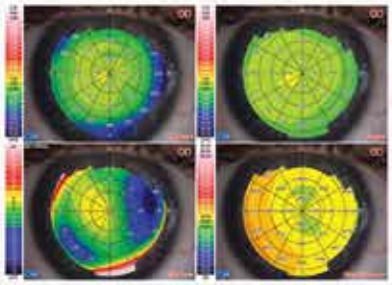
Advanced Analysis of the Tear Film and the Meibomian Gland





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Message from the President of The International Society of Dacryology and Dry Eye Ms Jane Olver, Consultant Ophthalmologist

“I am excited to let you know about our XIVth Congress to be held at The County Hall London on May 29th – 31st 2024. We offer a warm welcome to all healthcare professionals involved in the care of patients who have sore dry or watery eyes to attend, network and learn.”

Ms Olver is the London organiser and has invited leading industry companies and speakers to participate. She says “This is an international congress specifically aimed at the broad school of professionals interested in Dry and Watery Eye management and wanting the latest educational insights into treatment, and to know the expanding range of equipment available to them for quality assessments. The County Hall on London’s Thames bank is a fitting venue to assemble up to 500 delegates for the congress.”

The Meeting

Up to 500 UK delegates from Ophthalmology and Optometry and other Allied Health Professionals are expected to meet at County Hall London for a 3 day event in May this year. The first day consists of the Update Education Course, and the subsequent two days the Scientific Meeting with Symposia, Keynote lectures, practical demonstrations etc.

The exhibition will demonstrate the latest equipment in dealing with what is now a dry eye epidemic of some proportion, many of whom present with watery eyes. This is affecting not only older persons, but young adults and increasingly teenagers and even children. There will also be an in-depth discussion of the assessment and management of patients with watering eyes from blocked tear ducts.
Learn alongside fellow eye professionals from eminent speakers on the latest developments in the treatments and the use of new qualitative and quantitative systems now available.

The 3 days will provide comprehensive learning and lively networking for those already providing a dry eye or “Tears” clinic and for those who should seriously be starting to provide these services in the community. The burden of medical care is shared between the community and the hospital clinics, collaborating as well with GPs. Educating the patient on how to care for their eyes plays a major part in dry and watery eye management.

Excellent advice, challenging cases and useful takeaways and learning together with other professionals will be on offer in this unique opportunity in London.
More information is available at www.isd-de.org


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TFOS lifestyle: Impact of societal challenges on the ocular surface

Section 5-9

CONCLUSION

Fiona Stapleton, **Juan Carlos Abad**, **Stefano Barabino**, **Anthea Burnett**, **Geetha Iyerd**, **Kaevalin Lekhanont**, **Tianjing Li**, **Yang Liu**, **Alejandro Navas**, **Chukwuemeka Junior Obinwanne**, **Riaz Qureshi**, **Danial Roshandel**, **Afsun Sahink**, **Kendrick Shihl**, **Anna Tichenor** and **Lyndon Jones**.

1. Introduction

1.1. Approach

This report is part of the Tear Film & Ocular Surface Society (TFOS) Workshop, entitled 'A Lifestyle Epidemic: Ocular Surface Disease,' which was undertaken to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health. It examines societal challenges in ocular surface diseases using an adaptation of a framework used to map the relationship between the individual, their environment and their health [1]. This approach was designed to enable interventions to be addressed at a health policy level and consequently it reflects the interplay and dependencies between the different factors. The model also recognises that certain factors can be considered to fit within one or more of the levels identified. The most recent iteration of this model considers the impact of the digital world directly and indirectly on human health [2].

The direct impact of certain individual lifestyle factors in ocular surface diseases, including [8], is explored in detail in the respective Reports from the TFOS Lifestyle Workshop. The Societal Challenges Report will predominantly focus on how those factors contribute to societal norms that in turn influence presentation, outcome and management of ocular surface diseases and will refer to the relevant sub-committee reports for their direct effects.
For example, the Societal Challenges Report will explore the impact of the digital world on access to education of practitioners and patients, telehealth or access to services, rather than the impact of digital devices per se on the ocular surface; or the effect of climate change on determinants such as clean water or access to services, rather than the effect of climate change on the ocular surface.
Each section within this report will cross reference the relevant TFOS Lifestyle Reports to minimise overlap.
As for the other TFOS Lifestyle Reports, evidence is summarised in a narrative style review that, wherever possible, refers to outcomes from high-quality systematic review (Level I) evidence. The Evidence Quality Subcommittee provided a comprehensive database of appraised Level 1 evidence judged to be of potential relevance, which was factored into the writing of the report [9].
A key issue given the timing of this report was the impact of COVID-19 on the ocular surface. A systematic review to summarize the impact of the COVID-19 pandemic on the frequency and severity of ocular surface disease in both the general population and amongst those who had COVID-19, was conducted and is included in this report.

5. Regional/global socio-economic, cultural and environmental conditions (see TFOS lifestyle challenges [6] and TFOS Environmental Conditions Reports [7])

5.1. Remoteness/geography/seasonality (see TFOS Environmental Conditions Report [7])

Geographic location, social factors such as high- or low-income regions and remoteness influence access to eyecare services and the profile and severity of ocular surface diseases. In low-income countries, while there are no randomized controlled trials or systematic reviews that are powered to explore the prevalence of dry eye disease in urban and rural communities, the prevalence and severity of symptomatic dry eye disease, meibomian gland dysfunction and meibomian gland loss is higher in rural communities compared to urban areas [436,437]. Individuals living in rural areas experience more outdoor time, poorer hygiene, decreased access to medical facilities, inadequate amenities [438,439] and are predominantly farmers [436]. Such conditions predispose those in rural areas to ocular surface infections such as trachoma [417], eyelid disease and infections, meibomian gland loss and dry eye disease [436]. Other societal factors predominate in urban areas, including the use of digital devices, air conditioning and exposure to pollutants [436]. Dry eye disease is more common at high altitude [440], although there is considerable confounding with altitude and other weather conditions such as humidity (See TFOS Environmental Conditions Report [7]).

Rural and remote communities, particularly those which are home to Indigenous peoples, have greater morbidity and mortality rates from a range of health conditions and communicable diseases, including those related to skin, eye, and respiratory diseases, particularly in children [132]. Indigenous peoples are often marginalised and disadvantaged, with higher rates of poverty and remoteness to health care than non-indigenous populations. Most studies have evaluated blinding eye diseases, but there is also evidence for higher rates of ocular surface diseases, including trachoma and onchocerciasis [133]. Trachoma rates are significantly higher in Indigenous compared with non-Indigenous populations in Australia, with no evidence of a reduction in prevalence between 1993 and 2008 [132]. High rates of pterygium associated with visual impairment have been reported in Indigenous populations in Brazil [130,131].

Outdoor conditions are associated with variations in environmental factors including pollution, level of pollens, humidity levels, weather and seasonality, which influence the

prevalence of ocular surface diseases [441], including dry eye [10], allergic eye disease [442] and ocular surface infections [62]. These associations are described in detail in the TFOS Environmental Conditions Report [7].

These seasonal variations may be due to increased pollen outdoors during spring and low indoor humidity during winter in the case of dry eye disease [441]. Allergic eye disease is more prevalent in warmer, tropical climates such as in Arabian, African, and some Asian countries [443–445]. Warm and dusty weather [445], elevated temperature and relative humidity in semi-tropical weathers, which increase growth of moulds and filamentous fungi indoors [446] and the wet rainy season have all been linked to allergic conjunctivitis [445] and dry eye disease [441]. Warm and dusty conditions are exacerbated, for example, during the harmattan season in West African countries, which carries dust via the northeast trade winds from the Sahara desert over West African countries [445].

Seasonal and geographic variations have been reported in ocular surface infections [447–450] and there are wide regional differences in causative organisms and predisposing factors in infectious keratitis [62]. Warmer summer months appear to be associated with an increase in the reporting of infectious keratitis, and an increase in Gram-negative bacterial keratitis, particularly Pseudomonas sp [448,451–453]. Similarly, the onset of Acanthamoeba keratitis appears to be higher in the summer and autumn months [454]. There is less evidence for a summer peak in the onset of Candida sp. keratitis [451]. Fungal keratitis appears to peak in hot windy climates in the tropics [455,456], surrounding the months of harvest in farming communities in India. The incidence of fungal disease is significantly higher in Asia and Africa than in other regions of the world [129]. Climate influences the rate and severity of contact lens-related infectious keratitis, with more severe disease caused by environmental organisms more common in tropical regions and with high daytime temperatures [457].

5.2. Availability of services (treatment/devices/practitioner education)

Many ocular surface diseases have significant morbidity, including vision loss, and these may require long term management and frequent follow-up care. Such conditions include severe dry eye disease, ocular chemical injuries, Stevens Johnson syndrome and ocular pemphigoid, and frequently require tertiary eye care for diagnosis and ongoing management. This is an issue for rural and low-income communities particularly, and the primary health care center is generally the first point of contact for rural patients. Barriers to accessing services and a delay in accessing appropriate treatment for a range of health conditions underpin the higher prevalence of, and increased severity of, disease in rural and low-income regions [458].

Non-sight threatening diseases including conjunctivitis, pterygium and dry eye are consistently ranked amongst the most common reasons for presentation at health facilities in low- and middle-income countries, in both paediatric and adult populations [459–462].

5.3. Access to affordable services

In the World Report on Vision, the World Health Organization called for integrated people-centred eye care as part of universal health coverage, which includes quality essential health-care services and quality and affordable eye care [463]. A vertically running, stand-alone program focusing on a specific disease is no longer believed to be an effective approach. The World Report on Vision emphasizes strengthening primary eye care as an approach to achieve Universal Eye Health Coverage [463]. The World Health Organization defines universal eye health coverage as "ensuring that all people have access to required promotive, preventive, curative and rehabilitative health services, of sufficient quality to be effective, while also ensuring that people do not suffer financial hardship when paying for these services" [463]. This implies that all people should have access to the best quality health care without the risk of impoverishment. Universal eye health coverage should be comprehensive, equitable, of high quality, accessible, and affordable to all without any financial hardship. Corneal blindness fits within this directive and factors limiting access include socioeconomic characteristics, poverty, education, employment, sex, religion, caste, regional or geographical constraints, war and displacement.

Access to timely health services is the first step in achieving holistic health care. This involves the processes of eligibility to be allowed entry into the system, having an accessible health care location where the required services are available and enabling patients to source a health care provider that they trust and with whom they can communicate. Affordability is the ability of an individual to be able to cover the costs for health care within the parameters of their income. Thus, affordability of health services is determined by the cost of treatment as well as the ability of households to manage these costs, and their impact on the livelihood of household members [464].

Several reports have described a large variation in both the use and understanding of primary eye care from different regions and between various stakeholders. A good primary eye care program should ensure equity, community participation, inter-sectoral collaboration, and long- term sustainability for wider impact and healthy communities. How- ever, the scope of primary eye care varies significantly throughout regions. While primary health workers provide primary eye care as one of their responsibilities in most parts of Africa, in high-income nations such as the UK, USA, Canada and Australia, it is provided by specialized personnel such as optometrists, who are independent eye care service providers in these countries.

In countries, such as India, in the government sector, primary eye care is provided by trained para-medical ophthalmic personnel located in primary health centers, who work in liaison with medical officers. In the private sector/non-governmental sector, trained ophthalmic personnel provide care, most of whom are termed 'vision technicians' [465]. In the government sector however, there are integrated primary health and eyecare networks through primary health centers as well as community centers; however, the government system, as a whole, is weak in implementation [466]. The next section describes an example of this approach as it applies in India, recognising that this is one of several models.

5.3.1. Model of vision centers in India

As an example of an approach to overcome barriers to affordability and accessibility in eye care, a proportion of non-government organisations have implemented universal eye health coverage through their primary eyecare network of vision centers. Vision centers in India operate in line with India's National Program for Control of Blindness (http://npcb.nic.in/). The specific objective of the National Program for Control of Blindness is to provide and improve upon basic and advanced eye care respectively in all parts of the country.

Vision centers are permanent small eye care centres that are situated in remote areas, that allow the rural population to access eye care services within their community and which utilise the local resources available within the community to operate. Every vision center is manned by a well-trained technician and offers services that include refraction, basic ophthalmic examination, diagnosis of common ailments and referral as needed to a tertiary eye care institute attached to the vision center [467]. Vision centers are compact, with usually two or three rooms, and staffing that ranges from one to three staff to serve a target population of around 50, 000 patients and is located within a 50 km radius of the base hospital, although this may be further, depending on the ease of accessing the base hospital [467].

Barriers to access to care in India have been particularly explored in the context of cataract surgery. These include economic or transportation issues [468,469], fear of surgery [470], and lack of awareness about the disease [468].
Vision centers provide immediate triage of patients, based on disease severity, and patients with moderate to severe ocular surface disease can be referred to referral centres for advanced management. Vision centers work with the patients, their families and community, arrange hospital transport and systematically aid in removing barriers that keep patients from surgery and/or advanced care, in a cost-effective manner.

Moreover, they improve health-seeking behaviour.
Staff from within the local community are considered more approachable and accessible for those seeking health care. This prevents a delay in the referral of complex eye conditions and allows for follow-up closer to home, to monitor chronic ocular surface disorders without over-taxing the scarce services of the referral hospital, which are needed for more critical surgeries and care. Vision centers reduce dependency on outreach programs to transport patients, and result in better compliance, as well as follow-up care, in a financially sustainable fashion.

5.4. Culturally appropriate services, free of bias or discrimination

Eye care service utilization is a function of the availability, accessibility, affordability, and acceptability of services [463]. Cultural factors such as trust, perceptions of health, communication and language play a critical role in the acceptability of health services. Furthermore, distrust, racism, and discrimination can negatively influence the ability of some patients to seek care. For example, Indigenous peoples are more likely to access eye care if it is culturally appropriate and well-integrated within their community-based health service [471]. Similarly, higher levels of patient engagement and satisfaction have been reported when there is concordance in language and/or ethnicity (and in some cases gender) between patients and health care professionals [472]. In some cultures, gender-sensitivities arise when care is provided by a health care worker of the opposite gender [463].

In the context of ocular surface, culturally appropriate services are essential for elimination of trachoma in specific populations. In Australia, culturally safe and relevant health promotion resources have been developed with the aim to eliminate trachoma in remote Indigenous communities [473]. However, there is a need for more high-quality studies that provide insights on culturally relevant beliefs and practices [474,475].

5.5. Effect of sex and (trans) gender on access to services

Section 2.2 describes sex-related differences in the prevalence of various ocular surface diseases due to the impact of biology. The societal impact of sex or (trans) gender on ocular surface diseases may manifest as a lack of timely access to services for a range of reasons. Women in most low-income regions have worse visual impairment compared to their male counterparts [476] and the Lancet Global Health Commission on Global Eye Health reported 55% of global vision loss is experienced by women and girls and women are 8% more likely to be blind [477]. Several studies have demonstrated that women have more limited access to eye care services in certain regions [478,479]. Factors affecting the ability of women to seek eye care services include social and cultural factors, for example in some cultures women may not have freedom of mobility and lack independence to make decisions about their health. Women with childcare responsibilities may prioritise others before themselves for health and eye health including children, or their male counterparts [478]. Access to local female vision technicians, for example in the Indian vision center model, may improve uptake of services by females and help to reduce gender inequity.

There is evidence of discrimination and decreased access to health care services for transgender individuals in both developing and high- income countries [480–482]. Transgender individuals have reported discrimination from health workers, fear of rejection and stigma and financial constraints as factors hindering access to health care services in general, and to eye care services in particular [482].

5.6. Cost of diagnosis/treatment – insurance coverage/out of pocket expenses

The costs of diagnosis and management of ocular surfaces diseases and the bearer of these costs varies enormously by region. The cost of primary eyecare in some countries is borne by a public system but medical devices, surgical or medical therapies are variably subsidised [483]. Various means can be adopted in the public and private health sector to reduce the economic burden of health care to ensure that out-of-pocket expenses do not prevent the individual from accessing essential eye care services [484–486].

This in turn is largely determined by several factors, including per capita income, with high-income countries being able to spend more for out-of-pocket expenses [487]. From an individual perspective however, out-of-pocket expenditures for eye care services vary considerably within income groups, ranging from $32 in Sweden to $1200 in Switzerland in the high-income group, and from $6 in Madagascar to over $100 in Cambodia, Haiti, and Nepal in the low-income group [487]. Apart from the direct out-of-pocket expenses, the indirect costs borne by the individual tends to be equally impactful on the affordability of eye care. Ocular surface disorders, primarily those associated with dry eye disease or trichiasis, incur indirect costs, such as loss of earnings. These unaccounted-for factors generally underestimate the economic burden of the individual. In India, more than 80% of the total health care expenditure is borne through out-of-pocket expenses, primarily spent on purchase of medicines [488].

Apart from factors that differ across countries, interstate differences in financing and providing state of art health care in federated countries further contribute to widening the chasm of affordability among individuals.

5.7. Impact of climate change (see also TFOS lifestyle challenges [6] and TFOS Environmental Conditions Reports [7])

As with other possible factors which impact the ocular surface, changes in climate, air pollution and temperature affect the prevalence and severity of ocular surface disease [489–491]. Climate change and the resultant global warming and increased mean temperatures decreases crop yield [492]. This preferentially affects the poor and less privileged in society, especially in developing countries, leading to increased levels of food insecurity [493] (Section 3.1). The increased rate of natural disasters, continuous crop losses and loss of livelihood to farmers affected by these extreme weather conditions and their impact on agricultural yield adds to the very present threat to food security [492]. Such an effect on food security may impact children, increasing the prevalence of diseases associated with malnutrition such as vitamin A deficiency [494], and may compound other societal factors such as childhood education and poverty.

Climate change impacts water security and access to clean water as a direct consequence of flash flooding, heavy rainfall and precipitation, heatwaves and drought. These factors directly impact access to clean water and increase water pollution [495]. Climate change and the consequent rise in the frequency and severity of natural disasters, including floods, fires, drought and other extreme weather events, may disrupt services and amenities such as transportation network systems, which may decrease the ability of individuals to access health care services [496].

5.8. Conflict/displacement – refugee eye health, food and water security

Displacement and conflict affect physical, mental and emotional health [497]. Access to eye care services frequently has a low priority in crises such as war or displacement [498] and refugees are one of the most vulnerable groups for poor health outcomes. Blindness and visual impairment amongst refugees are significantly higher in displaced individuals than in other populations [498–500]. The prevalence of blindness in refugees varies widely depending on geographical location, from as low as 1.3% in Malawi [501], 11% in South Sudan [502], 21% in Uganda [500], and as high as 26% in Ethiopia [499]. In Canada and Australia, refractive error appears to be a leading cause of visual impairment in refugees [503,504]. The main causes of visual impairment in most of the refugee populations from the African continent includes cataracts, trachoma, glaucoma and refractive errors [499]. In a systematic review of causes of visual impairment in refugees internationally, trachoma was the leading infectious cause [505]. However, xerophthalmia resulting from vitamin A deficiency also appears to be common in refugee populations [500,506]. The prevalence of vitamin A deficiency among African refugees varies between 20.5% and 61.7% [507] and vitamin A deficiency is most prevalent in children and women. Displacement, poverty and war compound malnutrition and food security is vital to limit vitamin A deficiency and its blinding complications. Access to both adequate nutrition and sanitation would help to reduce the burden of ocular surface diseases in refugee populations.

5.9. Violence – war, acid attack, domestic violence, tear gas, rubber bullets

War and violent attacks may affect the eye and ocular health in several ways, most notably through ocular trauma from penetrating and perforating injuries to the cornea or globe, endophthalmitis, and secondary ocular infections [508]. While the need for protective eye wear has been advised in an effort to reduce the incidence of war-related eye injuries, there seems to be little evidence of mitigation in the rate of severe injuries [509], and it is noteworthy that open globe injuries are just as likely to occur as closed globe injuries from non-lethal weapons [510]. High morbidity in these situations is exacerbated by the destruction of hospitals during war time, compounding difficulties in accessing health care amidst serious sight-threatening and life threat- ening injuries [511]. This is especially relevant for ocular injuries, as surgical intervention is typically required for injuries from non-lethal weapons. Types of surgeries include lid, retinal detachment or globe repair, foreign body removal (including bullets) and evisceration [510]. Following the Syrian Civil war, approximately 57% of public hospitals were damaged, with 50% of their medical staff fleeing the country to safety [511]. Males tend to suffer greater eye injuries from war, however women and children are also affected [508]. Rubber bullets used by law enforcement may not be lethal in most cases, however they are known to cause ocular injuries such as lid lacerations, corneal tears, hyphema, and retinal detachment [512]. Projectile stones and pellets can cause traumatic ocular injuries with serious visual consequences [510]. In war or conflict situations, the combined effect of decreased security, inadequate access to health services and absence of health workers reduces access to eye care services, and diseases of the ocular surface are not given priority in these situations.

In addition to chemical injuries that may occur accidentally in the domestic setting, violent chemical attacks, such as acid attacks impact the ocular surface significantly and lead to significant epithelial loss, limbal ischemia, and even blindness [513]. In a hospital setting, of the 180 cases of chemical eye injuries reported, 19 cases were violent chemical injuries [514]. Assault represents 3.3–8.1% of ocular surface chemical injury cases in Finland and the UK [514–516], but 45.5% in Martinique [517] and 26%–83% in two retrospective Nigerian studies [518,519].

Chemical injuries significantly impact vision, quality of life, functional status and mental and physical wellbeing, resulting in considerable socioeconomic burden and psychological impact [394]. Injuries caused by alkaline chemicals cause saponification of ocular tissues, leading to deeper penetration and more extensive damage, while acids lead to protein coagulation within the ocular surface tissues preventing deeper penetration [520]. A systematic review has indicated that lengthy irrigation immediately after alkali burns with water is associated with better outcomes [521]. Other fluids suitable for irrigation are normal saline, lactated Ringer's solution, normal saline with sodium bicarbonate added, balanced salt solution, and diphoterine [521].

Inflammation of the ocular surface results in corneal and scleral shrinkage leading to increased intraocular pressure, corneal and conjunctival inflammation, loss of goblet cells, severe ocular surface dryness and scarring [522]. Surgical intervention is required in addition to medical therapy in more severe cases of ocular surface disease secondary to chemical burns, including amniotic membrane trans- plantation [523,524], limbal stem cell transplantation [522,525], penetrating keratoplasty or lamellar keratoplasty [522,526] and keratoprosthesis implantation [522]. Limited access to services following chemical injuries is associated with a poorer disease prognosis. A systematic review and meta-analysis indicated that surgery within a month of ocular burns to eyes, eyelids and eyelashes is likely to result in better long-term visual acuity, improved healing of epithelial defects and reduced limbal ischemia, however there may be a higher risk of infectious keratitis post-surgery [527].

Chemical injuries to the ocular surface may arise with other chemical agents used as riot control gases, such as chloroacetophenone, o-chlorobenzylidene malononitrile, and oleoresin capsicum [510,528]. These gases cause conjunctival congestion, corneal epithelial defects, corneal conjunctivalization, corneal vascularization and opacities and decreased vision [528].

Cases of violence are certainly not limited to war or law enforcement confrontation; domestic violence also leads to eye injuries from blunt trauma or even chemical injuries. About 45% of intimate partner violence is associated with ocular injury [529]. Injuries which may occur in cases of domestic violence include orbital fractures, closed globe injuries and chemical injuries such as intentional acid attacks (vitriolage) [530].

Vitriolage or vitriolic injuries, where acid or corrosive materials are used to maim, disfigure, torture or kill are associated with severe, permanent, disfiguring and incapacitating injuries with loss of tissue and organ function [531]. The motive behind vitriolage is largely an intent to cause long-term psychosomatic suffering from disfigurement, societal shaming and subsequent loss of identity. The perpetrators are commonly spurned suitors, disgruntled and violent domestic partners or business associates in dispute.

Vitriolage cases have been reported in the UK, Asia and Africa, although with the introduction of more stringent laws in Bangladesh, cases have been steadily decreased [531]. In neighbouring India and Pakistan, however, media reports indicate a disturbing increasing trend [532,533]. These numbers could be under representative due to underreporting in several instances related to fatal cases, subsequent suicide of the victim or fear of legal recourse [533–536]. Preventive measures include effective advocacy of legislative changes to regulate acid sale, enforcement of stricter punishments for perpetrators, and opportunities for redress and provision of support for victims [531,535].

5.10. Access to/regulation of dangerous substances

Ocular surface chemical injuries in children including conjunctivitis and keratitis have been attributed to leaking or burst detergent pods, particularly in children under 5 [537–539], lye, sodium hydroxide, accidental exposure to cleaning products, and residues from domestic products used by other household members, such as deodorants and perfumes [540–543].

Of 134 cases of ocular surface chemical injuries in children in India, 65% were caused by rupture of packets of 'chuna', a calcium hydroxide paste mixed into chewing tobacco where the alkaline contents caused ocular surface damage [541]. Similarly, alkali injuries due to exposure to calcium hydroxide during betel nut chewing have also been reported as important causes of ocular injury [544].

6. Information communication and technology – health communication

Digital technology can impact ocular diseases through effects on physical and mental health, health communication and access to services, in both positive and negative manners. For example, personalised medicine, telehealth, practitioner and patient education and connectedness of health care facilitated by digital technology and information communication may enhance diagnosis and management of disease. Conversely there may be physical impacts of the digital environment (See TFOS Digital Subcommittee Report [8]) and social impacts due to isolation, self-image perception and misinformation, which may depend on the type and degree of usage, age of consumer and underlying physical and mental health status.

6.1. Impact on mental, physical and social health

The speed and ease of information communication in the digital era has changed the way in which consumers access information, which may significantly impact mental, physical and social health.

Younger people increasingly use social media, thus may be at a higher risk of impact. Both screen viewing and mobile phone use may contribute to the development of depressive symptoms in young adolescents [545]. A cross-sectional study from Norway indicated that self-presentation in social media was associated with increased mental health problems and decreased quality of life in adolescents [546]. Two cross-sectional studies have similarly indicated that older adults may experience depression and reduced quality of life associated with different types of media exposure and the degree of usage [547,548]. Conversely, older adults may derive benefits, including reduced loneliness and the building of social connections in both assisted and independent living communities [549], which may positively impact ocular surface diseases.

Self-image perception can be influenced by social media use. Taking 'selfies' can be associated with significant increased social anxiety, decreased self-confidence and an increased desire to undergo cosmetic surgery [550]. In a cross-sectional study, prolonged exposure to social media, especially cosmetic surgery–related material, is associated with an increased likelihood of considering cosmetic procedures in the future [551].

6.2. Patient and practitioner specific issues which impact access to care

The digital population as of January 2023 was over five billion internet users worldwide or approximately 63% of the global population [552]. Likely due to the ease of access and convenience, patients are increasingly utilizing and searching the Internet for healthcare information, which can affect interactions between patients and their doctors in both a positive and negative way. A national survey in 2013 showed approximately one in three American adults having used the internet to search for a medical condition for diagnosis [553]. Less than half of those searching (46%) report that the information discovered on the internet led them to seek the attention of a medical professional, whereas 38% reported taking care of the medical condition at home. While this broad survey was not based on ocular conditions specifically, it is apparent that access to health care information via the internet can influence whether a patient presents to a clinician for advice. This same survey reported that 72% of internet users used the medium to search for health information online. However, a survey from Canada revealed that most patients value a physician's advice and opinion over information found on the internet [554]. Peer interaction through advocacy and social media groups may provide patient support and assist with feelings of isolation, although there is limited evidence to confirm this.

With digital access, telemedicine, or the ability for a physician to provide care remotely without an in-office visit becomes available [555]. While patients generally view telemedicine as a favourable modality due to elimination of the need for travel and improved ability to be able to communicate with a provider, the opinion of physicians is less definitive,

with a perception of superior overall quality for in-person visits, which may in part be due to a lack of experience with tele- health [556]. Education, guidelines and technological support through professional organisations may help to facilitate this approach.

7. Impact of the COVID-19 pandemic (see TFOS lifestyle challenges [6] and TFOS environmental conditions subcommittee [7] reports)

The impact of the COVID-19 pandemic and associated precautionary measures, including wearing of masks or protective equipment, online work and education and limited mobility and travel, on ocular surface diseases and societal factors, including mental health and access to eyecare services was explored in publications between January 2020 and January 2022.

7.1. Mental health

The prevalence of mental illness has increased during the pandemic, specifically depression, anxiety and harmful behaviors [381]. Social isolation and loneliness may underpin these adverse psychiatric co-morbidities [381], along with reduced access to appropriate services, which may increase the risk or severity of ocular surface disease, including dry eye disease. A large longitudinal study in the UK has shown that the effects of the pandemic and associated precautionary measures on mental health differ by demographic and social factors [557], which may help to identify populations most vulnerable to pandemic-related sequalae.

Medical treatments for mental health conditions including antipsychotic drugs such as phenothiazines and lithium, and tricyclic antidepressants, have themselves been linked to abnormal ocular surface pigmentation, corneal edema, eye irritation, ocular itching, reduced tear break-up time, and decreased lacrimation [558,559] (See TFOS Lifestyle Challenges Subcommittee Report [6]).

During the pandemic many clinics were forced to close due to government or state mandates, limiting access to services for those with ocular surface disease [560,561]. A reduction in the number of eye exams being performed and postponement of visits for comprehensive eye exams and follow ups for management of chronic eye conditions, likely negatively affected the eye health of many patients [562]. In the United Kingdom, it is estimated that more than 10,000 patients at risk of sight-threatening macular disease missed out on essential eye care [562].

During the pandemic, the demand for telemedicine increased, such that virtual visits increased by 257%–700% [563]. While virtual visits directly benefited some patients, for others requiring a more thorough examination of the ocular surface, for example, telemedicine may have had less direct benefit, although it may have helped to triage these patients.

The pandemic confirmed that utilization of telehealth in eye care may not increase access to care for all patient types and groups. A retrospective study analysed clinical visits at a university eye care center in 2020 during the pandemic and evaluated patient variables associated with the use of telehealth [564]. Male, black, older, non-English speakers and those with no more than a high school education were less likely to choose telehealth in preference to inperson visits.

8. Systematic review of the impact of the COVID-19 pandemic on the frequency and severity of ocular surface diseases

8.1. Introduction

The COVID-19 pandemic has exerted a profound influence on society and people's lives due to either the disease itself, the conditions that arose from the disease, or the public health measures and their psychological and societal consequences. COVID-19 infection and the pandemic have affected the systemic health of the population. There is also the possibility that specific body systems, such as that of the eye, are affected. In particular, the ocular surface, may be vulnerable to COVID-19 infection and associated consequences.

Studies have described both direct and indirect impacts of COVID-19 on several aspects of the ocular surface [565–571], including ocular surface manifestations of COVID-19 or related conditions, such as long COVID and multisystem inflammatory syndrome in children and adults following COVID-19 infection. Development or progression of ocular surface diseases secondary to (1) various public health measures, such as face mask wearing, eye protection, hygiene practices (such as use of hand sanitizer and other disinfectants, ultraviolet C disinfection), vaccinations; lockdowns, isolation, quarantine, physical distancing, online learning, and working from home; (2) therapeutic interventions, such as high-dose steroids, ventilation, and other intensive care unit care; (3) emotional and behavioural consequences of the pandemic, such as mental health problems, sleep disturbances, restricted access to medical services, poor compliance to treatments, telehealth, and the economic downturn (See Section 7).

The objective of this systematic review was to summarize the impact of the COVID-19 pandemic on the frequency and severity of ocular surface diseases, both the impact of COVID-19 pandemic on the general population (with or without baseline ocular surface diseases), and among those who had COVID-19 infection.

8.2. Methods

The systematic review was prospectively registered through PROS- PERO (CRD42022299681) and was conducted by 6 authors of this report (TL, RQ, KL, YL, DR, FS).

8.2.1. Eligibility criteria

The review included studies of human populations from any country or region affected by the COVID-19 pandemic, without restriction by age, sex, race, or other factors. The study populations were not required to have baseline ocular surface diseases. The exposures of interest included the direct impact of COVID-19 infection on ocular surface diseases, as well as COVID-19 pandemic related public health measures (face mask wearing, lockdown, vaccination) and their societal consequences (increased remote learning, digital device use and screen time). Comparators could include no COVID-19 infection, a period prior to the COVID-19 pandemic, or a lower exposure to the same COVID-19 related public health measures and their societal consequences. Outcomes of interest included incidence, prevalence, and severity of ocular surface disease-related diagnoses, signs, or symptoms at any time point.

There was no restriction related to the study context/settings. Eligible studies could be population-, hospital-, clinic-, community-, school-, or university-based.

Published primary comparative studies with at least 50 participants overall, were included. Comparative studies could utilize a cohort, a case-control, a cross-sectional (including survey), or a pre-post design.

Studies without a comparison group or a comparison period were excluded. There was no restriction regarding how studies controlled for potential confounders or how the between group comparison was made. Studies that assessed hospital, emergency room, or healthcare utilization (even when a comparison with a pre-COVID period was made) were also ineligible because these studies did not provide direct measures of the frequency or severity of ocular surface disease. Studies that did not report any ocular surface disease-related outcomes were excluded as were conference abstracts and narrative reviews.

8.2.2. Search strategy

Given that the topic concerns the COVID-19 pandemic, PubMed was searched from January 1, 2019 to December 14, 2021 and Embase from January 1, 2019 to January 4, 2022 without language restrictions. With input from experienced information specialists, the search strategies were designed to include MeSH (for PubMed) or Emtree (for Embase) controlled-vocabulary terms, along with free-text words, related to COVID-19 and various ocular surface diseases. Appendix 1 includes the full search syntaxes for both databases. Reference lists of the included studies or for unpublished studies were not searched.

8.2.3. Study selection

The PubMed and EMBASE search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) and duplicates were removed before screening. After pilot testing, two authors independently screened each title/abstract and then each full text report for potentially eligible studies. At both stages, discrepancies were resolved through discussion and/or consultation with a third author.

8.2.4. Data extraction and risk of bias assessment

A Google form was used for data extraction and risk of bias assessment. For each included study, one author extracted data and a senior author verified the data including study topic, objective, main conclusion, study design, study location, study population, details about exposure and comparator, and ocular surface disease-related outcomes and results.

For risk of bias assessment, domains from the Newcastle-Ottawa Scale were used to assess: (1) risk of selection bias in cohort and case- control studies (or the representativeness of the sample in cross- sectional studies); (2) risk of bias in the measurement of exposures; (3) risk of bias in the measurement of outcomes; and (4) risk of bias due to confounding [572]. Risk of bias was assessed by two senior authors using single extraction and verification. Discrepancies were resolved through discussion.

8.2.5. Syntheses

The following study characteristics were summarized, study design features, study participant characteristics, descriptions of exposures, outcomes, results, and risk of bias. Although planned, it was not possible to conduct any meta-analysis because of the heterogeneity in study designs, populations, and outcomes.
The wide range of outcomes and inadequacy in reporting of many also prohibited calculation of effect sizes or other meaningful quantitative summaries. Consequently, studies that were similar were grouped and the evidence was qualitatively synthesized, following published guidance [573].
The certainty of the body of evidence was not graded.

8.2.5.1. Results

Fig. 2 shows the PRISMA flow diagram for this systematic review.
The database searches yielded 9338 unique records. After screening 129 full-text reports, 40 studies were included in this systematic review [424,425,574–611]

Fig. 2

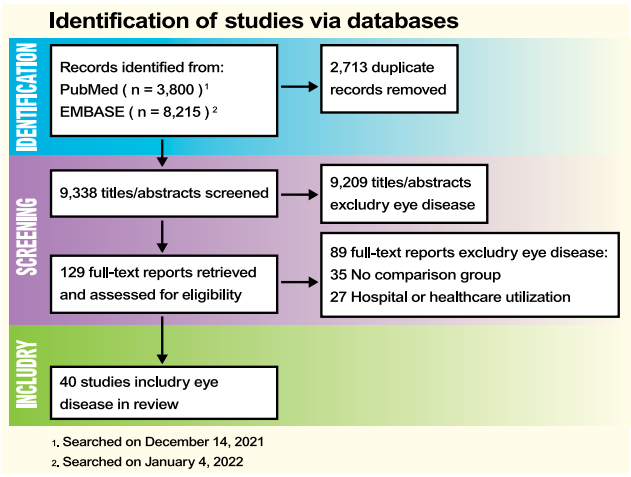
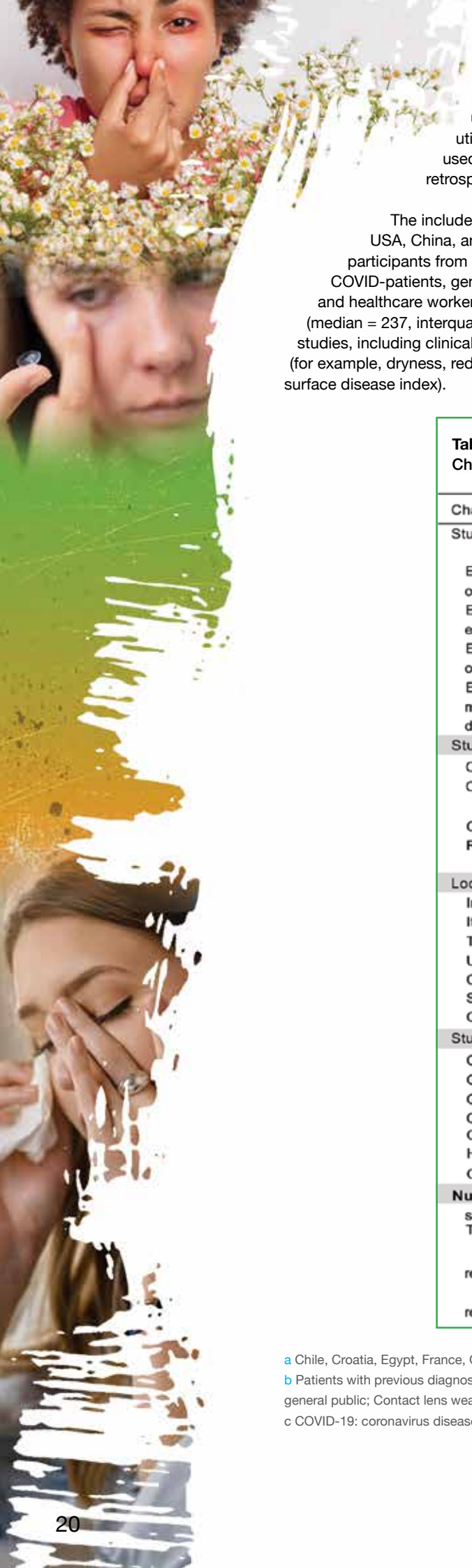


Table 1 on the next page presents a summary of the study characteristics. Individual study characteristics are presented in Appendix 2. The studies included covered four broad topic areas: effects of increased digital device use, screen time, and online classes on ocular surface diseases (n = 14, 35%); effects of face masks and other personal protective equipment on ocular surface diseases (n = 10, 25%); effects of COVID-19 infection on the frequency and severity of ocular surface diseases (n = 11, 28%); and effects



of COVID-19 pandemic related public health measures (such as social distancing, vaccination) and hygiene practices (such as hand- sanitizer use) on ocular surface diseases (n = 5, 12%). Twenty-six (65%) studies utilized a cross-sectional design; only eight (20%) and one (3%) respectively used a cohort or case-control design. The remaining five studies (13%) were retrospective chart reviews.

The included studies were conducted across multiple countries; India, Italy, Turkey, USA, China, and Spain contributed more than one study. One survey study had participants from multiple countries [424]. The study populations were variable, including COVID-patients, general (non-COVID) patients, public, college/university students, children, and healthcare workers. 19,841 participants were studied across all included studies (median = 237, interquartile range: 110 to 439). A wide range of outcomes were measured in these studies, including clinical tests (for example, tear break-up time), self-reported symptoms and events (for example, dryness, redness, eye pain), and patient-reported questionnaires (such as the ocular surface disease index).

Table 1
Characteristics of studies included in the systematic review.

Characteristic	n	(%)
Study topic		
Effects of digital device use, screen time, and online classes on ocular surface diseases[c]	14	(35%)
Effects of face masks and other personal protective equipment on ocular surface diseases	10	(25%)
Effects of COVID-19 on the frequency and severity of ocular surface diseases	11	(28%)
Effects of COVID-19 pandemic related public health measures and hygiene practices on ocular surface diseases	5	(13%)
Study design (excluding healthcare utilization: n ¼ 40)		
Cross-sectional (survey or non-survey)	26	(65%)
Cohort	8	(20%)
Case-control	1	(3%)
Retrospective chart review	5	(13%)
Location of study		
India	7	(18%)
Italy	6	(15%)
Turkey	6	(15%)
United States	4	(10%)
China	4	(10%)
Spain	2	(5%)
Other (single study each) [a]	11	(28%)
Study population		
COVID-19 patients (current or recovered)	7	(18%)
General patients	6	(15%)
General public	6	(15%)
College/university students	6	(15%)
Children (<18)	4	(10%)
Healthcare workers	3	(8%)
Other [b]	8	(21%)
Number of participants (total reported n across studies ¼ 19,841)	**median**	**(IQR)**
Total number of participants	236	(109,439)
Exposure group (among studies assessing and reporting separate exposures and controls (n = 14))	64	(33,127)
Control group (among studies assessing and reporting separate exposures and controls (n = 14))	62	(39,91)

a Chile, Croatia, Egypt, France, Germany, Japan, Portugal, Romania, Russian Federation, Saudi Arabia, United Kingdom.
b Patients with previous diagnosis of Sjogren syndrome, dry eye disease, photokeratitis, or pollen allergy; Students and the general public; Contact lens wearers; Individuals receiving COVID tests.
c COVID-19: coronavirus disease 2019, sd: standard deviation.

Table 2 shows the results of the risk of bias assessment. In summary, 9/40 (23%) studies were rated at high risk of bias, 25/40 (63%) were rated at moderate risk of bias, and the remaining 6/40 (15%) were rated at low risk of bias. For all studies, the assessment of exposure and outcome were judged to be either free from bias or somewhat free from information bias, although one can argue that self-reported exposure and/or outcome information could be subject to inaccurate or biased recall. The study sample selection and representativeness were often unclear or not free from bias and very few studies adjusted for potential confounders in their analysis. Consequently, the association not being free from confounding was another major cause for increasing the overall risk of bias to moderate or high.

Tables 3a-3d presents the results from included studies by topic. Meaningful duration of use could not be extracted and presented for any exposure due to inconsistent reporting and different measures of "increased" use (for example, different categorizations, continuous estimated time, dichotomized

Table 2
Risk of bias assessments for studies included in the systematic review (n = 40).

Was the sample representative (cross- sectional studies)?	Was the study sample free of selection bias (other study designs)?	Is the assessment of exposure free from information bias?	Is the assessment of outcome free from information biases?	Is the association examined free from confounding?	Overall Risk of Bias (RoB)
Cross-sectional studies					
Cartes 2022 [580]	Yes	Somewhat	Somewhat	Yes	Low RoB
Li 2022 [610]	Yes	Somewhat	Somewhat	Somewhat	Low RoB
Saldanha 2021 [424]	Yes	Yes	Somewhat	Somewhat	Low RoB
Alabdulkader 2021 [578]	No	Somewhat	Somewhat	Somewhat	Moderate RoB
Bahkir 2020 [575]	Somewhat	Yes	Somewhat	No	Moderate RoB
Bitirgen 2021 [576]	Unclear	Yes	Yes	No	Moderate RoB
Boccardo 2021 [577]	No	Somewhat	Somewhat	Somewhat	Moderate RoB
Bozkurt 2021 [579]	Unclear	Yes	Yes	No	Moderate RoB
Galindo-Romero 2021 [582]	No	Somewhat	Somewhat	No	Moderate RoB
Gangaputra 2020 [584]	Somewhat	Yes	Somewhat	No	Moderate RoB
Ganne 2021 [585]	Somewhat	Somewhat	Somewhat	Somewhat	Moderate RoB
Garcia-Ayuso 2021 [27]	Somewhat	Somewhat	Somewhat	Somewhat	Moderate RoB
Krolo 2021 [586]	Yes	Somewhat	Somewhat	No	Moderate RoB
Kuroyedov 2020 [587]	Unclear	Somewhat	Somewhat	No	Moderate RoB
Martinez-Perez 2021 [592]	Unclear	Yes	Somewhat	No	Moderate RoB
Mengi 2022 [594]	No	Yes	Somewhat	No	Moderate RoB
Pardhan 2020 [599]	No	Yes	Somewhat	No	Moderate RoB
Shah 2021 [605]	Somewhat	Somewhat	Somewhat	No	Moderate RoB
Wang 2021 [608]	Somewhat	Somewhat	Somewhat	No	Moderate RoB
Elhusseiny 2021 [425]	No	No	No	No	High RoB
Long 2020 [589]	No	Somewhat	Somewhat	Unclear	High RoB
Nivedetha 2020 [596]	Unclear	Somewhat	Somewhat	No	High RoB
Oruc 2020 [597]	No	Somewhat	Somewhat	No	High RoB
Pavithra 2020 [600]	Unclear	Somewhat	Somewhat	No	High RoB
Serban 2021 [604]	No	Yes	Somewhat	No	High RoB
Usgaonkar 2021 [607]	No	Somewhat	Somewhat	No	High RoB
Cohort studies					
Acet 2021 [574]	Unclear	Yes	Yes	No	Moderate RoB
Gambini 2021 [583]	Somewhat	Yes	Yes	No	Moderate RoB
Mastropasqua 2021 [593]	Unclear	Somewhat	Yes	No	Moderate RoB
Ozturk 2021 [598]	Unclear	Somewhat	Yes	No	Moderate RoB
Rokohl 2020 [601]	Yes	Yes	Somewhat	No	Moderate RoB
Sarkar 2021 [602]	Somewhat	Yes	No	No	Moderate RoB
Maniaci 2021 [590]	Unclear	Somewhat	Somewhat	No	High RoB
Scalinci 2021 [603]	Unclear	Somewhat	Yes	No	High RoB
Retrospective chart reviews					
Lavista 2021 [483]	Yes	Yes	Yes	Somewhat	Low RoB
Martin 2021 [591]	Yes	Yes	Yes	No	Low RoB
Wang 2021 [609]	Yes	Yes	Yes	No	Low RoB
Negishi 2021 [595]	Somewhat	Yes	Yes	Somewhat	Moderate RoB
Silkiss 2021 [606]	Yes	Yes	Yes	No	Moderate RoB
Case-control studies					
D'Amico Ricci 2021 [581]	Somewhat	Somewhat	Yes	No	Moderate RoB

"increase" in time, etc.). Narratively, during the COVID-19 pandemic, increased screen time, digital device use, or online classes resulted in new symptoms of dry eye disease in participants and worsening of ocular surface disease-related signs and symptoms across all age groups (**Table 3a**). Prolonged use of digital devices and associated digital eye strain exacerbated signs and symptoms of existing dry eye disease. The overall number and severity of symptoms was positively associated with the duration of screen time. Despite the findings being consistent, most of these studies were based on surveys of students or the public recruited from the Internet; these samples were selective in nature and their responses were subject to inaccurate or biased recall.

Similarly, prolonged and consistent face mask wearing negatively affected people with dry eye, as evidenced by increased ocular surface inflammation; decreased Schirmer scores; decreased tear break-up time; increased dryness, discomfort, foreign body sensation, contact lens intolerance, and other patient-reported symptoms (**Table 3b**).

Table 3a
Results from studies of the effects of screen time, digital device use, or online classes on ocular surface diseases (n = 14).

Study outcomes (n = # studies with that outcome)	Improved with exposure		No change with exposure		Worsened with exposure	
	n	(%)	n	(%)	n	(%)
'Digital eye strain' or 'computer vision syndrome' symptoms [a] (n = 7)	0	(0%)	0	(0%)	7	(100%)
Dry Eye Symptom Questionnaires [b] (n = 3)	0	(0%)	0	(0%)	3	(100%)
Ocular Surface Disease Index (n = 2)	0	(0%)	0	(0%)	2	(100%)
Tear Break Up Time (n = 1)	0	(0%)	0	(0%)	1	(100%)
Central Corneal Thickness (n = 1)	0	(0%)	1	(100%)	0	(0%)
Single Ocular Surface Disease Symptoms and Events						
Dryness (n = 4)	0	(0%)	0	(0%)	4	(100%)
Redness (n = 4)	0	(0%)	1	(25%)	3	(75%)
Eye pain (n = 4)	0	(0%)	1	(25%)	3	(75%)
Tearing/watering (n = 4)	0	(0%)	1	(25%)	3	(75%)
Blurred vision (n = 4)	0	(0%)	2	(50%)	2	(50%)
Itching (n = 3)	0	(0%)	1	(33%)	2	(66%)
Aching/sore eyes (n = 2)	0	(0%)	0	(0%)	2	(100%)
Excessive blinking (n = 2)	0	(0%)	1	(50%)	1	(50%)
Burning sensation (n = 2)	0	(0%)	1	(50%)	1	(50%)
Sensitivity to light (n = 2)	0	(0%)	1	(50%)	1	(50%)
Tired eyes (n = 1)	0	(0%)	0	(0%)	1	(100%)
Double vision (n = 1)	0	(0%)	0	(0%)	1	(100%)
Gritty eyes (n = 1)	0	(0%)	0	(0%)	1	(100%)
Excessive rubbing of eyes (n = 1)	0	(0%)	0	(0%)	1	(100%)
Eye strain (n = 1)	0	(0%)	0	(0%)	1	(100%)
Foreign body sensation (n = 1)	0	(0%)	0	(0%)	1	(100%)
Heavy eyelids (n = 1)	0	(0%)	0	(0%)	1	(100%)

a Feeling of a foreign body, blurring of vision, excessive blinking, itching, dryness of eyes, burning, watering of eyes, redness of eyes, eye pain.
b m-SPEED, Dry Eye Questionnaire - 5, Overall "dry eye symptoms".

Table 3b
Results from studies of the effects of facemasks and other personal protective equipment on ocular surface diseases (n = 10).

Study outcomes (n = # studies with that outcome)	Improved with exposure		No change with exposure		Worsened with exposure	
	n	(%)	n	(%)	n	(%)
Ocular Surface Disease Index (Continuous - Score) (n = 3)*	1	(25%)	1	(25%)	2	(50%)
Ocular Surface Disease Index (Binary - Symptomatic) (n = 1)*			2	(100%)		
Dry Eye Symptom Questionnaires [a] (n = 2)					2	(100%)
Overall Ocular Symptoms [b] (n = 2)					2	(100%)
Schirmer Test I (n = 2)					2	(100%)
Central Dendritic Cell Density (n = 1)					1	(100%)
Fluorescein and Lissamine Green Staining (n = 1)					1	(100%)
Tear Break Up Time (n = 1)					1	(100%)
Allergic ocular symptoms (n = 1)	1	(100%)				
Single Ocular Surface Disease Symptoms and Events						
Dryness (n = 1)					1	(100%)
Eye discomfort (n = 1)					1	(100%)
Blurred vision (n = 1)					1	(100%)
Foreign body sensation (n = 1)					1	(100%)
Need to remove contact lenses (n = 1)					1	(100%)
Chalazion (n = 1)					1	(100%)

*One study examined ODSI as continuous and binary for two different exposures.
a Dry Eye related Symptoms (DEQS), Dry Eye Symptoms Overall. b "Overall ocular symptoms" include: itching, tearing, and redness.

However, face mask use reduced nasal and ocular allergic symptoms among individuals with pollen allergy, likely due to the protection provided by face masks against exposure to the airborne allergen. The risk of bias in these studies seems to be acceptable.

Although many primary studies and systematic reviews on the ocular surface manifestations of COVID-19 infection were identified in the searches, most were excluded due to an absence of a comparison group. Of the 11 included studies that examined the effects of COVID-19 infection on ocular surface diseases (**Table 3c**), the findings were mixed as to whether there was any association between COVID-19 infection and conjunctivitis (infectious, non-infectious, and non- specific types). Studies revealed that, compared with healthy controls, COVID-19 positive patients reported ocular surface symptoms more frequently and may have impaired stability of the tear film. COVID-19 patients reported soreness and dryness of their eyes and the severity of symptoms seemed to be correlated with the severity of the infection. Of note, most of these studies did not adequately control or adjust for confounding factors (such as age, sex, other comorbidities).

Table 3c
Results from studies of the effects of COVID-19 infection on ocular surface diseases (n = 11).

Study outcomes (n = # studies with that outcome)	Improved with exposure		No change with exposure		Worsened with exposure	
	n	(%)	n	(%)	n	(%)
Tear Break-Up Time (n = 4)			2	(50%)	2	(50%)
Overall Ocular Symptoms [a] (n = 2)					2	(100%)
Ocular Surface Disease Index (Continuous - Score) (n = 2)			1	(50%)	1	(50%)
Schirmer Test II (n = 2)			1	(50%)	1	(50%)
Corneal staining (n = 2)			2	(100%)		
Non-invasive First Tear Break-Up Time (n = 1)					1	(100%)
Tear film damage (n = 1)					1	(100%)
Tear osmolarity (n = 1)					1	(100%)
Conjunctival impression cytology						
Conjunctival hyperemia (n = 1)			1	(100%)		
Nelson classification (n = 1)					1	(100%)
Tseng classification (n = 1)					1	(100%)
Nucleus to cytoplasm ratio (n = 1)					1	(100%)
Neutrophil presence (n = 1)					1	(100%)
Lymphocyte presence (n = 1)			1	(100%)		
Corneal confocal microscopic parameters						
Corneal nerve branch density (n = 1)					1	(100%)
Corneal nerve fiber density (n = 1)			1	(100%)		
Corneal nerve fiber length (n = 1)			1	(100%)		
Single Ocular Surface Disease Symptoms and Events						
Itching/irritation (n = 3)			1	(33%)	2	(66%)
Painful/sore eyes (n = 3)			1	(33%)	2	(66%)
Foreign body sensation (n = 3)			1	(33%)	2	(66%)
Red eyes (n = 3)	1	(33%)			2	(66%)
Conjunctivitis (n = 3)	1	(33%)			2	(66%)
Dryness (n = 2)			1	(50%)	1	(50%)
Epiphora (n = 2)	1	(50%)			1	(50%)
Blurred vision (n = 2) Eye swelling (n = 1)			2	(100%)	1	(100%)
Burning sensation (n = 1)					1	(100%)
Watery eyes (n = 1)			1	(100%)		
Mucous discharge (n = 1)			1	(100%)		
Changes in the eyelids (n = 1)			1	(100%)		
Gritty eyes (n = 1)			1	(100%)		

a "Overall ocular symptoms" include: burning sensations, itching, watering, mucoid and purulent discharge, photophobia, foreign body sensation, conjunctival swelling, eyelid swelling, feeling of pressure, double image metamorphopsia, redness, reduced visual acuity, and pain.

The remaining studies summarized an increased trend of paediatric eye exposures to alcohol-based hand sanitizers, increased incidence of photokeratitis due to UV lamp exposure, and the effects of public health measures on ocular surface diseases and changes in internet searching patterns about conjunctivitis (**Table 3d**).

Table 3d
Results from studies of the effects of public health measures and hygiene practices on ocular surface diseases (n = 5).

Study outcomes (n = # studies with that outcome)	Improved with exposure		No change with exposure		Worsened with exposure	
	n	(%)	n	(%)	n	(%)
Overall Ocular Symptoms [a] (n = 1)					1	(100%)
Single Ocular Surface Disease Symptoms and Events						
Dryness (n = 1)			1	(100%)		
Use of artificial tears (n = 1)			1	(100%)		
Corneal ulceration (n = 1)			1	(100%)		
UV keratitis (n = 1)					1	(100%)
Ocular injury due to hand sanitizer (n = 1)					1	(100%)
Nonallergic conjunctivitis emergency department visits (n = 1)	1	(100%)				
Corneal abrasion emergency department visits (n = 1)			1	(100%)		
Eye pain (n = 1)					1	(100%)
Losing access to dry eye treatments (n = 1)					1	(100%)

a "Overall ocular symptoms" include: dryness, burning, itching, foreign body sensation, frequent and/or rapid blinking, sensitivity to light, watering, redness, ocular tiredness/fatigue, eye pain, difficulty keeping eyes open because of symptoms, blurry vision, fluctuating vision, eye symptoms interfered with screen use, reading, or work.

One survey showed that individuals with moderate dry eye disease, particularly those with Sjögren syndrome, may disproportionately experience consequences of increased eye strain and individuals with severe dry eye disease may disproportionately experience reduced access to dry eye treatments.

8.3. Discussion

During the ongoing COVID-19 pandemic, a growing body of evidence has described the impact of COVID-19 on ocular surface health. In this systematic review, 40 comparative studies of various exposures related to the COVID-19 pandemic were identified. Most studies reported increased screen time, extensive use of digital and screen-based technologies, or distance learning because of the pandemic, and consistently reported the development or progression of digital eye strain or computer vision syndrome symptoms, and dry eye symptoms and signs. These findings were independent of geographical region. Most studies did not report other concurrent health interventions related to the pandemic (such as vaccination timing, lockdowns, mask-wearing).

Prolonged and consistent face mask wear appeared to induce or exacerbate symptoms and signs of dry eye disease, intolerance to contact lenses, and increase the prevalence of chalazia. The drying effects may arise due to the change of direction of air flow upwards while breathing while wearing a mask [577,612], creating airflow across the ocular surface. This was demonstrated using thermal imaging and many face mask wearers report the sensation of air blowing upwards into their eyes [612–614]. In an anterior segment optical coherence tomography study of dry eye patients, there was a significant decrease in tear meniscus height and area with a significant increase in blink frequency after exposure of the ocular surface to airflow [615], which may be increased in a poorly fitting mask [616]. Conceivably, in those using both masks and goggles, the temperature and humidity of the periorbital region may increase [606,617], which may increase the likelihood of eyelid inflammation [606,618,619].

In contrast to symptoms of dry eye, allergic ocular symptoms improved with the use of face masks, most likely due the barrier properties of face masks against nasal exposure to airborne allergens.

With ocular surface manifestations of COVID-19, long COVID, or multisystem inflammatory syndrome after COVID-19, numerous studies have investigated ocular surface symptoms and signs in patients with these conditions or evaluated the association with timing and severity with ocular surface presentations to systemic disease, however, the majority are non-comparative studies. Previous systematic reviews and meta-analyses included small case series and case reports and were generally inconclusive [565,566,571,574,620–625]. In the current systematic review, only 11 comparative studies involving patients with COVID-19 were selected for analysis. The present review found that COVID-19 patients could present with a wide range of non-specific ocular surface symptoms and signs, largely depending on the systemic disease severity. Studies that examined conjunctivitis as an outcome had mixed results, thus, the link between COVID-19 and conjunctivitis remains controversial. The relationships between the occurrence of ocular surface symptoms or signs, the detection of virus on the conjunctiva or in tears, and the possibilities of ocular transmission are beyond the scope of this systematic review.

A few studies confirming the adverse effects of other countermeasures against COVID-19 on the ocular surface, such as hand sanitizers and ultraviolet C germicidal lamps were identified [547,588,591,604, 626]. Hand sanitizer caused ocular surface burns with toxic keratopathy, photophobia, limbal involvement and epithelial loss in children [627], adults [628] and healthcare workers [629]. Compared with pre-pandemic, where most injuries were seen in healthcare workers, most cases during the pandemic occurred in children [630]. Ultraviolet germicidal lamps became widespread during the pandemic, and adverse effects included irradiation-induced photokeratitis.

There were no studies that investigated the effects of COVID-19 treatments, such as high-dose steroids, ventilator, and other intensive care unit care, as well as the psychological and behavioural consequences of the pandemic on the ocular surface (Section 7).

The studies included were limited to those with at least 50 participants and those which included a comparison group. The risk of bias assessment revealed that 85% of the studies exhibited moderate-to-high risk of bias.
When interpreting the results of this review, it should be emphasized that these findings were derived from heterogeneous studies because of the diversity in the study designs, populations, and outcomes.

Although widespread vaccination has reduced the case number and hospital admissions, preventive measures such as face mask wearing and working/studying from home are still recommended in many countries/ regions at the time of writing this report. In addition, emergence of new variants may result in an extension of the mitigating strategies for an uncertain period. As the virus continues to mutate, the far-reaching impact of COVID-19 will likely persist. Further research, especially prospective cohort studies with large numbers of participants, is warranted to explore and better understand the direct and indirect effects of the COVID-19 pandemic on ocular surface health. These studies will have the added effect of improving our understanding of societal/ public health measures during a pandemic and their associations with health and wellbeing of the population to better prepare for a possible future pandemic.

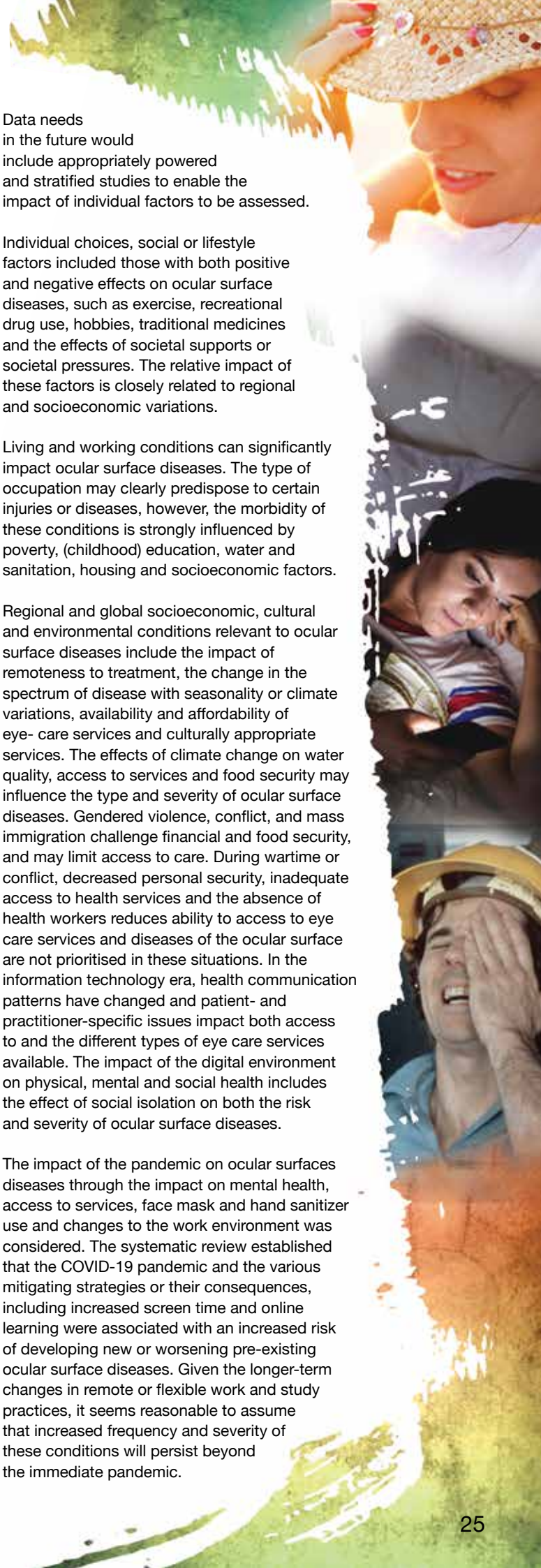
8.4. Conclusion

The COVID-19 pandemic and related mitigating strategies appear to be associated with an increased risk of developing new or worsening pre-existing ocular surface symptoms and signs in most populations studied. Determining the role of individual risk factors may be challenging due to the nature of the studies and multiple confounding factors.

9. Conclusions and recommendations

This report has explored societal challenges in ocular surface diseases through interactions between the individual, social, cultural, regional and global factors and has also considered the impact of information technology on access to eyecare services, which may influence the likelihood of ocular surface disease and the risk and impact of more severe disease (**Table 4**) on the following two pages.
The COVID-19 pandemic has offered a further level of interaction by directly or indirectly impacting many of these societal factors. This report also considered a key clinical question in the form of a systematic review to critically evaluate the available evidence to understand whether the COVID-19 pandemic has changed the severity or outcome of ocular surface diseases.

Societal challenges are associated with both acute and chronic ocular surface diseases. While the impact of age, race and biological factors on many ocular surface diseases are well established, the effects of sex may be confounded by other social or gender constructs including access to health care, employment, poverty, and education.
In addition, differences in rate of disease in different populations for example Indigenous vs non-Indigenous may be confounded by broader societal issues such access to health care resources, poverty, education and disadvantage/ marginalisation.



Data needs in the future would include appropriately powered and stratified studies to enable the impact of individual factors to be assessed.

Individual choices, social or lifestyle factors included those with both positive and negative effects on ocular surface diseases, such as exercise, recreational drug use, hobbies, traditional medicines and the effects of societal supports or societal pressures. The relative impact of these factors is closely related to regional and socioeconomic variations.

Living and working conditions can significantly impact ocular surface diseases. The type of occupation may clearly predispose to certain injuries or diseases, however, the morbidity of these conditions is strongly influenced by poverty, (childhood) education, water and sanitation, housing and socioeconomic factors.

Regional and global socioeconomic, cultural and environmental conditions relevant to ocular surface diseases include the impact of remoteness to treatment, the change in the spectrum of disease with seasonality or climate variations, availability and affordability of eye- care services and culturally appropriate services. The effects of climate change on water quality, access to services and food security may influence the type and severity of ocular surface diseases. Gendered violence, conflict, and mass immigration challenge financial and food security, and may limit access to care. During wartime or conflict, decreased personal security, inadequate access to health services and the absence of health workers reduces ability to access to eye care services and diseases of the ocular surface are not prioritised in these situations. In the information technology era, health communication patterns have changed and patient- and practitioner-specific issues impact both access to and the different types of eye care services available. The impact of the digital environment on physical, mental and social health includes the effect of social isolation on both the risk and severity of ocular surface diseases.

The impact of the pandemic on ocular surfaces diseases through the impact on mental health, access to services, face mask and hand sanitizer use and changes to the work environment was considered. The systematic review established that the COVID-19 pandemic and the various mitigating strategies or their consequences, including increased screen time and online learning were associated with an increased risk of developing new or worsening pre-existing ocular surface diseases. Given the longer-term changes in remote or flexible work and study practices, it seems reasonable to assume that increased frequency and severity of these conditions will persist beyond the immediate pandemic.

Table 4
Summary of main societal factors by ocular disease classification.

Classification	Disease	Biology, genetics & co-morbidities	Individual lifestyle/ societal factors	Living and working conditions	Socioeconomic/ cultural/ Environmental conditions	Pandemic-related
Trauma	Eye/orbital injuries	Male (employment/ hobbies); female (domestic violence)	Sports such as soccer and hockey, recreational fishing, fireworks, eye lid tattooing; toy guns	Occupational exposure to projectiles, observed in miners, construction workers, law enforcement, armed services, laboratory staff, food service industry workers, agricultural workers, fire workers, and mechanics	War and violent attacks; rural and low-income regions	Access to practitioners
	Lid-wiper epitheliopathy	Insomnia; depression	Contact lens wear; eye rubbing			
	Ocular surface chemical injuries (OSCI)	Children under 5 (domestic accident); Female (acid attacks, domestic violence); Male (employment/hobbies)	Leaking or burst detergent pods; calcium hydroxide paste mixed in chewing tobacco or betel nut	Occupational exposure to chemicals, observed in abattoir workers exposed to sheep, turkey, and fish bile; chemical or construction workers; health care workers	Violent chemical attacks and assault; domestic violence (vitriolage); conflict associated with riot/ tear gas; health-seeking behaviour	Hand sanitizer injury in non-healthcare workers
	Toxic conjunctivitis		Use of hand sanitizer; surface disinfectant; contact lens wear		Traditional medicine use such as Kermes (red dye from insect), honey, cow dung, Ushaar (xerophytic shrub)	
Infection	Non-viral corneal infection	Sex and age (dependent on indication); prior ocular surgery, ocular surface disease; trauma; diabetes; HSV; HIV; rheumatoid arthritis	Contact lens wear; recreational drug use; alcohol use, snorting cocaine	Ocular trauma; agricultural work; animal handlers	Low educational level; low GDP; limited access to appropriate services (war, displacement, religious, gender); traditional medicines, breastmilk, honey or alum; higher daytime temperature (Contact lenses); warmer months	
	Fungal keratitis	Male; Malay ethnicity (in Asia); Indigenous populations		Ocular trauma with vegetative material; agricultural work; outdoor occupations; rural environments	Hot windy climates in the tropics; high daytime temperatures; poverty; educational level; low gross domestic product per capita; higher rates in India and Africa	
	Acanthamoeba keratitis	All ages	Contact lens wear	Ocular trauma; contaminated water; fishing; water sports	Summer and autumn months	
	Infectious corneal blindness	Female; ↑ age; diabetes, HIV	Snorting cocaine, methamphetamine use	Rural areas	Low educational level; low socioeconomic status and/or poverty; traditional medicines	
	Trachoma	Childhood (active conjunctival disease); age; female (corneal scarring); Indigenous populations	Face washing	Poor sanitation; overcrowding; lack of access to clean water;	Low-income countries; low socioeconomic status and/or poverty; rural communities; low education status; migrants; possible climate change effects on water quality; remoteness and	Altered access to services during pandemic

Table 4 continued...

Classification	Disease	Biology, genetics & co-morbidities	Individual lifestyle/ societal factors	Living and working conditions	Socioeconomic/ cultural/ Environmental conditions	Pandemic-related
					(religious, regional, geographic constraints, war, displacement); health-seeking behaviours; absence of culturally-appropriate services; climate change impacts access to	
	Oncocerciasis	Indigenous populations		Contaminated river water	clean water Remoteness; poverty; limited access to services; possible climate change effects on water quality;	
	Demodex blepharitis	↑ Age; meibomian gland dysfunction	Contact lens wear			
	Herpes zoster keratitis/Herpes zoster ophthalmicus (HZO) Herpes simplex virus keratitis	↑ Age (also associated with severe vision loss); prior exposure Diabetes; immunocompromise				
Inflammation	Dry eye disease	↑ Age; female; Asian or East Asian ethnicity. Co-morbidities – Sjögren syndrome; chronic pain syndromes; atopy, arthritis; thyroid disease; acne rosacea; prior ocular surgery, menopause; diabetes; pterygia, forms of arthritis; dys- or hyper-lipidemia; renal failure; ischemic heart disease; cardiac arrhythmias; peripheral vascular disease; stroke; migraine; myasthenia gravis; autoimmune diseases; pulmonary circulation disorders; diabetes; hypothyroidism; liver disease; peptic ulcer; hepatitis B status; deficiency anemias, depression, psychoses; certain cancers; chronic fatigue syndrome; osteoarthritis; connective tissue diseases; Graves' disease; autistic disorders; Crohn's disease; sarcoidosis, rosacea; liver cirrhosis; sleep apnea; sinusitis; nasolacrimal duct obstruction; moderate heritability	Systemic/topical medications (Proton pump inhibitors; anticholinergic drugs; anti-glaucoma medications; oral contraceptives; antidepressants; antiallergy medications; contact lens use; smoking, obesity, metabolic syndrome; lack of physical exercise; sedentary lifestyle; excessive caffeine consumption; diet; elective eye surgeries; former smokers	Visual display terminal workers; digital device use; night shift work; air-conditioning; unemployment; retirement; higher education (may be confounded by higher screen time)	Windy conditions; low humidity; low humidity and particulate matter of 2.5 µm or less (PM2.5); air pollution – bushfire and other smoke; low income countries rural communities	Face mask wear; increased screen time; increased time spent in remote learning or working online from home; access to services changed – increased telehealth and education of patients and practitioners through the digital transformation; unemployment or reduced employment increased health related problems
	Meibomian gland dysfunction	↑ Age; no increased risk in females; increased risk of asymptomatic disease in males; rosacea; demodex	Contact lens wear	Night shift work	Low income countries – rural communities	
	Neurotrophic keratitis	Diabetes; HSV	Snorting cocaine, methamphetamine use			
	Conjunctivochalasis	↑ Age				
	Autoimmune diseases	Female; ↑age;				
	Chalazion/ hordeolum					Face mask wear
	Cicatricial	Ocular pemphigoid;			Topical use of Kermes,	

Table 4 continued...

Classification	Disease	Biology, genetics & co-morbidities	Individual lifestyle/ societal factors	Living and working conditions	Socioeconomic/ cultural/ Environmental conditions	Pandemic-related
	conjunctivitis	Steven Johnson syndrome;			a red dye obtained from an insect	
	Superior limbic keratoconjunctivitis	Female; thyroid disease; insomnia; depression	Contact lens wear			
Allergy	Seasonal/perennial allergic conjunctivitis	Children and young adults (first three decades); may occur in older adults; atopy	Use of topical ocular medications, particularly anti-glaucoma drugs	Farmer, animal handler; gardener; higher rate in prison populations	Wet rainy season; warm & dusty weather, seasonal variations with increased pollen conditions; low indoor humidity	Reduced symptoms with mask use
	Giant papillary conjunctivitis	Children and young adults (first three decades); atopy;	Contact lens wear; keratoconus; prosthetic shell;			
	Vernal keratoconjunctivitis	Children and young adults (first three decades); atopy; keratoconus			Traditional medicine use such as honey	
	Atopic keratoconjunctivitis	Children and young adults (first three decades); may occur in older adults; atopic dermatitis	Use of topical ocular medications, particularly anti-glaucoma drugs		Changes in climate, diet, living conditions, lifestyles, air pollutants, comorbidities, and concomitant medications	
	Contact blepharo-conjunctivitis	Middle aged or older adults	Use of topical ocular medications, particularly anti-glaucoma drugs; hand sanitiser			
Neoplasia	Pinguecula	↑ Age	Sun exposure			
	Pterygium	↑ Age, male	Sun exposure	Outdoor employment; occupational exposures; higher rate in prison populations	Low- and middle-income countries	
	Conjunctival melanoma	↑ Age (55–75 years, also risk for more severe presentation and outcome); Caucasian; other ocular melanosis				
	Conjunctival lymphoma	↑ Age (7th - 8th decade, also risk for poorer outcome)				
	Conjunctival squamous metaplasia/ xerophthalmic	Vitamin A deficiency; usually children; young females in high-income countries	Poor nutrition; anorexia nervosa; eating disorders; chronic alcohol consumption	Higher rate in prison populations	Migrant/displaced populations; childhood education; poverty; natural disasters reduce access to nutritious food particularly in children	Food chain supplies may have been affected during pandemic
	Ocular surface squamous neoplasia (OSSN)	↑ Age, male; HIV/HPV status in younger age groups			Temperate climate for older age groups; high solar UV radiation exposure in younger individuals	
Hereditary/ Congenital	Corneal thinning	Keratoconus			Topical use of traditional medicine, Alum, a hydrated salt comprised of potassium aluminium sulphate used in making foods	
	Corneal epithelial	Corneal dystrophy			Topical use of cow	

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Benefits of Systane Artificial Tears in Dry Eye Disease Management

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Abstract

Dry eye disease (DED) is a multifactorial ocular condition that impairs the stability of the tear film, leading to ocular discomfort and visual disturbances. The etiology of DED can be attributed to various factors such as aging, medications, environmental factors, and medical conditions. The symptoms of DED can significantly impact patients' quality of life by causing reduced productivity and social functioning, poor work performance, and psychological distress. Timely diagnosis and effective management of symptoms and signs of DED are essential to prevent impacts on quality of life. Artificial tears are a commonly used management option for DED, providing symptomatic relief for patients with mild to moderate DED. The Systane® family of artificial tears, including Systane® ULTRA, Systane® HYDRATION, and Systane® COMPLETE, has demonstrated clinical efficacy and safety for DED management. This review provides a comprehensive overview of the published evidence on the clinical efficacy and safety of Systane® and the improvement in quality of life associated with ongoing management. Additionally, the review highlights the clinical benefits of using artificial tears perioperatively in cataract surgery and the economic advantages of using artificial tears compared to alternative therapies for DED. Overall, this review aims to provide eye care professionals (ECPs) with an evidence-based resource to optimize patient outcomes through an informed decision-making approach in the management of DED.

Background

Burden of Dry Eye Disease

Dry eye disease (DED) is a complex disease of the tear film and ocular surface resulting in symptoms of eye discomfort, vision disturbance, and tear film instability that can lead to ocular surface injury.[1] Global prevalence estimates of DED ranging from 15% - 64%, and are expected to increase as the global population grows and ages,[1-7] placing a growing burden on patients and the economy. Many risk factors can contribute to DED and exacerbate symptoms. Non-modifiable risk factors can include but are not limited to age, female gender, Asian ethnicity, and meibomian gland dysfunction (MGD).[1] In contrast, some risk factors are modifiable, such as the use of visual display use, contact lens use, environment, and hormone replacement therapies.[1]

The impact of DED on quality of life is comparable to other disabling conditions, and even mild to moderate disease state can reduce quality of life (Figure 1).8 Patients with DED experience restrictions in activities and their social life,9; 10 reporting up to 34% impairment in daily activities,[11] and the chronic nature of the disease can affect numerous aspects of an individual's social life.[1] They are more likely to report difficulties in activities such as reading and writing, driving, and professional work, than those without DED.[12] Pain associated with DED can have psychological and physical impacts. A meta-analysis of 32 studies by Basilious et al., (2021) showed that patients with DED had increased odds of depression and anxiety (1.8 and 2.3 times higher odds, respectively) compared with controls.[13]

With DED, patients often face challenges related to presenteeism where basic work tasks such as reading, writing, and screen-based work become difficult, leading to a decline in productivity. Finding an effective and non-burdensome management option for dry eye symptoms that suits all patients presents an additional challenge.

With high global prevalence estimates, DED is an important contributor to direct economic burden. As a common reason to seek medical eye care, DED significantly increases health care resource utilization and direct medical costs.[1] The total annual healthcare cost was calculated to be $1.94 Million USD

per 1,000 DED patients managed by ophthalmologists in the United Kingdom (U.K.),[14] and the annual direct medical cost of managing patients with dry eye in the United States (U.S.) was $5.78 Billion USD.[15] In certain regions, the financial burden of dry eye may fall heavily on patients, especially if patients must pay out of pocket for ocular exams, diagnostic tests, and pharmacological therapy.[16; 17] Additionally, DED contributes to productivity loss, which is responsible for a substantial portion of the economic burden of dry eye, and it worsens with increasing severity of dry eye.[11; 18] Individuals with DED may have difficulty reading or using devices, and may avoid workplace environments that aggravate symptoms.[1; 19] A growing body of evidence supports the impact of DED on work productivity with studies from the U.S.,[20; 21] Saudi Arabia,[22] and the U.K.,[23] demonstrating that the severity of DED was significantly associated with work productivity loss. For instance, Greco et al., (2021) found that high ocular surface disease index (OSDI) scores were associated with higher absenteeism and presenteeism, with an increase of 4.3% in work impairment and 4.8% in activity impairment for each 10-unit difference in OSDI.[20]

Importance of Tear Film Health and Dry Eye Disease Management

The tear film, comprised of lipid and mucoaqueous layers, is imperative to maintaining ocular health. Deficiency in the lipid and mucoaqueous layers contributes to evaporative and aqueous deficient types of DED, respectively. Often, patients will exhibit mixed DED that reflects dysfunction in both lipid and mucoaqueous layers of the tear film. Failure to correct deficiencies and provide adequate treatment for DED may result in chronic eye pain and progression to burdensome ocular surface disease.24-26 Furthermore, when left untreated, DED may interfere with accuracy of keratometry and intraocular lens (IOL) power prediction for cataract surgery.27 During cataract surgery, various procedural exposures, such as topical anesthetics, phototoxicity, desiccation, and surgical trauma, can contribute to the development of DED.28; 29 However, studies on the prevalence of DED following cataract surgery remain limited and rates of postoperative DED vary widely, ranging from 27% to 100%.[28; 30; 31] Although DED post-cataract surgery is typically a transient condition lasting up to three months, without proper management it may develop into a chronic condition in 10% of cases.30 While the use of postoperative artificial tears is considered standard of care, their universal adoption may vary across regions.28 Proper management of pre- and post-operative DED may provide numerous benefits, including accelerated wound healing, optimized visual outcomes, and improved patient comfort during the recovery period.[28; 29] The complexity and lack of standardized diagnostic and management approaches for DED can lead to challenges in care.[1; 24] Eye care professionals (ECPs) may benefit from a more efficient and effective methods for the diagnosis, management, and treatment of DED.

The Systane Family of Artificial Tears

Tear replacement, through artificial tear use, is the mainstay of management for DED, regardless of etiology.[24; 32; 33] Alcon's Systane® family of artificial tears provides a management option for all major types of DED to provide patients with targeted relief. Across the artificial tears, core ingredients include polyethylene glycol 400 (PEG), propylene glycol (PG), and hydroxypropyl guar (HPG). These agents adhere to damaged epithelial cells, and provide protection through increasing the volume of the tear film. Particularly, HPG is a notable ingredient as this gelling agent functions to replenish the mucoid layer and improve tear retention on the ocular surface.34; 35 With a viscosity similar to tears, HPG adapts to tear film pH, forming reversible cross-links with borate and divalent ions like calcium, a unique feature compared to typical polymers.[36-38] Systane's HPG gelling technology binds to damaged areas, creating a protective gel matrix on the ocular surface, delivering rapid and sustained relief for dry eye symptoms.[39-41] It outperforms traditional eye drops, improving tear film integrity and offering clinical benefits for contact lens wearers.[42; 43]

The high concentration of HPG in Systane® ULTRA has been found to be beneficial for aqueous deficient DED.[44; 45] The hyaluronic acid (HA) component in Systane® HYDRATION's dual polymer formulation further supports the replenishment of the aqueous layer and restoration of damaged cells.[46] Systane® HYDRATION may also benefit patients post-operatively (eg, cataract surgery) to promote wound healing.[46] Systane® COMPLETE combines HPG with nanosized phospholipids and is suitable for all major types of dry eye, it targets both layers of the tear film with its nano droplet size and improves ocular surface coverage while minimizes blurring.47 Lastly, Systane® BALANCE is suitable for evaporative dry eye, including MGD.48 This review will focus specifically on Systane® ULTRA, Systane® HYDRATION, and Systane® COMPLETE.

The understanding and diagnosis of different dry eye types have improved, and various management options, including artificial lubricants, are available to target these types. However, despite these management options, many patients still experience dry eye symptoms. With the introduction of new lubricants, it is crucial for clinicians to stay updated on their potential application for different dry eye types. The Systane® portfolio offers a range of options for clinicians to address dry eye disease types. This review highlights the clinical and economic benefits of the Systane® portfolio and aims to assist ECPs in selecting the appropriate dry eye management option for their patients.

Many patients often rely on their own judgement to select an over-the-counter artificial tear. However, many patients are generally happy to receive advice from an eye care professional, who may share their recommendation (eg, for preservative free tears).

Methods

A comprehensive literature review was conducted to collect clinical evidence for Systane®. Literature searches were conducted using MEDLINE. Key topics of interest included Systane® specific ingredients, preservatives, artificial tear use before and after cataract surgery, and economic implications of DED and artificial tear use. Key words used included "Systane", "dry eye", "PolyQuad", "artificial tears", "cataract surgery". Inclusion criteria included Systane® specific ingredients (hydroxypropyl guar, propylene glycol, polyethylene glycol 400) or mention of Systane® brand name, comparative and single-arm trials in human subjects, and articles published between 2004 to January 2022. Non-English articles and study designs that did not allow for independent assessment of Systane® were excluded. Following article screening, 83 articles were included for analysis. Relevant congress presentations for Systane® were also included.

Results

Eighty-three studies and four congress presentations for Systane® were included. Of the included studies, 40 were randomized studies, five were meta-analyses, 17 observational studies, and 21 expert opinions or pre-clinical studies.

Clinical Evidence

Efficacy of artificial tears for the management of DED can be objectively evaluated with ocular surface staining, and the measurement of tear break-up time (TBUT). Ocular staining assesses the integrity of the ocular surface, with dye binding to areas of epithelial damage.24 Ocular surface staining is strongly associated with disease severity and a clinically meaningful reduction in ocular staining indicates a restoration of the ocular surface.[49; 50] When looking at the breadth of comparative evidence for ocular staining, Systane® formulations provided similar or better improvement of ocular staining compared to other artificial tears. In 18 comparisons between Systane® and other artificial tears across 13 studies in which a p-value was reported, Systane® showed a statistically significant improvement versus other artificial tears in five comparisons, while 12 comparisons did not show a statistical difference, and Systane® was outperformed in only one comparison in Noecker et al., (2006) (Table 1).[34; 35; 40; 51-60] Compared to baseline, Systane® formulations significantly improved ocular staining. Systane® formulations demonstrated a statistically significant improvement from baseline in 10 out of 15 (67%) studies reporting a p-value for ocular staining, while five studies showed no statistical difference from baseline (Table 1).[51-55; 58; 60-68]

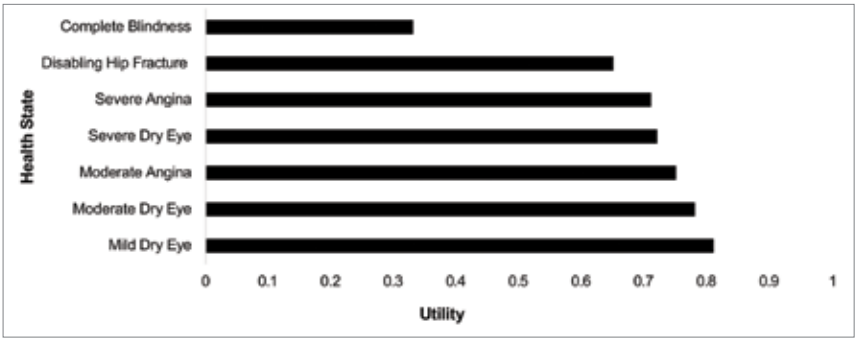
A TBUT of less than 10 seconds (when using 50uL fluorescein) and less than five seconds (using micro-quantities of fluorescein) indicates dry eye.24; 69 Systane® formulations provided similar or better improvement in TBUT compared with other artificial tears. Of 23 comparisons across 17 studies, no artificial tear product demonstrated a statistically significant advantage in TBUT compared with Systane® [34; 35; 41; 44; 52; 53; 55; 58-61; 70-75]
Three comparisons that reported a p-value showed a statistically significant improvement in TBUT with Systane® compared to other artificial tears (Table 2).[41; 55; 73] Compared to baseline, Systane® formulations statistically significantly improved TBUT in 16 out of 19 (83%) studies reporting a p-value, while three studies showed no statistical difference from baseline (Table 2).[36; 55; 58-60; 62-65; 67; 68; 70; 74-80]
Systane® also demonstrated similar performance to advanced therapies such as Botulinum toxin injections and Punctal Plugs for improvements in TBUT at three to six months,[77] and statistically significantly greater improvement than the antibiotic-steroid combination Tobradex.[73; 77]

Improvement in patient reported symptoms of DED, although subjective, is a key indicator of artificial tear efficacy as patients may experience far greater discomfort than clinical signs indicate,[1; 24] and patients are seeking symptomatic relief. Instruments such as the Impact of Dry Eye on Everyday Life (IDEEL) survey, OSDI, and Dry Eye Questionnaire (DEQ-5) can provide validated, reliable, and DED-specific patient reported outcomes. Systane® was comparable to other artificial tears for IDEEL score, with no statistically significant differences reported.[35; 52; 57; 81; 82;] The Systane® group also demonstrated a statistically significant improvement from baseline in 13 out of 14 (89%) studies reporting a p-value for OSDI, including in Sanchez et al., (2010) which assessed DED post-cataract surgery (Table 3).[36; 41; 53; 55; 58; 59; 62; 70; 76; 77; 81-84]

A prospective, multicenter study by Miller et al., (2022) demonstrated the effectiveness of Systane® in relieving symptoms of watery eyes, in patients with DED, with a statistically significant decrease in DEQ-5 scores from baseline.85

In establishing a preferred diagnostic protocol to identify signs of DED, TBUT and corneal staining are commonly used. However, the importance of patient-reported outcomes (eg, OSDI, ocular comfort index) has also been highlighted. Early identification of symptoms is crucial to facilitate effective disease management, considering the chronic nature of DED that usually necessitates ongoing treatment. Emphasizing patient education and reinforcing compliance are essential for symptom improvement.

Figure 1. Health related quality of life for dry eye disease (DED) compared with other health states. Utility is a rating of quality of life; higher utility indicates a better quality of life, with 1 representing perfect health and 0 representing death.[8]



Safety and Adverse Events

Evidence supports the safety of Systane® in improving the symptoms of DED. Of 15 comparisons across 14 studies that focused on Systane® ULTRA, COMPLETE, and BALANCE, no difference in safety was seen between Systane® and other artificial tears.[35; 44; 52; 53; 56; 57; 59-61; 71; 72; 74; 86; 87] Benelli et al., (2010) assessed the impact on visual disturbances of Systane®, Blink^ tears, and Cellufresh^, and reported comparable effects of the three arms in reducing mean higher order aberrations from baseline.[34] Systane® provides relief from the symptoms of dry eye with the use of gentle preservatives or preservative-free formulations. The gentle preservative PolyQuad® results in less disruption to the ocular surface compared to benzalkonium chloride (BAK),88 and has been shown to offer comparable tolerability to a preservative-free eye drop.[61; 89; 90] Human epithelial cells exposed to PolyQuad® showed significantly better cell viability, less apoptosis, and less oxidative stress compared to BAK.89 Systane® ULTRA, Systane® HYDRATION, and Systane® COMPLETE are also available in multidose preservative-free options featuring PureFlow® Technology, a non-return valve system combined with a silicone membrane that prevents the re-introduction of liquid and potential for contamination.[91; 92] Systane® ULTRA preservative-free formulation has been shown to be equally as effective as the PolyQuad® formulation in significantly improving ocular staining and TBUT compared with baseline.59 This may be an ideal management option for patients needing frequent use of artificial tears, without compromising its effectiveness. Preservative-free Systane® formulations were also shown to statistically significantly improve TBUT and OSDI from baseline after 3 months of use,55 and reduce signs and symptoms of dry eye after one month of cataract surgery ($p<0.05$).[77]

Systane® Formulations

Within the Systane® portfolio of artificial tears products, each formulation is designed to address specific subtypes of patients with DED. The available literature presents evidence demonstrating the effectiveness of Systane® artificial tears formulations, including Systane® ULTRA, HYDRATION, and COMPLETE, in managing DED symptoms, as compared to alternative artificial tears products. A comprehensive comparison of these formulations will elucidate the unique benefits of each product, providing valuable information for ECPs in selecting the most suitable option for their patients.

Systane® ULTRA

Two studies examined the effectiveness of Systane® ULTRA and alternative artificial tears at reducing clinical signs of DED. Maharana et al., (2017), a retrospective study, found that compared to Carboxymethyl Cellulose (CMC), Systane® ULTRA resulted in a significantly higher percentage change in TBUT up to four weeks, 18.9% versus 51.1% for the Systane® group ($p=0.006$).[41] In the same study, Systane® ULTRA also resulted in a significantly better percentage change in OSDI, compared to CMC ($p=0.00$).[41] However, a randomized study by Wong et al., (2017) compared Systane® ULTRA to an alternative eye drop, Optimel Manuka^, and found that the alternative had a significantly lower OSDI score than Systane®, but neither treatment group led to a significant change from baseline.58 Although both Optimel Manuka^ and Systane® ULTRA statistically significantly lowered ocular discomfort compared to baseline, Optimel Manuka^ was significantly more effective at improving dry eye symptoms compared to Systane® ULTRA ($p=0.05$).[58] When comparing endpoints with baseline measurements, a significant improvement in patient-reported symptoms after treatment with Systane® ULTRA has been shown with the standard patient evaluation of eye dryness (SPEED) questionnaire ($p<0.001$).[36; 93; 94] Systane® ULTRA also provided a statistically significant reduction in OSD I score from baseline at three to six weeks.[36; 41; 53; 62; 83; 84] Similarly, compared to baseline, patients using Systane® ULTRA for two weeks reported significant improvement in dryness, comfort, and an increase in the comfortable lens wear time.[93] Compared to advanced therapies such as Botulinum toxin injections and Punctal Plugs, Systane® ULTRA has shown similar performance at three and six months, with no difference seen in TBUT, Schirmer's test, and OSDI score.[95]

Systane® HYDRATION

The available evidence on Systane® HYDRATION highlights its effectiveness and ability to provide ocular comfort. In an international prospective, randomized study, Systane® HYDRATION (HPG-HA) was statistically similar to a sodium hyaluronate (SH) containing artificial-tear, Hyabak^ tears.[35] Patients reported similar mean treatment effectiveness using the IDEEL survey, with the Hyabak^ group reporting higher treatment convenience scores.[35] The reduction in convenience was likely related to transient blur from the higher viscosity of the dual polymer, designed to increase retention and ocular comfort. Further studies are needed to understand the advantage of a dual-polymer for symptoms and ocular comfort, as long-term benefits may not have been captured.[35] Compared with baseline, Systane® HYDRATION showed statistically significant improvement in IDEEL and OSDI scores in patients with digital device related dry eye symptoms and aqueous deficient DED.[81; 82] The unique features of Systane® HYDRATION may be useful for patients who are recovering from ocular surgery.[48] A recently published study of 419 patients assessed the use of Systane® HYDRATION one week prior to cataract surgery and up to eight weeks post- surgery, and identified a

protective effect from iatrogenic DED, over and above post-operative use alone.[96] Pre-op use of Systane® HYDRATION significantly improved symptoms at one and four weeks after surgery based on SPEED scores ($p<0.03$) and significantly improved corneal staining at week four compared to postoperative administration alone ($p=0.013$).96 In an in vitro cell study, Systane® HYDRATION demonstrated superior performance of its dual-polymer formula in restoring the ocular surface and

promoting a healthy ocular epithelium.[97] Specifically, in cultured human corneal epithelial cells, Systane® HYDRATION produced significantly better hydration compared with single-polymer HA alone,[97] as showcased by the quantity of viable cells following rinsing off the pre-treatment solutions. Similarly, in human keratinocyte cells, Systane® HYDRATION exhibited moderate shear thinning behavior, and achieved the highest mucoadhesiveness and lowest coefficient of friction among other over-the-counter eye drops including Thealoz^, Refresh^, ReNu^, and LaimCare^, demonstrating its potential to provide effective and prolonged relief.[98] Additionally, an in vivo preclinical study using mouse models examined the effectiveness of Systane® HYDRATION in re-epithelializing the cornea following injury. The results demonstrated that Systane® HYDRATION had the highest corneal repair rate and significantly higher re- epithelialization compared to six commercially available HA-containing artificial tears (Optive Fusio^, Vismed^, Thealoz Duo^, Hyabak^, and Hylo-Comod^), as demonstrated by the percentage of corneas with negative fluorescein staining.[46]

Systane® COMPLETE

Systane® COMPLETE has demonstrated advantages over several prominent artificial tears.[99] Compared to Refresh Optive^ and Soothe XP^, Systane® COMPLETE resulted in better cell viability, better protection from desiccation, and prolonged lubrication.[99]
The nano-delivery system and higher concentrations of HPG in Systane® COMPLETE resulted in significantly less friction observed post-treatment and a significant increase in elastic filament strength compared to Systane® BALANCE.[100]

A randomized study by Muntz et al., (2020) examined the prophylactic benefits of Systane® COMPLETE in patients exposed to a simulated adverse environment, as exposure to adverse environmental factors in the modern workplace is becoming increasingly problematic. Non-invasive tear breakup time (NIBUT) was significantly improved compared to baseline with an average increase of 2.1 seconds ($p<0.05$).[79]
Tear film lipid layer grade was also significantly improved when compared to baseline.[79] No studies on Systane® COMPLETE identified by this review reported OSDI or IDEEL outcomes. However, three prospective randomized studies assessed symptoms and patient comfort using the symptom assessment questionnaire in dry eye (SANDE), SPEED, and DEQ-5 questionnaires.[60; 67; 79]
Systane® COMPLETE significantly improved SANDE score for symptom severity and frequency following exposure to a simulated adverse environment, reducing by an average of 22 points from baseline.[79] In two prospective randomized studies, Systane® COMPLETE effectively reduced DED signs, and reduced contact lens associated discomfort when used prior to lens application, including reduced ocular staining from baseline, improved TBUT from baseline, and a significant improvement in SPEED questionnaire scores while having no significant impact on visual acuity.[60; 67]

A prospective study by Miller et al., (2022) examined the effectiveness of Systane® COMPLETE in relieving symptoms of watery eyes in DED patients. Following continuous use for four weeks, a statistically significant decrease in DEQ-5 scores from baseline was seen, where the proportion of patients with scores of two to four was reduced by 41.2%.[85]

Ophthalmologist preference for preservative-free artificial tears has been highlighted, emphasizing the concern of potential harm from excessive preservative load to the ocular surface. The choice of artificial tears plays a pivotal role in effective disease management.

Artificial Tears Before and After Cataract Surgery

Growing evidence supports the benefit of artificial tears for patients both before and after cataract surgery.[27- 31; 96; 101-104] The use of artificial tears in cataract pre-operative assessment prior to keratometry has been shown to significantly modify mean anterior corneal astigmatism and total corneal astigmatism measurements, and significantly lower mean absolute error in predicted astigmatism, particularly in patients with a TBUT of five seconds or less.[27] A recent retrospective study examined the use of Systane® Idra (variant of Systane® HYDRATION) in preventing DED post-cataract surgery and identified several post- operative benefits for tear film stability, signs and symptoms of dry eye when artificial tears were used in the week prior to cataract surgery.[30; 96] Specifically, perioperative use of artificial tears was associated with significant improvements in ocular staining scores and TBUT compared to those who did not use them ($P<0.05$). Additionally, a prospective study assessed the effects of Systane® ULTRA and COMPLETE on keratometry and IOL power calculation for cataract surgery,[102] and found comparable outcomes in relation to keratometric values and IOL power prediction error. Another prospective randomized study by Labiris et al., (2017) examined TBUT in post-cataract

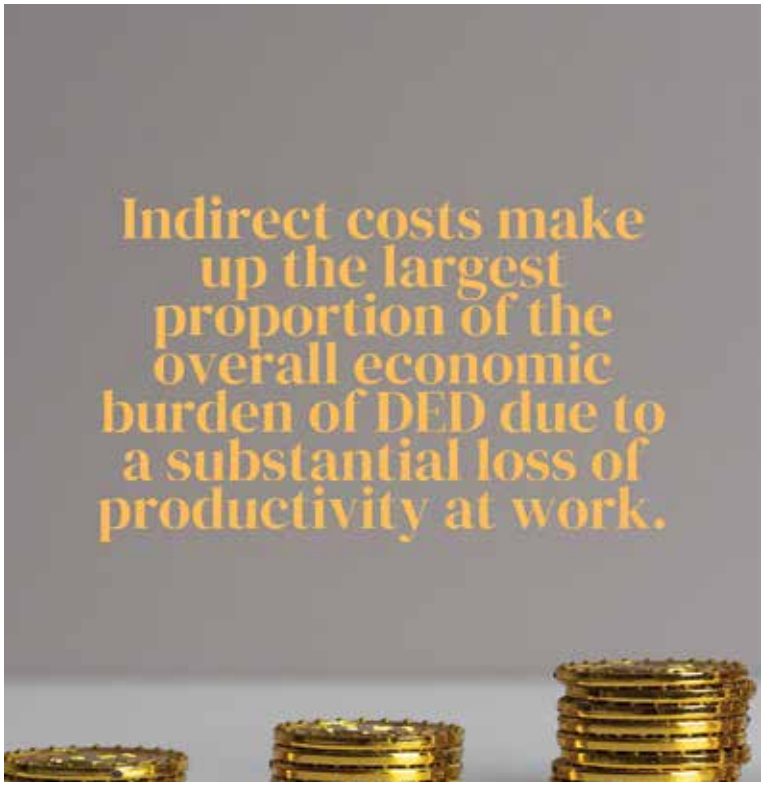
patients who routinely used Systane® Ultra compared to those who did not use artificial tears, and the results showed statistically significantly better TBUT in those who used artificial tears for six weeks following surgery ($P<0.05$).[75] These findings suggest the potential benefits of using artificial tears to prevent DED related to cataract surgery.

DED screening is an essential step in the cataract surgery journey for patients. Upon the detection of DED in the pre-operative stage, managing dry eye symptoms at minimum with artificial tears is imperative as this helps with ocular re-measurements prior to cataract surgery and controlling post-operative dry eye symptoms.

Potential Economic Value of Systane®

Indirect costs make up the largest proportion of the overall economic burden of DED due to a substantial loss of productivity at work.10 A U.S. study on productivity loss in working-age patients estimated those with mild and moderate DED reported loss of up to eight days per working year.[15] If dry eye-related productivity losses were eliminated, an estimated $18,075 – $27,112 USD per patient per year could be saved.[15] A recent pharmacoeconomic analysis from Europe used decision tree modeling to explore the cost- effectiveness of preservative-free and preserved artificial tear formulations in patients with primary open- angle glaucoma and DED.[105] When effectiveness was assessed using Schirmer's test, preservative-free

formulations dominated preserved formulations with lower costs and higher efficacy in controlling DED.[105] Additionally, in a cost effectiveness analysis, Systane® was calculated to cost an additional $93 USD per year compared to Refresh Tears^, but it was significantly more effective.[106] Compared to 41% of patients in the Refresh Tears^ cohort, 75% of patients in the Systane® cohort reported an improvement in symptoms of dryness, which resulted in a cost of $9,520 USD per quality-adjusted life year (QALY),[106] rendering Systane® significantly below the threshold required for a product to be considered cost-effective in the U.S.[106] Moreover, as the first line option for DED symptom relief, artificial tears are comparably more economical to pharmacological treatments and surgical



procedures.[10; 107] Other advanced therapies such as antibiotics and Punctal Plugs have an annual costs $570 USD[10] and $576 USD[107] per patient, respectively, whereas the annual cost for Systane® is $372 USD.[106] In addition to the low cost, Systane® also achieved significantly better TBUT and OSDI scores compared to antibiotics.[77] A prospective randomized study by Fouda et al., (2017) examined the effectiveness of Systane® compared to Botulinum toxin injections and Punctal Plugs.[95] Results showed that outcomes such as TBUT, Schirmer's test, and OSDI scores were comparable between Systane® and Botulinum toxin injections and Punctal Plugs at three and six months.[95] From an economic perspective, the relatively low cost and effectiveness of Systane® compared to advanced therapies may render it an ideal management option for patients with DED.

Summary

DED is a multifaceted condition that necessitates proper diagnosis and effective management. Overall, evidence supports the efficacy of Systane® in strengthening tear film stability and in alleviating symptoms of major types of DED. Each Systane® formulation contains unique features which target different patient needs, reduces clinical signs of DED, and improves patient quality of life. The variety of formulation options provides a reduction in dry eye-related discomfort across different disease subtypes while ensuring safety through gentle preservative and preservative free formulations. Based upon the established clinical and safety profile of Systane®, it is considered a cost-effective management option compared to alternative artificial tears and treatment options.

Definitions and Calculations

Health care resource utilization includes costs incurred by health care system, such as resources used for patient management and management/ treatment of disease.

Direct medical costs include costs associated with medical intervention such as diagnostic tests, physician office visits, and medications.

Presenteeism refers to being present at work when an individual is not fully productive due to illness, injury, stress, or other personal issues, which can lead to reduced productivity, increased errors, or accidents.

Annual cost for Punctal Plugs: Aligned with the 2023 National Medicare Payment, considering the insertion of two plugs twice per year, each priced at $144 USD (non-facility limiting charge).

^Registered and trademarks are the property of the product owner/ manufacture.

All costs were inflated to 2023 U.S. dollars.

Tables

Table 1. Within group and between group comparison in ocular staining performance for Systane® artificial tears.

Study	Treatment Arms	Definition	Time Point	Baseline	Endpoint	Change from Baseline	P-value	P-value
Noecker 2006	Systane® (General)	Mean corneal sum staining scores	Week 1	2.9	2.7	N.A	0.18	0.053
	Refresh Liquidgel			2.7	1.9	N.A	N.A	
Noecker 2006	Systane® (General)	Mean conjunctival sum staining scores	Week 1	1.1	1.1	N.A	N.A	0.016
	Refresh Liquidgel			0.72	0.50	N.A	N.A	
Wong 2017	Systane® Ultra	Mean (SD) fluorescein staining (0 to 4)	Week 2	0.30 (0.40)	0.60 (0.60)	0.30 (0.70)	N.A	0.42
	Optimel Manuka + Dry Eye Drops			N.A	N.A	0.10 (0.50)	N.A	
Puker 2021	Systane® Complete	Mean (SD) Corneal Staining (BHVI grading scale 0-20)	Week 2	1.0 (1.5)	0.4 (0.8)	-0.5 (1.4)	0.068	0.30
	Sensitive Eyes			1.1 (2.2)	1.1 (1.3)	0.0 (2.3)	N.A	
	No treatment			1.8 (2.8)	0.8 (2.0)	1.0 (3.4)	N.A	
Kading 2010	Systane® Ultra	Mean (SD) corneal staining graded using NEI staining grid (0=normal and 3=severe)	Week 2	0.33 (0.67)	0.33 (0.63)	N.A	N.A	0.23
	Sensitive Eyes Rewetting Drops			0.43 (0.7)	0.55 (1.0)	N.A	N.A	
Martin 2018	Systane® Balance	Mean (SD) corneal staining	1 month	1.5 (0.2)	0.9 (0.2)	N.A	N.A	N.A
	Optive Plus			1.3	1.0	N.A	N.A	
	Refresh Contacts			1.5	1.0	N.A	N.A	
Benelli 2010	Systane® (General)	Percentage of patients with grade 0 or 1 conjuctival and corneal staining scaled from 0 (no staining) to 4	1 month	Grade 0: 45% Grade 1: 55%	Grade 0: 90% Grade 1: 10%	45% improved one grade	N.A	
	Cellufresh			Grade 0: 80% Grade 1: 20%	Grade 0: 95% Grade 1: 5%	15% improved one grade	N.A	0.082 *
	Blink Intensive Tears			Grade 0: 55% Grade 1: 45%	Grade 0: 90% Grade 1: 10%	35% improved one grade	N.A	0.75*
Guthrie 2015	Systane Balance	Mean (SD) severity of corneal staining graded using a zero (no staining) to three (severe) scale	1 month	0.8 (0.6)	0.6 (0.5)	N.A	<0.01	0.03
	Habitual contact lens and rewetting drops			N.A	N.A	N.A	N.A	
Labetoulle 2017	Systane Ultra	Mean (SE) TOSS score	Day 35	5.5 (0.27)	3.5 (0.34)	-2.2 (0.33)	N.A	0.32
	Optive			5.5 (0.27)	3.9 (0.35)	-1.7 (0.34)	N.A	
Christensen 2004	Systane® (General)	Conjunctival staining	Week 6	N.A	N.A	N.A	N.A	0.025
	Refresh Tears			N.A	N.A	N.A	N.A	
Christensen 2004	Systane® (General)	Mean decrease in corneal staining	Week 6	N.A	N.A	52%	<0.01	N.A
	Refresh Tears			N.A	N.A	41%	<0.01	
Cohen 2014	Systane® Gel drops	Mean (SD) corneal staining scores	Week 6	6.9 (2.5)	3.3 (2.4)	-3.4 (2.5)	<0.01	0.029
	Refresh Liquidgel			6.4 (2.2)	4.0 (2.6)	-2.5 (2.6)	<0.01	
Astakhov 2013	Systane® (General)	Mean score on the fluorescein test, using the Oxford scale	Day 84	0.16	0.04	-0.12	0.03	N.A
	Hylabak			N.A	N.A	-0.15	N.A	
Davitt 2010	Systane® (General)	Mean corneal staining scores	Day 42	4.8	2.9	-1.8	<0.01	0.01
	Optive			5.3	4.2	-1.7	<0.01	
Labetoulle 2018	Systane® Hydration	Mean (SD) TOSS score Mean conjunctival staining scores	Day 42	5.3 (1.4)	4.1 (2.1)	-1.1 (1.8)	N.A	0.48
	Hyabak			5.0 (1.1)	4.1 (1.98)	-0.9 (1.4)	N.A	
Jacobi 2012	Systane® (General)	Mean (I-III quartile) fluorescein staining scores using the Bijsterveld grading system	Month 3	4.0	3.0	-1.0	0.58	0.08
	Visine Intensiv			4.0	4.0	0.0	0.68	
Belalcázar-Rey 2021	Systane® Ultra	Percentage of patients with fluorescein staining grade 0	Month 3	32%	N.A	21%	N.A	0.085
	SH/CS-PF			40%	N.A	13%	N.A	
Belalcázar-Rey 2021	Systane® Ultra PF	Percentage of patients with fluorescein staining grade 0	Month 3	24%	N.A	30%	N.A	0.085
	SH/CS-PF			40%	N.A	13%	N.A	
Hartstein 2005	Systane® (General)	Mean corneal staining score	Week 4	N.A	N.A	-4.1	<0.001	N.A
Gifford 2006	Systane® (General)	Mean total corneal staining	Week 4	4.7	2.8	N.A	<0.001	N.A
Guzey 2010	Systane® (General)	Mean (SD) fluorescein staining	Week 8	4.9 (1.5)	3.3 (1.2)	N.A	<0.001	N.A
Urzua 2012	Systane®	Median Oxford fluorescein staining score of cornea and conjunctiva	Week 2	IV	III	N.A	>0.05	N.A
Sindt 2013	Systane® Balance	Mean (SD) corneal staining total score	Week 4	4.1 (2.3)	3.1 (2.1)	-1.0 (1.3)	<0.001	N.A
Aguilar 2014	Systane® Balance	Mean (SD) cornea staining score	Week 4	1.2 (0.85)	N.A	-1.16	N.A	N.A
Fernandez 2015	Systane® (General)	Mean (SD) corneal staining	Day 30	5.4 (3.6)	2.7 (3.1)	-2.7	<0.001	N.A
Baudouin 2017	Systane® Balance	Mean (SD) TOSS score	Day 35	3.5 (2.1)	N.A	-0.81 (0.14)	N.A	N.A
Wong 2017	Systane® Ultra	Mean (SD) fluorescein staining (0 to 4)	Week 2	0.30 (0.4)	0.60 (0.6)	0.30 (0.7)	0.06	N.A
Asbell 2018	Systane® Ultra	Mean (SD) TOSS score	Week 4	5.1 (1.3)	N.A	-1.19 (0.26)	N.A	N.A
Martin 2018	Systane® Balance	Mean (SD) corneal staining	Week 4	1.5 (0.2)	0.9 (0.2)	N.A	N.A	N.A
Labetoulle 2018	Systane® Hydration	Mean (SD) TOSS score	Week 6	5.3 (1.4)	4.1 (2.07)	-1.1 (1.8)	N.A	N.A
Tong 2018	Systane® Ultra	Mean (SD) corneal staining (central)	Month 1	0.09 (0.31)	N.A	N.A	N.A	N.A
Aguilar 2018	Systane® Balance	Mean (SD) Corneal Staining sum score	Week 4	5.7 (2.8)	3.1 (2.3)	N.A	<0.01	N.A
Pucker 2020	Systane® Complete	Mean (SD) Corneal Staining (BHVI grading scale 0-4) Extent	Week 2	1.7 (2.4)	1.4 (2.4)	-0.32 (2.5)	0.75	N.A

Abbreviations: SD, Standard Deviation; TOSS, Total Ocular Symptom Score. *Compared to Systane®.

Table 2. Within group and between group comparison in tear break-up time (TBUT) for Systane® artificial tears. Outcomes were measured in seconds.

Study	Treatment Arms	Definition	Time Point	Baseline	Endpoint	Change from Baseline	P-value	P-value
Benelli 2010	Systane® (General)	Mean (SD) TBUT based on eyes with worse (smaller) TBUT value at day 1	Day 30	6.2 (1.0)	7.8 (1.0)	1.6 (1.0)	N.A	N.A
	Cellufresh			N.A	N.A	1.3 (1.1)	N.A	0.56*
	Blink Intensive Tears			N.A	N.A	-13.3 (6.8)	N.A	0.56*
Comez 2013	Systane® (General)	Mean (SD) TBUT	Week 12	6.0 (2.0)	N.A	7.0 (3.4)	P<0.05	0.66 (between all arms)
	Eyestil			N.A	N.A	6.1 (3.3)	N.A	
	Tears Naturale II			N.A	N.A	5.8 (2.3)	N.A	
	Refresh Tears			N.A	N.A	5.6 (2.8)	N.A	
Gensheimer 2012	Systane® (General)	Extension of TBUT at 120 min	120 minutes	N.A	N.A	N.A	N.A	0.12
	Eyeon Protect			N.A	N.A	N.A	N.A	
Llamas-Moreno 2013	Systane® (General)	Mean (SD) TBUT	Day 60	4.7 (2.6)	7.3 (2.5)	N.A	0.32	0.088
	Xiel ofteno			5.2 (2.3)	6.1 (2.5)	N.A	0.22	
Jacobi 2012	Systane® (General)	Mean (SD) TBUT	Month 3	8.5 (4.8)	14.1 (4.9)	N.A	0.002	0.02
	Visine Intensiv			8.2 (4.7)	10.8 (5.7)	N.A	0.25	
Ousler 2007	Systane® (General)	Mean TFBUT	60 minutes	2.9	3.9	N.A	N.A	N.A
	Refresh tears			3.7	3.6	N.A	N.A	<0.05*
	Refresh Endura			3.3	3.7	N.A	N.A	N.A
Perez-Balbuena 2016	Systane® (General)	Mean TBUT	Day 60	5.2	7.4	N.A	N.A	N.A
	Xiel ofteno			5.5	7.4	N.A	N.A	
Waduthantri 2012	Systane® Ultra	Mean (SD) right eye TBUT	Week 6	N.A	N.A	0.13	N.A	0.795
	Refresh Tears			N.A	N.A	0.40	N.A	
Torkildsen 2017	Systane® Ultra	Mean TBUT (sec) after 5 minutes	60 minutes	2.3	2.8	N.A	0.44	N.A
	Rohto Dry-Aid			2.4	3.3	N.A	0.012	
Wong 2017	Systane® Ultra	Mean (SD) NIBUT	Week 2	10.7 (3.5)	10.8 (4.4)	0.080 (3.9)	0.93	0.83
	Optimel Manuka			N.A	10.6 (4.9)	-0.14 (5.8)	0.91	
Maharana 2017	Systane® Ultra	Mean (SD) TBUT (Change from baseline in mean percentage change)	4 weeks	7.6	10.0	51.1%	N.A	N.A
	Genteal Eye Drops			N.A	N.A	48.9%	N.A	0.98*
	CMC 0.5%			N.A	N.A	18.9%	N.A	0.006*
Wang 2010	Systane® Gel drops	Mean (SD) right eye TBUT	4 weeks	6.3 (2.1)	9.3 (2.1)	N.A	N.A	N.A.
	Liposic Opthalmic Liquid Gel			6.3 (1.8)	9.4 (1.7)	N.A	N.A	
Labetoulle 2018	Systane® Hydration	Mean (SD) TFBUT	Day 42	3.2 (2.0)	3.7 (2.4)	0.46 (1.7)	N.A	0.58
	Hyabak			3.6 (2.2)	4.2 (3.4)	0.61 (3.4)	N.A	
Belalcázar-Rey 2021	Systane® Ultra	Mean (SD) TBUT (seconds)	90 days	7.2 (1.0)	N.A	1.36 (2.5)	<0.05	0.68
	SH/CS-PF			7.0 (1.0)	N.A	1.2 (2.2)	<0.05	
Jerkins 2020	Systane® Balance	Mean (SD) TBUT (seconds)	35 days	2.9 (1.1)	3.9 (2.3)	0.99 (1.9)	N.A	0.31
	Refresh Optive Advanced			2.9 (1.2)	3.8 (2.1)	0.86 (1.6)	N.A	
Pucker 2021	Systane® Complete	Mean (SD) Sodium Fluorescein TBUT (seconds)	2 weeks	8.8 (4.9)	10.5 (4.7)	1.6 (4.6)	0.088	0.86
	Sensitive Eyes			8.3 (4.2)	10.7(6.4)	2.4 (5.7)	0.05	
Labiris 2017	Systane® Ultra + FCTD	Mean (SD) TBUT (seconds)	6 weeks	8.9 (1.11)	9.6 (1.45)	N.A	<0.05	>0.05
	Hylocomod + FCTD			9.0 (1.1)	9.4 (1.3)	N.A	<0.05	
Cohen 2014	Systane® Gel drops	Mean (SD) TBUT (seconds)	Week 6	4.6 (2.8)	N.A	N.A	N.A	>0.05
	Refresh Liquidgel			4.6 (3.1)	N.A	N.A	N.A	
Davitt 2010	Systane® (General)	Mean (SD) TBUT (seconds)	N.A	4.2 (1.9)	N.A	N.A	N.A	>0.05
	Optive			4.5 (2.3)	N.A	N.A	N.A	
Gifford 2006	Systane® (General)	Mean NaFl TBUT	Week 4	5.7	7.6	N.A	0.0015	N.A
Versura 2008	Systane® (General)	Mean right eye TBUT	Week 4	6.8	8.5	N.A	0.0001	N.A
Durrie 2008	Systane® (General)	Mean (SD) TBUT	Day 30	7.4 (3.7)	6.3 (3.2)	N.A	N.A	N.A
Guzey 2010	Systane® (General)	Mean (SD) TFBUT	Week 8	6.7 (1.5)	8.9 (1.8)	N.A	<0.01	N.A
Sanchez 2010	Systane®	Mean (SD) TBUT	Month 1	6.8 (1.7)	9 (2.5)	N.A	0.0007	N.A
Urzua 2012	Systane®	Mean (SD) TBUT	Week 2	3 (2.2)	4 (2.3)	N.A	>0.05	N.A
Waduthantri 2012	Systane® Ultra	Mean (SD) right eye TBUT	Week 6	N.A	N.A	0.13 (1.46)	N.A	N.A
Comez 2013	Systane® (General)	Mean (SD) TBUT	Week 12	6.0 (2.0)	N.A	7.0 (3.4)	<0.001	N.A
Llamas-Moreno 2013	Systane® (General)	Mean (SD) TBUT	Month 2	4.7 (2.6)	7.3 (2.5)	N.A	0.32	N.A
Sindt 2013	Systane® Balance	Mean (SD) TBUT (replicate 1)	Week 4	5.3 (2.3)	6.0 (2.2)	0.6 (2.1)	<0.05	N.A
Aguilar 2014	Systane® Balance	Mean (SD) NIBUT	Week 4	4.6 (0.69)	7.4 (0.51)	2.8 (0.74)	NR	N.A
Perez-Balbuena 2016	Systane® (General)	Mean TBUT	Month 2	5.2	7.4	N.A	0.046	N.A
Fernandez 2015	Systane® (General)	Mean (SD) TBUT	Day 30	2.39 (1.64)	4.19 (2.25)	1.8	0.0001	N.A
Torkildsen 2017	Systane® Ultra	Mean TBUT after 5 minutes	60 minutes	2.27	2.75	N.A	0.44	N.A
Gokul 2018	Systane® Balance	Mean (IQR) NIBUT	N.A.	5.2 (4.4–6.5)	7.8 (6.4–9.1)	N.A	<0.001	N.A
Gokul 2018	Systane® Ultra	Mean (IQR) NIBUT	N.A.	5.1 (4.4–6.6)	7.0 (5.5–8.1)	N.A	<0.001	N.A
Aguilar 2018	Systane® Ultra	Mean (SD) TBUT	Month 3	4.8 (1.0)	6.8 (0.9)	2.0 (1.0)	<0.0001	N.A
Ng 2018	Systane® Ultra	Mean (SD) NIBUT in the worst eye	Week 3	4.5 (2.9)	6.7 (4.6)	NR	<0.05	N.A
Tong 2018	Systane® Ultra	Mean (SD) NIBUT	Month 1	9.36 (6.3)	9.8 (6.3)	0.43 (6.9)	N.A	N.A
Muntz 2020	Systane® Complete	Mean (SD) NIBUT	N.A.	8.3 (3.8)	10.4 (5.6)	N.A	<0.001	N.A
Muntz 2020	Systane® Ultra	Mean (SD) NIBUT	N.A.	8.2 (4.1)	8.3 (4.7)	N.A	0.03	N.A
Pucker 2020	Systane® Complete	Mean (SD) Sodium Fluorescein TBUT (seconds)	Week 2	7.7 (5.2)	8.6 (4.7)	0.87 (3.8)	0.28	N.A
Yeu 2020	Systane® Complete	Mean (SD) Sodium Fluorescein TBUT (seconds)	Week 4	2.6 (1.0)	4.0	1.4 (2.8)	N. A	N.A
Craig 2021	Systane® Ultra	Mean (SD) TBUT	Month 6	N.A	N.A	4.5 ± 5.6	N. A	N. A
	Systane® Complete							

Abbreviations: IQR, Interquartile Range; NIBUT, Non-Invasive Break-Up Time; SD, Standard Deviation, TBUT, Tear Break-Up Time; TFBUT, Tear Film Break-Up Time. *Compared to Systane®.

Table 3. Magnitude of improvement from baseline in patient-reported symptoms for the Systane® family of products, using the ocular surface disease index (OSDI) questionnaire.

Study	Treatment	Definition	Time point	Baseline	Endpoint	Change from Baseline	P-Value
Davitt 2010	Systane® (General)	Mean (SD) OSDI score	Month 3	N.A.	N.A.	-8.6	0.001
Sanchez 2010	Systane®	Mean (SD) OSDI score	Month 1	9.5 (8.0)	3.3 (2.5)	N.A.	0.002
Jacobi 2012	Systane® (General)	Mean (SD) OSDI score	Month 3	50.0 (19.1)	31.3 (18.2)	N.A.	0.01
Urzua 2012	Systane®	Mean OSDI score	Week 2	51.0	41.0	N.A.	N.A
Comez 2013	Systane® (General)	Mean (SD) OSDI score	Week 12	41.4 (13.9)	N.A	-26.4 (10.5)	<0.001
Llamas-Moreno 2013	Systane® (General)	Mean (SD) OSDI score	Month 2	19.8 (7.1)	10.8 (6.4)	N.A	N.A
Fernandez 2015	Systane® (General)	Mean (SD) OSDI score	Day 30	41.5 (23.6)	32.91 (23.2)	8.6	0.02
Pinto-Bonilla 2015	Systane® (General)	Mean (SD) OSDI score	Week 1	N.A	N.A	-9.0 (11.9)	N.A
Perez-Ballbuena 2016	Systane® (General)	Mean OSDI score	Day 60	19.3 (7.5)	7.9 (8.2)	N.A	<0.001
Wong 2017	Systane® Ultra	Mean (SD) OSDI score	Week 2	19.2 (12.0)	22.3 (16.6)	3.1 (11.7)	0.26
Ng 2018	Systane® Ultra	Mean (SD) OSDI score	Week 3	44.9 (15.2)	28.3 (17.0)	N.A	<0.001
Belalcázar-Rey 2021	Systane® Ultra	Mean (SD) OSDI Score	Month 3	16.3 (6.3)	N.A	-9.3 (8.7)	<0.05
Belalcázar-Rey 2021	Systane® Ultra PF	Mean (SD) OSDI Score	Month 3	16.1 (8.3)	N.A	-9.8 (10.2)	<0.05
Craig 2021	Systane® Ultra	Mean (SD) OSDI Score	Month 6	N.A	N.A	16.6 ± 12.8*	<0.05
	Systane® Complete						
Pucker 2022	Systane® Hydration PF	Mean (SD) OSDI Score	Week 2	24.8 (6.0)	14.3 (8.6)	N.A	<0.05

Abbreviations: OSDI, Ocular Surface Disease Index; PF, Preservative-free; SD, Standard Deviation. *average improvement in OSDI symptomology score.

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What's in the news?

Results of Phase III Trial Show Promise of Potential First-in-Class Treatment for Dry Eye Disease

PL9643 ophthalmic solution is a melanocortin agonist with a novel mechanism of action that produced a clinically meaningful and statistically significant reduction in pain associated with dry eye disease.

A novel therapy for dry eye disease (DED) achieved clinically meaningful and statistically significant results in the pivotal Phase III MELODY-1 clinical trial.1 PL9643 ophthalmic solution, developed by Palatin Technologies, Inc., is a melanocortin agonist with a novel mechanism of action that, if approved, would be a first-in-class therapy for DED.[2]

"Even with a high vehicle response, PL9643 treatment was clinically meaningful and statistically significantly effective on an [intent-to-treat (ITT)] basis in reducing patient symptoms for the co-primary pain endpoint and multiple other symptom endpoints," Carl Spana, PhD, president and CEO of Palatin, said in a press release. "We are pleased that PL9643 treatment demonstrated excellent safety and tolerability data, including superior efficacy results compared to vehicle across multiple sign endpoints."[1]

DED is a chronic, multifactorial condition of the ocular surface, which is characterized by hyperosmolarity, inadequate production and instability of tear film, and damage and inflammation of the ocular surface. An estimated 16.4 million US adults have been diagnosed with DED, which can have a significantly negative impact on quality of life, causing ocular discomfort, fatigue, and visual disturbance.[3,4]

The development of DED is frequently linked to aging, with women twice as likely to develop DED as men. The condition commonly manifests during pregnancy, menopause, and post menopause.

The multi-center, randomized, double–masked, vehicle–controlled MELODY-1 trial analysed the safety and efficacy of PL9643 in patients with moderate-to-severe DED. The study design was based on positive findings from a Phase II trial and an end-of-phase meeting with the FDA that discussed key elements of the clinical program.[5]

The MELODY-1 trial's co-primary efficacy endpoints were the clinical symptom of pain and the clinical sign of conjunctival lissamine green staining, in addition to other symptom and sign secondary endpoints. PL9643 was administered over 12 weeks with a four-week run-in period in 575 patients who were randomly assigned to receive the study drug or vehicle.

After adjusting the ITT data to account for both age and sex in the primary statistical analysis, the drug produced clinically meaningful and statistically significant outcomes for the co-primary symptom endpoint of pain, with a visual analog score reduction of >10 points from baseline, ($p<0.025$) and multiple other symptom endpoints. For the co-primary sign and secondary sign endpoints, PL9643 produced positive effects compared with vehicle in the ITT population but did not reach statistical significance, nor did it achieve statistical significance for the co-primary endpoints and secondary endpoints in the unadjusted planned analyses.[1]

In terms of safety, PL9643 was well-tolerated, with fewer treatment-related adverse effects in those administered PL9643 (5.6%, N=16/288) compared with vehicle (6.3%, N=18/287), and fewer study discontinuations (7.0%, N=20/288) compared with vehicle (11.1%, N=32/287).

"It is important to note that it is rare for one clinical study in DED to show efficacy for both a sign and a symptom. While additional analyses are ongoing, the initial results reinforce the potential of PL9643 as a treatment to address both symptoms and signs of DED," Spana said in the release.
"Our comprehensive data analysis is ongoing, and upon completion, we plan to meet with the FDA to discuss and get feedback on the design of the next pivotal Phase III clinical trial. Furthermore, we will continue with our efforts for a collaboration partner for our DED program."[1]

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B12 deficiency: Corneal sensation

by **Mr. Jyotin Pandit**

In a busy ophthalmology clinic, it is easy to disparage patients persistently complaining of “dry eye” symptoms and move on to the next patient with more interesting pathology. Yet some will have unrecognised causes that have been missed by previous occupants of the cubicle. Symptoms such as photophobia and ocular pain (or lack of it despite significant corneal signs) can be “red flags” that point to an underlying diagnosis. Neurosensory abnormalities have been included in the definition of Dry Eye Disease since 2017 (Craig 2017).

A female patient in her sixties came to our clinic complaining of a multitude of ocular symptoms, including pain, photophobia, epiphora and foreign body sensation.

A series of well-meaning junior staff had prescribed a variety of different topical lubricants, to no avail. When she came to see me, she brought a small shoebox containing her many bottles. She complained bitterly about the pain she felt in her eyes and the sensitivity to light.

I examined her ocular surface and found bright white conjunctivas, with no abnormal lashes, no concretions in the conjunctival fornix or calcified pingueculae to account for her symptoms, even after everting her upper eyelids Tear meniscus height was normal, tear osmolarity was in the normal range, visual acuity was good and there were no punctate erosions. I requested some blood tests to look for Sjogren’s syndrome. As she was going to stuck with a needle anyway, I added tests for Vitamin B12 and folate to the form.

Her vitamin B12 level came back as 150pg/mL, which is well below the normal range. I saw her a few months later and she told me she had been on omeprazole for more than 20 years. Her tests for Intrinsic Factor Antibody and Gastric Parietal Cell antibody were negative.

Proton pump inhibitors are some of the most widely prescribed medications in the UK. In 2020, omeprazole was the second commonest drug dispensed in England (Lelwala 2023). PPIs block the production of acid in the stomach and are responsible for a wide range of vitamin and mineral deficiencies. I advised her GP to start her on IM Vitamin B12 injections and to monitor her B12 and folate levels in the future.

Vitamin B12 is a water-soluble compound containing a single cobalt atom, produced by certain bacteria and only found in animal products such as meat, eggs and milk. It is essential in the maintenance of the nervous system and in the production of blood cells.

Vitamin B12 deficiency is common. An oft-quoted review of surveys undertaken in the US and the UK stated that the prevalence in the general population was 6% (Allen 2009) but the true figure is likely to be much higher. A survey of young women in the UK found a prevalence of 12.4% (Sukumar 2016) and a more recent survey in Ireland found 1 in 8 people (12.5%) of the general population deficient in B12 (O’Connor 2020).

Neurological complications are the most common manifestations of vitamin B12 deficiency, and these can cause a wide variety of symptoms and signs. Neuro-sensory abnormalities may manifest as paresthesia, tinnitus, and loss of proprioception. Ocular manifestations include pupillary abnormalities and nystagmus, visual field defects and corneal hyperesthesia. Patients with Neuropathic Ocular Pain (NOP) who were B12 deficient noticed a dramatic improvement in signs and symptoms after treatment with vitamin B12 (Shetty 2015, Ozen 2017).

Pernicious anaemia is an uncommon cause of vitamin B12 deficiency. Nevertheless, tests for Intrinsic Factor antibodies should be carried out if vitamin B12 levels are found to be deficient (Vaqar 2023). If in doubt, elevated methyl malonic acid levels are more specific for vitamin B12 deficiency. High homocysteine levels also occur in folic acid deficiency, as well as vitamin B12 deficiency.

Once adequate levels of vitamin B12 have been achieved then it is important to monitor them regularly.
Untreated vitamin B12 deficiency can have devastating consequences, including depression, dementia, paralysis from subacute degeneration of the spinal cord and blindness from optic atrophy.

So, consider the probability of vitamin B12 deficiency, next time you see a patient with minimal signs and persistent symptoms of “dry eye disease”.

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