Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

New news since TFOS DEWS II

June 3, 2020

Associate Professor Jennifer P. Craig heads the Ocular Surface Laboratory at the University of Auckland in New Zealand. She publishes widely and enjoys presenting on all things dry eye around the world, virtually, if not in person!

The field of dry eye has evolved dramatically in the last 30 years and in the last 3 years, the phrase 'TFOS DEWS II' has become increasingly well recognized. The Tear Film and Ocular Surface Society (TFOS) has played an instrumental role in this transformation through tireless efforts to fulfil its mission of advancing research, promoting literacy and education, and stimulating interactions among basic scientists, academic clinicians and industry representatives in the field of the tear film and ocular surface. Figure 1 shows the exponential growth in research interest in dry eye, as reflected by the scientific literature. The number of 'Dry Eye' articles published in the decade following the original TFOS Dry Eye Workshop (TFOS DEWS) report was released in 2007, increased 2.7-fold relative to the previous decade. Today, not even three years since the TFOS DEWS II reports became available, almost 70% of the last decade's research in dry eye – over 2,000 articles – have been published already. The TFOS reports play a critical role in consolidating the evidence published within the global literature to assist in guiding future research by identifying the gaps and shortcomings in knowledge. As we approach the 3rd anniversary of the publication of TFOS DEWS II outcomes, it seems an appropriate time to take a step back and reflect on the latest developments over this time.

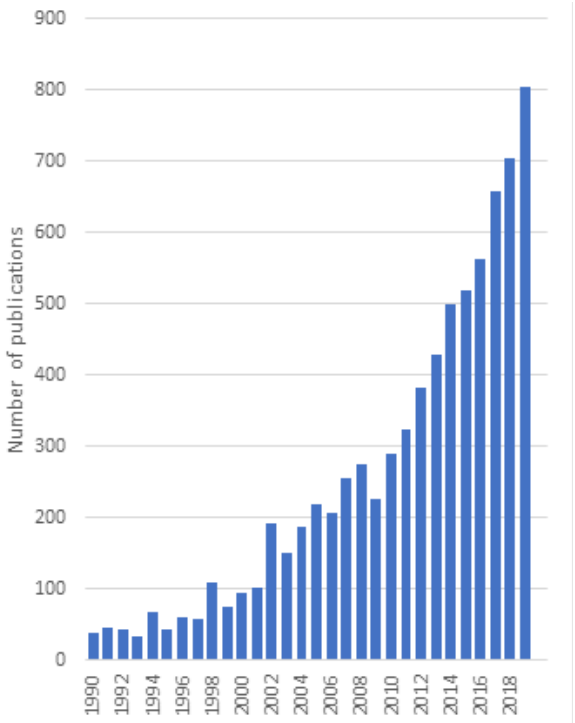

Figure 1: Growth in dry eye literature in the last 30 years

Dry eye disease prevalence and risk factors

Reviewing population-based studies of at least 500 participants, the TFOS DEWS II Epidemiology subcommittee reported a broad range of dry eye prevalence values (5 – 50%), which was recognized to reflect variability in diagnostic criteria rather than true population differences.[1] In furthering our understanding of the natural history of dry eye disease, and its associated risk factors, a need for more population-based studies was identified, and it's pleasing to see a growing literature seeking to address this.

In response to the Epidemiology report's observation of a dearth of population-based studies from the Southern Hemisphere in 2018, some of the first dry eye prevalence data for Latin America was published. Castro et al. reported a prevalence rate of 12.8% based on 3,107 responses to a short questionnaire, focusing on self-reported dry eye symptoms and risk factors, from participants across Brazil.[2] Female sex, older age (≥60 years), history of ocular surgery, contact lens wear, cancer treatment, computer use >6 hours per day, antidepressants and anti-allergy medications proved to be the most significant risk factors.

The adult dry eye prevalence rate for the Netherlands was found to be 9.1% according to the responses of almost 80,000 participants, self-reporting marked symptoms and/or a previous dry eye diagnosis.[3] A broad range of independent risk factors for dry eye were identified, including female sex, contact lens use, eye surgery, keratoconus, Graves' disease, as well as systemic conditions such as rosacea, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, osteoarthritis, connective tissue diseases, atherosclerosis, autism, depression, 'burnout', Crohn's disease, sarcoid, lichen planus, liver cirrhosis, sleep apnea, sinusitis, thyroid function, and air pollution (NO2). Interestingly, high blood pressure and high BMI appeared to be protective, as was current smoking, while ex-smokers were noted to experience dry eye more commonly.[3]

In Palestine, a cross-sectional study of 769 randomly selected, non-contact lens wearing participants (mean age 44±19 years) from 16 towns across the State, was conducted.[4] Despite pre-dating publication of the TFOS DEWS II report, the study employed diagnostic criteria that required the presence of both symptoms (OSDI≥13) and signs, which align largely with those recommended by TFOS DEWS II.[5] A high dry eye prevalence rate of 64% was reported in Palestine, and key risk factors were identified as older age and female sex.[4] The arid environment of the Middle East with high temperatures, along with stress and anxiety attributed to geopolitical conflict were considered to be other possible risk factors although psychological status was not specifically evaluated in this study.

Global consistency in dry eye diagnosis will assist in more valid comparisons of dry eye prevalence across the world. The TFOS DEWS II diagnostic criteria proposed to offer such consistency,[5] are increasingly being adopted in the latest research studies. A recent study exploring systemic risk factors for dry eye in New Zealand, reported that 29% of the sample of 372 community participants fulfilled the TFOS DEWS II criteria for dry eye disease, (11% with signs of aqueous tear deficiency and 26% with meibomian gland dysfunction (MGD)).[6] Multivariate logistic regression analysis identified systemic rheumatological disease and antidepressant medication as independent risk factors for aqueous deficient dry eye, and age, East Asian ethnicity, migraine, thyroid disease, and oral contraceptive therapy as the key risk factors for MGD.[6]

Diagnosing dry eye disease

Based on the literature available at the time, the TFOS DEWS II Diagnostic Methodology subcommittee proposed clear diagnostic criteria for dry eye disease that require a positive symptom score and the presence of at least one clinical dry eye sign (from tear film instability, tear hyperosmolarity or ocular surface staining).[5] Clarity and consistency in diagnostic criteria has allowed significant work to be undertaken since 2017 in evaluating and comparing the diagnostic accuracy of various diagnostic tools.

There has been a focus on diagnostic accuracy in the literature, with publications critically evaluating both the subjective symptoms and objective signs as markers of dry eye disease. Wang et al. found that the OSDI and SANDE questionnaires showed the best diagnostic accuracy of 5 commonly administered questionnaires, and with similar optimal cut-off scores (>14 for OSDI and >4 for SANDE) to the currently accepted values.[7] The findings highlight the importance of questionnaire selection and consistency in use across individual practice settings, as the questionnaires cannot be considered interchangeable. The same research group reported that tear film osmolarity showed moderate diagnostic accuracy, and possessed better discriminative ability than interocular difference in osmolarity.[8] The optimal diagnostic cut-off for osmolarity from this study of 866 individuals matched that of TFOS DEWS II (≥308mOsm/L), but the cut-off for interocular difference in osmolarity in this group was a little higher than that of TFOS DEWS II (>8mOsm/L), at >10mOsm/L. Evaporative dry eye disease markers were not exempt from scrutiny and, from a sample of over 400 participants, it was shown that tear film lipid layer grade was more predictive of evaporative dry eye disease status than meibomian gland drop out.[9] This adds weight to existing literature,[10] suggesting that gland drop out may have greater utility in predicting functional *potential* than current tear film status. A clear relationship between gland drop out and tear film function appears to exist only in the most advanced cases of MGD.[10]

Applying the TFOS DEWS II recommended diagnostic criteria wherever possible will be important for conducting meta-analyses in future that will allow us to truly understand dry eye prevalence.[5] However, for those in time-constrained or resource-constrained clinical settings where full testing is not possible, the full work up might not be possible. Acknowledging the limitations of abbreviated diagnostic protocols, and the sensitivity and specificity with which a diagnosis can be made, relative to the global recommended criteria, is important. A rapid and non-invasive alternative to the full TFOS DEWS II diagnostic work up was proposed in 2019, and its diagnostic accuracy tested relative to the full TFOS DEWS II work up on data from 235 participants.[11] Utilizing a SANDE cutoff of >30 to gauge symptoms, and <10 seconds on non-invasive break up time (NIBUT) as a global marker of homeostatic imbalance, this rapid and non-invasive alternative to the full TFOS DEWS II diagnostic work up offered the ability to diagnose dry eye disease with a sensitivity of 86% and specificity of 94%. Optimal cut-offs of 0.2mm for tear meniscus height as a marker of aqueous deficiency and a lipid layer grade of ≤3 in lipid layer grade as a marker of evaporative dry eye allowed for further disease subtyping.[11]

Others, too, have sought to streamline aspects of the diagnostic process. Pult and Wolffsohn recently described the development and evaluation of the OSDI-6, a shortened version of the original 12-item OSDI, which they showed to be strongly repeatable and predictive of the original OSDI score.[12]

Recent advances in dry eye management

Development of novel therapeutic strategies for managing dry eye has continued apace in recent years, with a shift from generic palliative approaches towards more targeted treatments specific to the pathophysiology of dry eye. The directive from the TFOS DEWS II Management and Therapy subcommittee to strive for higher quality studies,[13] supported by methodological guidance from the Clinical Trials subcommittee,[14] has been met with greater enthusiasm to conduct systematic reviews and meta-analyses which critically appraise the current literature and identify gaps in knowledge, and a greater commitment to undertake double-masked randomized controlled trials (RCTs) that seek to minimize risk of bias while evaluating therapeutic benefit.

A number of systematic reviews published in the last three years, on topics including topical ophthalmic drugs,[15,16] serum eye drops,[17] and artificial tear supplements,[18] have been useful in drawing attention to areas where the evidence is less convincing than one might expect for many of the dry eye treatments that have been widely adopted in clinical practice. A recurring conclusion from these thorough reviews, is the need for an increased number of well-designed clinical trials, with attention paid to recruitment criteria, adequate control and masking, larger sample sizes, longer follow-up periods, and consistency in the application of appropriately selected clinical endpoints, in order to prove true benefit.

A Cochrane review, published by Downie et al.,[19] confirmed that the jury remains out with regard to the benefits of omega-3 polyunsaturated fatty acids in dry eye disease. This review helped place the provoking findings from the 2018 DREAM study,[20] in perspective, but highlighted the need for further research in this area. Therapeutic benefit of intense pulsed light (IPL) in managing meibomian gland dysfunction (MGD) was similarly deemed equivocal in a Cochrane review based on the literature available at the time of publication,[21] although a recently published randomized, double masked, placebo-controlled, parallel group, 105-day trial, addressing many limitations of the previous studies, has since confirmed safety and efficacy of Intense Regulated Pulsed Light® (E-Eye, ESW Vision) for MGD, in the absence of confounding effects from concurrent gland expression.[22] Once again, more scientific evidence is required in this area to confirm optimal dosing (fluence, pulse profile, and the number and spacing of treatment sessions), and to elucidate the mechanism(s) of action underlying the observed improvements in meibomian gland function.

Lifitegrast 5% (Novartis) has shown statistical superiority in a symptom or sign endpoint versus control in large multicenter clinical trials.[23] Recently, its safety and tolerability was reviewed on the basis of pooled data from five prospective multicenter RCTs, involving over 2,400 participants.[24] Adverse events worthy of noting for prospective patients were mostly mild-to-moderate ocular discomfort and redness at the site of instillation, and dysgeusia (usually a metallic taste). While transient ocular symptoms (resolving within around 3 minutes) were noted by over 15% of participants, and there was a 7% drop out rate overall, on balance, the preparation was deemed to be safe and well-tolerated.[24]

An exciting area in dry eye management involves novel biological therapies. Progress has been reported on chitosan-N-acetylcysteine (Lacrimera®, Cromapharma), which seeks to restore tear film homeostasis in moderate to severe dry eye by forming a glycocalyx-like polymer-mucin network at the ocular surface.[25] Improved tear film stability and reduced corneal staining have been observed with once daily topical eye drop application in moderate-to-severe dry eye, in two unmasked case series.[25,26] Another novel biologic of note is recombinant human lubricin (proteoglycan 4) (Lubris Biopharma). Lubricin is a large glycoprotein, found in synovial fluid which may reduce friction on the ocular surface during blinking. Lubricin has been confirmed to be more effective in managing moderate dry eye disease than 0.18% sodium hyaluronate drops in a two-week, randomized, double masked trial.[27]

Recent research suggests there may be therapeutic potential for bioactive lipids derived from polyunsaturated fatty acids (PUFA). As potent signaling molecules capable of modulating inflammatory responses, this could prove useful in certain forms of dry eye disease and possibly in managing subclinical inflammation associated with contact wear.[28] Topically applied Manuka Honey, derived from *Leptospermum* species, has also shown therapeutic potential, either alone, or in a complexed form, according to recently published RCTs,[29,30] as has natural castor oil, in periocular application.[31]

As MGD has increasingly become recognized as a leading cause of dry eye disease, there has been growing demand for effective treatments to manage lid disease in order to support a healthy ocular surface, improve quality of life for patients and minimise the risk of iatrogenic dry eye secondary to contact lens wear or ophthalmic surgery.

Positive outcomes following LipiFlow® Thermal Pulsation therapy (Johnson & Johnson Vision),[32] have prompted the development of novel devices based on a similar principle. The iLux® MGD Treatment System (Alcon) similarly offers eyelid heating and simultaneous gland expression, but in the form of a handheld device where the clinician can visualize the lid margin and control the application of heat and pressure to customize the treatment. An open-label, 1-month trial in which participants were randomized to treatment with either the portable iLux® or LipiFlow® showed equivalence in efficacy, at 4 weeks post-application, with both treatments reducing symptoms, increasing tear film stability and improving gland secretion.[33] The time frame over which this equivalence is

maintained has yet to be established. The TearCare® system (Sight Sciences) is another portable device which offers heat delivery direct to the lid margins and this is followed by in-office therapeutic gland expression.[34,35] Early results from small unmasked pilot studies appear promising, with the novel device reported to outperform standard warm compress therapy, but there is a need for high quality RCTs, with an increased sample size, and with investigator masking to be conducted in future to confirm this therapy's true potential.

Where to next?

The breadth of developments in the last 3 years, that can only be touched on in an article of this nature, confirms the fast-evolving nature of dry eye research. There's an increasing number of scientists, both clinical and basic, who are working directly, or indirectly, towards improving the lives of affected patients, and producing high quality research. These inspired and creative individuals, with the support of industry, and organizations such as TFOS, will ensure we continue to learn more about its pathophysiology, its natural history and relevant risk factors, as well as establish superior methods of identifying and managing the disease. Interest in the field is expanding at a phenomenal rate, and that can only be good news for the many millions of patients who are affected by dry eye disease, and who desperately await the answers.

REFERENCES

1. Stapleton F, Alves M, Bunya VY, *et al*. TFOS DEWS II Epidemiology Report. *Ocul Surf* 2017;15:334-65.
2. Castro JS, Selegatto IB, Castro RS, *et al*. Prevalence and Risk Factors of self-reported dry eye in Brazil using a short symptom questionnaire. *Sci Rep* 2018;8:2076.
3. Vehof J, Snieder H, Jansonius N, Hammond CJ. Prevalence and risk factors of dry eye in 79,866 participants of the population-based Lifelines cohort study in the Netherlands. *Ocul Surf* 2020.
4. Shanti Y, Shehada R, Bakkar MM, Qaddumi J. Prevalence and associated risk factors of dry eye disease in 16 northern West bank towns in Palestine: a cross-sectional study. *BMC Ophthalmol* 2020;20:26.
5. Wolffsohn JS, Arita R, Chalmers R, *et al*. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf* 2017;15:539-74.
6. Wang MTM, Vidal-Rohr M, Muntz A, *et al*. Systemic risk factors of dry eye disease subtypes: A New Zealand cross-sectional study. *Ocul Surf* 2020.
7. Wang MTM, Xue AL, Craig JP. Comparative Evaluation of 5 Validated Symptom Questionnaires as Screening Instruments for Dry Eye Disease. *JAMA Ophthalmol* 2019;137:228-9.
8. Wang MTM, Ormonde SE, Muntz A, Craig JP. Diagnostic profile of tear osmolarity and inter-ocular variability for dry eye disease. *Clin Exp Ophthalmol* 2020;48:255-7.
9. Wang MTM, Dean SJ, Muntz A, Craig JP. Evaluating the diagnostic utility of evaporative dry eye disease markers. *Clin Exp Ophthalmol* 2020;48:267-70.
10. Blackie CA, Korb DR, Knop E, Bedi R, Knop N, Holland EJ. Nonobvious obstructive meibomian gland dysfunction. *Cornea* 2010;29:1333-45.
11. Wang MTM, Xue AL, Craig JP. Screening utility of a rapid non-invasive dry eye assessment algorithm. *Cont Lens Anterior Eye* 2019;42:497-501.
12. Pult H, Wolffsohn JS. The development and evaluation of the new Ocular Surface Disease Index-6. *Ocul Surf* 2019;17:817-21.
13. Jones L, Downie LE, Korb D, *et al*. TFOS DEWS II Management and Therapy Report. *Ocul Surf* 2017;15:575-628.
14. Novack GD, Asbell P, Barabino S, *et al*. TFOS DEWS II Clinical Trial Design Report. *Ocul Surf* 2017;15:629-49.
15. Holland EJ, Darvish M, Nichols KK, Jones L, Karpecki PM. Efficacy of topical ophthalmic drugs in the treatment of dry eye disease: A systematic literature review. *Ocul Surf* 2019;17:412-23.
16. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst Rev* 2019;9:CD010051.
17. Franchini M, Cruciani M, Mengoli C, *et al*. Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis. *Blood Transfus* 2019;17:200-9.
18. Ribeiro M, Barbosa FT, Ribeiro LEF, Sousa-Rodrigues CF, Ribeiro EAN. Effectiveness of using preservative-free artificial tears

versus preserved lubricants for the treatment of dry eyes: a systematic review. *Arq Bras Oftalmol* 2019;82:436-45.

19. Downie LE, Ng SM, Lindsley KB, Akpek EK. Omega-3 and omega-6 polyunsaturated fatty acids for dry eye disease. *Cochrane Database Syst Rev* 2019;12:CD011016.
20. Dry Eye A, Management Study Research G, Asbell PA, et al. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. *N Engl J Med* 2018;378:1681-90.
21. Cote S, Zhang AC, Ahmadzai V, *et al*. Intense pulsed light (IPL) therapy for the treatment of meibomian gland dysfunction. *Cochrane Database Syst Rev* 2020;3:CD013559.
22. Xue AL, Wang MTM, Ormonde SE, Craig JP. Randomised double-masked placebo-controlled trial of the cumulative treatment efficacy profile of intense pulsed light therapy for meibomian gland dysfunction. *Ocul Surf* 2020;18:286-97.
23. Tauber J, Karpecki P, Latkany R, *et al*. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. *Ophthalmology* 2015;122:2423-31.
24. Nichols KK, Donnenfeld ED, Karpecki PM, *et al*. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: Pooled analysis of five randomized controlled trials in dry eye disease. *Eur J Ophthalmol* 2019;29:394-401.
25. Messina M, Dua HS. Early results on the use of chitosan-N-acetylcysteine (Lacrimera((R))) in the management of dry eye disease of varied etiology. *Int Ophthalmol* 2019;39:693-6.
26. Nepp J, Knoetzl W, Prinz A, Hoeller S, Prinz M. Management of moderate-to-severe dry eye disease using chitosan-N-acetylcysteine (Lacrimera(R)) eye drops: a retrospective case series. *Int Ophthalmol* 2020.
27. Lambiase A, Sullivan BD, Schmidt TA, *et al*. A Two-Week, Randomized, Double-masked Study to Evaluate Safety and Efficacy of Lubricin (150 mug/mL) Eye Drops Versus Sodium Hyaluronate (HA) 0.18% Eye Drops (Vismed(R)) in Patients with Moderate Dry Eye Disease. *Ocul Surf* 2017;15:77-87.
28. Flitter BA, Fang X, Matthay MA, Gronert K. The potential of lipid mediator networks as ocular surface therapeutics and biomarkers. *Ocul Surf* 2020.
29. Tan J, Jia T, Liao R, Stapleton F. Effect of a formulated eye drop with Leptospermum spp honey on tear film properties. *Br J Ophthalmol* 2020.
30. Craig JP, Cruzat A, Cheung IMY, Watters GA, Wang MTM. Randomized masked trial of the clinical efficacy of MGO Manuka Honey microemulsion eye cream for the treatment of blepharitis. *Ocul Surf* 2020;18:170-7.
31. Muntz A, Sandford E, Claassen M, *et al*. Randomized trial of topical periocular castor oil treatment for blepharitis. *Ocul Surf* 2020.
32. Greiner JV. Long-Term (3 Year) Effects of a Single Thermal Pulsation System Treatment on Meibomian Gland Function and Dry Eye Symptoms. *Eye Contact Lens* 2016;42:99-107.
33. Tauber J, Owen J, Bloomenstein M, Hovanesian J, Bullimore MA. Comparison of the iLUX and the LipiFlow for the Treatment of Meibomian Gland Dysfunction and Symptoms: A Randomized Clinical Trial. *Clin Ophthalmol* 2020;14:405-18.
34. Badawi D. TearCare((R)) system extension study: evaluation of the safety, effectiveness, and durability through 12 months of a second TearCare((R)) treatment on subjects with dry eye disease. *Clin Ophthalmol* 2019;13:189-98.
35. Badawi D. A novel system, TearCare((R)), for the treatment of the signs and symptoms of dry eye disease. *Clin Ophthalmol* 2018;12:683-94.