CLINICAL PRACTICE PATTERNS IN THE MANAGEMENT OF DRY EYE DISEASE: A TFOS INTERNATIONAL SURVEY

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Purpose: To examine clinical management and prescribing patterns for dry eye disease (DED), in relation to severity and subtype, by eyecare practitioners across the globe.

Methods: An online-anonymous cross-sectional survey (on Qualtrix) translated into 14 languages was distributed to eyecare practitioners across the globe. The survey included six questions around the management of DED, in relation to severity and subtype.

Result: The survey was completed by 1,139 eyecare professionals (37% ophthalmologists and 58% optometrists) from 51 countries. Management varied significantly by continent and country ($p<0.01$). The most commonly recommended management approaches internationally, included general advice (87%), low (85%) and high (80%) viscosity-enhancing unpreserved lubricants and lid wipes/scrubs (81%). Some treatments were prescribed largely independent of severity (e.g. artificial tears and nutritional supplements) while oral antibiotics, punctal occlusion, topical anti-inflammatory/immunosuppressants, secretagogues, biologics, therapeutic contact lenses and surgical approaches were prescribed by more practitioners as severity increased. Essential fatty acids, lipid sprays/drops, lid hygiene, warm compresses, intense pulsed light therapy and antibiotics (topical or oral) were more commonly recommended for evaporative DED, while artificial tears, moisture chamber goggles, punctal occlusion, therapeutic contact lenses, secretagogues and biologics were used more commonly for aqueous deficient DED.

Conclusions: DED management differs between continents and countries. A wide range of management strategies are utilised at each severity level and across subtypes. The survey results enable clinicians to benchmark their practice to their peers, indicate where further research is required to optimise patient management and to inform industry on how best to target product development.

Keywords: aqueous deficient dry eye; clinical management; dry eye disease; evaporative dry eye; severity; subtype

Short Title: TFOS DED International Management Patterns

Introduction

Dry eye disease (DED) is a multifactorial condition characterised by the loss of tear film homeostasis, and perpetuated by a vicious cycle of tear film instability, hyperosmolarity, and ocular surface inflammation.[1] The diagnosis of dry eye disease requires the presence of both clinical signs and symptoms. The TFOS DEWS II diagnostic methodology report identified the need for a standardised, minimally invasive approach to DED diagnosis, recommending the use of either the Ocular Surface Disease Index (OSDI) or Dry Eye Questionnaire (DEQ-5) questionnaires for screening dry eye symptomology, in combination with one of the global positive signs of homeostatic breakdown (tear instability, hyper or interocular differences in osmolarity or ocular surface staining).[2]

Following a diagnosis, the subtype of dry eye [1] should be determined as more evaporative (as indicated by lipid layer thickness interferometry, meibomian gland structure imaging and functionality testing) or aqueous deficient (as indicated by tear meniscus height).[2] This subtype, along with the severity of symptoms and identified modifiable risk factors, can then be used to develop an appropriate treatment plan.[3]

Previous studies investigating management therapies for dry eye disease subtypes have tended to focus on evaporative dry eye disease [4-12]. In terms of subtype, Alio and colleagues found little difference in the effectiveness of autologous platelet-rich plasma in the management of aqueous deficient compared to evaporative dry eye [13], whereas, while Essa and colleagues found the artificial tears they tested performed similarly, osmolarity balanced artificial tears were the preferred treatment in individuals with aqueous deficient dry eye and liposomal sprays were more efficacious for individuals with evaporative dry eye [14]. There has been limited research on the efficacy of management therapies across different severity levels of dry eye disease, with one study reporting that cyclosporine is more efficacious in more severe dry eye disease [15].

The TFOS DEWS II reports provided global consensus recommendations for the diagnosis and management of dry eye disease. Nonetheless, there remains limited evidence informing clinicians as to which treatment might work better for differing severities and subtypes of DED. Previous studies have reviewed management practice patterns between specific countries [16], between different professions located within the same country [17-19] and have evaluated differences between clinical patterns and evidence-based guidelines across Australia [20] (Table 1). To date only a few studies could be identified, which have compared global trends, such as one on aqueous deficient DED management approaches [21].

The main purpose of the current survey was to examine the clinical DED prescribing and management patterns of eye care practitioners around the globe, in relation to severity and subtype. This approach enables clinicians to benchmark their practice to their peers, identify areas of varying practice across the world, and indicate where further research is required to optimise patient management and inform industry on how best to target product development.

Table 1. Previous studies on patterns of clinical diagnosis and managment of dry eye disease (all anonymous internet surveys)

Study	Comparison	Topics	Surveyed	Professionals	Results	Comments
Downie et al., 2013[20]	Australian practice behaviours to internationally recognised guidelines for DED diagnosis and management	- Practitioner demographics - Diagnostic techniques - Management strategies (Mild/Moderate/Severe) - Evidence base for the practice patterns	144	Optometrists	- DED professionals tend to perform more diagnostic techniques and newer procedures - Mg: - Mild: AT and eyelid hygiene - Moderate: Unpreserved lubricants - Severe: Gel preparations	- Trend of Omega-3 fatty acids recommendation as severity of the increases. - Coricosteroids and anti-inflammatory eye drops also prescribed fro moderate and severe DED.
Downie et al., 2016[16]	UK and Australia practice behaviours for DED diagnosis and management	- Practitioner demographics - Diagnostic techniques - Management strategies (Mild/Moderate/Severe) - Evidence base for the practice patterns	317	Optometrists	- Patient symptoms, MGE and FBUT most important for both UK and Australian practitioners for diganosis - Mg: - Mild: Eyelid hygiene and lubricant AT - Moderate: Unpreserved gels - Severe: Topical ointments and PP	- Dx: UK tend to use more TMH, LIPCOF, standarised grading of conjunctival LG staining and OSDI - Dx: Australia tend to use more FBUT - Severity: UK assesment through patient symptoms - Mg: UK recommentds higher intake of omega-3 and less preserved AT for mild DED. Australia recommends topical corticosteroids for moderate and severe DED
Sy et al., 2015[21]	Global eye care practitioners	- Practitioner demographics - management of aqueous deficient patient case study - Access to treatments - Treatment algorithms	115	Cornea specialists (66 %), general ophthalmologists (16 %), non-clinical researchers (6 %), optometrists (6 %) and other (6 %)	The most commonly prescribed topical treatments included cyclosporine A, fluorometholone, loteprednol etabonate and autologous serum eye drops. The most commonly prescribed non-topical medications included essential fatty acid supplements, low-dose oral doxycycline and flaxseed supplements as well as PP.	Treatment response was monitored with corneal fluorescein staining, foreign body and burning sensation.
Van Tilborg et al., 2015[17]	Dutch optometrists and GPs on symptoms, causes, diagnosis and treatment of DE	- Knowledge - Investigative methods - Therapy preference	231	Optometrists (138) GPs (93)	- Dx: No agreement. GP: rarely use Dx tests. LG and NaFl staining and FBUT Optometrists: mainly FBUT, LG and NaFl staining -Mg: Agreement only in prescription of gel/ointment	- Mg: Optometrists: Tend to prescribe more unpreserved AT, lid hygiene and heat therapy GPs: Tend to prescribe more preserved AT

Williamson et al., 2014[18]	Perception of optometrists and ophthalmologists on DED management in North Carolina	- Knowledge about patient symptoms - Diagnostic - Treatment approaches	100	Optometrists Ophthalmologists	-Dx: BUT, NaFl staining -Mg: Patient history, AT, warm compress and lid scrubs	- Dx combination BUT, NaFl and LG staining Optometrists: NaFl staining and history Ophthalmologists: Schirmer test
Xue et al., 2017[19]	Diagnostic and management protocols of New Zealand optometrists and ophthalmologists for DED	- Practitioner demographics - Diagnostic techniques - Management strategies (Mild/Moderate/Severe) - Evidence base for the practice patterns	203	Optometrists (174) Ophthalmologists (29)	-Dx: Symptomatology, MGE, FBUT Optometrists: MGE Ophthalmologists: NaFl staining -Mg: Mild: Unpreserved AT, Preserved AT and eyelid hygiene Moderate: Eyelid hygiene, Omega-3, unpreserved AT and gels Severe: Eyelid hygiene, unpreserved AT and gels	In a severe condition unpreserved gel, topical ointment, cyclosporine A, topical corticosteroids, systemic tetracyclines, PP and autologous serum prescribed by both professions

AT – Artificial Tears, DED – Dry Eye Disease, GP – General Practitioner, Dx – Diagnose, Mg – Management, MGE – Meibomian Gland Examination, FBUT - Fluorescein Tear BreakUp Time, P
LG – Lissamine Green, NaFl – Fluorescein, BUT – BreakUp Time (undefined method), TMH – Tear Meniscus Height, LIPCOF – Lid Parallel Conjunctival Folds, OSDI – Ocular Surface Disease

Methods

Survey design

The survey (Table 2) was designed by the authors based on the DED management options reported by TFOS DEWS II [3] and sought to examine how management decisions were based according to the severity and subtype of DED [1, 2]. The survey was designed in English, translated into 14 languages (Brazilian Portuguese, Chinese/Mandarin Chinese, Czech, French, German, Italian, Spanish, Polish, Portuguese, Rumanian, Russian and Serbian). In each case the translation was back translated and checked by an independent native-speaking eye care professional to ensure consistency was maintained in the meaning of the questions. The anonymous, online survey was administered using the Qualtrics platform (Utah/Seattle, Washington, USA).

Table 2. Summary of questions presented in the survey

Question Categories	Possible Responses
Practitioner demographics	Mode of practice; Ophthalmologist, optometrist or other Years of clinical experience Country of practice
Type of dry eye patients managed (ranking)	1. No presenting specific symptoms: identified incidentally on questioning 2. Intermittent presenting symptoms: occasional effect on quality of life 3. Intermittent presenting symptoms: occasional effect on quality of life 4. Moderate symptoms: frequent impact on quality of life 5. Severe symptoms: constant debilitating effect on quality of life
Are you LICENSED to use this within your scope of practice in your country? Do you ever PRESCRIBE this option? What SUBTYPE(S) of dry eye disease do you consider this treatment appropriate for (select as many as apply)? What SEVERITY(S) of dry eye disease do	1. Advice 2. Essential fatty acid supplements 3. Artificial Tears a. Low viscosity-enhancing lubricant PRESERVED b. High viscosity-enhancing lubricant PRESERVED c. Low viscosity-enhancing lubricant, UNPRESERVED d. High viscosity-enhancing lubricant UNPRESERVED 4. Ointments 5. Lipid containing lubricants (drops/spray) 6. Lid hygiene a. Lid wipes/scrubs b. Demodex cleansing lid wipes c. In-office demodex lid control d. Lid margin debridement e. In-office lid hygiene (e.g. BlephEx) f. Therapeutic meibomian gland expression 7. Moisture chamber spectacles /goggles 8. Punctal occlusion (with plugs) 9. Warm compresses a. Home-made warm lid compress, such as face-cloth b. Commercially available warm lid compress/face mask c. In-office thermal pulsation of lids (e.g. LipiFlow) 10. In-office Intense Pulsed Light therapy 11. Topical antibiotics (e.g. azithromycin) 12. Systemic antibiotics a. Systemic azithromycin b. Oral antibiotics (e.g. doxycycline) 13. Topical Anti-inflammatory/ Immunosuppression

you consider this treatment appropriate for (select as many as apply)?	a. Topical corticosteroids b. Topical cyclosporine c. Topical tacrolimus d. Topical lifitegrast 14. Secretagogues a. Topical secretagogues b. Oral secretagogues 15. Biologics a. Autologous/allogeneic serum b. Amniotic membrane 16. Therapeutic contact lenses 17. Surgical approaches a. Intraductal probing b. Other surgical approaches

Ethical approval

This study followed the tenets of the Declaration of Helsinki and was approved by Aston University and University of Auckland ethics committees. The data were collected anonymously and accessible only by the researchers. Prior to completing the questionnaire, a written statement informed the potential participant about the length of the survey, that submission of the questionnaire implied consent to participate, and that, as the data were anonymous, no changes to submitted data could be made. Responses could be submitted only once from a single device.

Participants

A link to the online survey was distributed via e-mail, through TFOS Ambassadors, conference seminars, professional colleges, and alumni university communities, and by word-of-mouth advertising. The survey was accessible from February 2018 and the data extracted in August 2019.

Data analysis

For the statistical analysis, countries were grouped into continents; Europe and the United Kingdom (EU), North America (NA), Latin America (LA), Australasia (AA), and Asia/Middle East (AME). Insufficient responses were received from Africa to permit statistical analysis, but these data were included in the global analysis. When comparing countries within a continent, only those countries with a survey response

rate ≥30 were included in the statistical analysis to allow 80% power to detect a ±5% difference taking a significance level of $p<0.05$ (G*Power).

Data analysis was performed with SPSS (version 23; New York, USA). Only completed surveys were included. Descriptive statistics such as median and range, or mean and standard deviation, were employed to describe the clinical DED severity and subtype when reviewing the therapy approach of practitioners. Due to the ordinal nature of the data, Mann-Whitney test was used to compare data between continents and countries. Fisher's exact test was using to compare categorical data. Based on a Bonferroni adjustment, a p-value of 0.003 or less was considered to denote statistical significance when comparing the continents approach to dry eye management, whilst a p-value of 0.016 or less (EU and AME) or 0.025 or less (NA, LA and AA) was considered significant when comparing the differences between countries.

Results

Practitioner demographics

Completed questionnaires were collected from a total of 1,136 eye care professionals, (37% ophthalmologists, 58% optometrists and 5% opticians) from 51 countries across 6 continents:

- Europe/UK and Scandinavia (n=459): Austria (n=22), Belgium (n=1), Bosnia and Herzegovina (n=5), Czech Republic (n=9), France (n=16), Germany (n=9), Greece (n=2), Ireland (n=13), Italy (n=18), Montenegro (n=2), Netherlands (n=25), Norway (n=9), Poland (n=17), Portugal (n=14), Romania (n=30), Serbia (n=26), Slovakia (n=4), Spain (n=84), Switzerland (n=11), United Kingdom (n=142).
- North America (n=126): Canada (n=66), United States of America (n=60).
- Latin America (n=135): Argentina (n=40), Barbados (n=1), Brazil (n=22), Chile (n=9), Colombia (n=18), Dominican Republic (n=1), Mexico (n=41), Peru (n=2), Venezuela (n=1).

- Australasia (n=111): Australia (n=58), New Zealand (n=53).
- Asia and the Middle East (n=288): Georgia (n=2), Hong Kong (n=34), India (n=11), Iran (n=11), Israel (n=1), Kuwait (n=1), Japan (n=1), Malaysia (n=22), Pakistan (n=3), Philippines (n=23), Russia (n=62), Singapore (n=20), Sri Lanka (n=1), South Korea (n=20), Taiwan (n=18), Thailand (n=48), Turkey (n=10).
- Africa (n=17): Cambodia (n=1), Ghana (n=2), Nigeria (n=1), South Africa (n=13).

It is not clear why practitioners from some countries engaged more with the unpaid survey than others, but it may reflect workload levels and the frequency of requests they receive to complete other surveys. The average years of experience was 11.8 ± 7.9, being similar between the different professional backgrounds (p=0.101) (Figure 1).

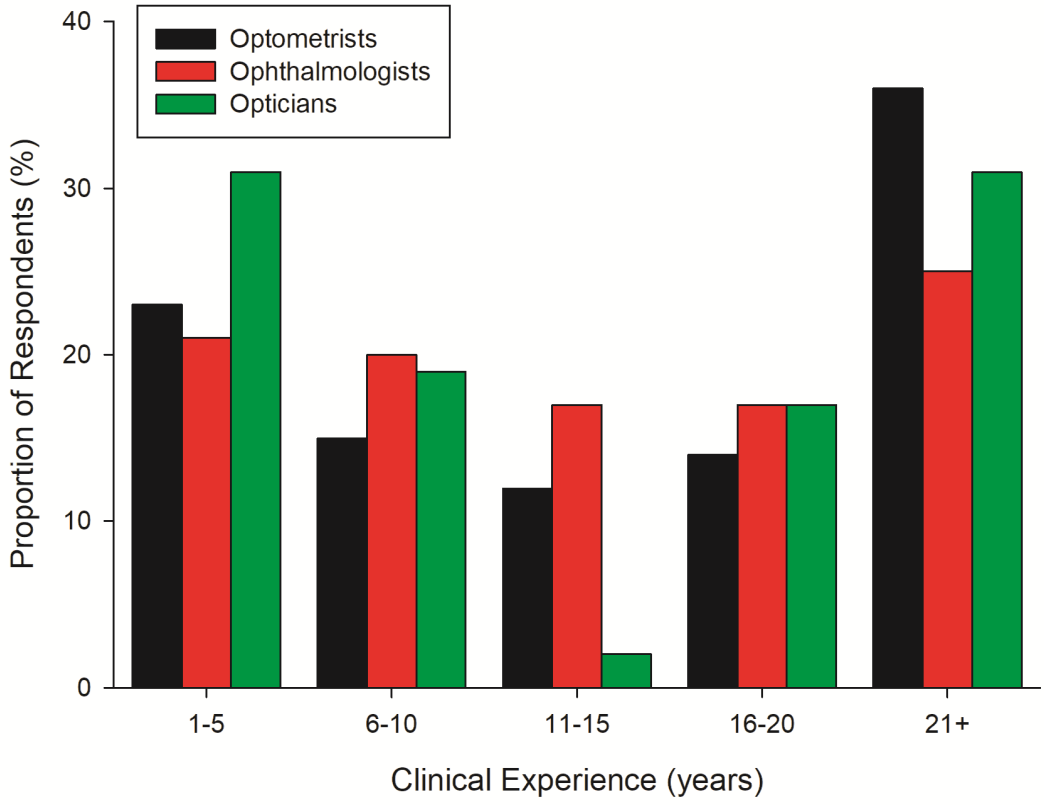

Figure 1: Years of clinical experience by profession.

Types of Patients Examined

Of the study respondents (n=1139), 1085 eyecare professionals completed the question describing the severities of DED they manage; patients with intermittent to moderate symptoms of DED were most commonly encountered in clinical practice (accounting for 34% of symptomatic patients, n=303/890). While 13% (n=140) reported they most commonly saw patients with severe symptoms, 56% (n=608) reported this was the least common patient they encountered.

Global management and therapies approach

Of those that responded, 85% (n=968) reported that they were actively managing DED. Of those who did not prescribe, 96% (n=164/171) reported providing advice to patients on topics such as hydration, healthy eating, and the office environment. As highlighted in Table 3, not all eye care professionals are licenced to apply any individual management strategy

Many treatment options for dry eye were observed to be utilised by respondents (3). Independent of DED severity and subtype, the most commonly used management approaches across the globe are advice (87%), low (85%) and high (80%) unpreserved viscosity-enhancing lubricants and lid wipes/scrubs (81%). Figure 1 displays graphically the mean level of severity and subtype reported by practitioners in their adoption of each dry eye management strategy and the average range over which they consider it to be appropriate.

Table 3. Proportion of [licenced] practitioners who use the different management options for dry eye based on continent

Management approach ⇩	[Licensed practitioners] Prescribing practitioners by continent					
Region studied ⇨	Europe	North America	Latin America	Australasia	Asia and Middle East	WORLDWIDE
Advice (e.g. hydration, healthy eating, office environment etc)	[85%] 80%	[98%] 91%	[85%] 85%	[94%] 91%	[90%] 86%	[90%] 87%
Essential fatty acid supplements	[66%] 53%	[94%] 87%	[63%] 60%	[89%] 85%	[66%] 49%	[76%] 67%
Low viscosity-enhancing lubricant PRESERVED	[75%] 48%	[94%] 83%	[80%] 77%	[90%] 75%	[76%] 42%	[83%] 71%
High viscosity-enhancing lubricant PRESERVED	[72%] 45%	[96%] 83%	[76%] 76%	[90%] 72%	[74%] 66%	[82%] 69%
Low viscosity-enhancing lubricant UNPRESERVED	[81%] 80%	[94%] 87%	[79%] 85%	[93%] 94%	[81%] 80%	[85%] 85%
High viscosity-enhancing lubricant UNPRESERVED	[79%] 76%	[94%] 85%	[76%] 73%	[94%] 92%	[76%] 72%	[84%] 80%
Ointment	[64%] 60%	[97%] 92%	[77%] 77%	[92%] 88%	[67%] 61%	[80%] 75%
Lipid containing lubricants (drops/spray)	[74%] 61%	[96%] 75%	[69%] 60%	[90%] 79%	[61%] 46%	[78%] 64%
Lid wipes / scrubs	[78%] 74%	[97%] 93%	[76%] 74%	[95%] 93%	[74%] 72%	[84%] 81%
Demodex treating lid wipes	[48%] 35%	[96%] 74%	[58%] 45%	[88%] 57%	[43%] 27%	[67%] 48%
In-office demodex lid control	[36%] 18%	[90%] 52%	[50%] 35%	[84%] 44%	[32%] 18%	[58%] 33%
Moisture chamber spectacles / goggles	[40%] 21%	[90%] 42%	[41%] 22%	[79%] 38%	[50%] 28%	[60%] 30%
Punctal occlusion (with plugs)	[37%] 26%	[90%] 62%	[61%] 48%	[82%] 46%	[49%] 34%	[64%] 43%
Home made warm lid compress such as face-cloth	[69%] 59%	[92%] 56%	[76%] 75%	[92%] 75%	[72%] 63%	[80%] 66%
Commercially available warm lid compress / face mask	[63%] 56%	[95%] 90%	[56%] 44%	[90%] 76%	[60%] 41%	[73%] 61%
Lid margin debridement	[42%] 30%	[89%] 62%	[45%] 26%	[81%] 48%	[45%] 35%	[60%] 40%
In-office lid hygiene (e.g. microblepharoexfoliation)	[41%] 25%	[87%] 52%	[44%] 26%	[83%] 38%	[37%] 22%	[58%] 33%
Therapeutic meibomian gland expression	[49%] 39%	[96%] 66%	[65%] 62%	[91%] 70%	[42%] 34%	[69%] 54%
In-office thermal pulsation (e.g. LipiFlow)	[20%] 3%	[80%] 44%	[26%] 10%	[63%] 8%	[22%] 8%	[42%] 15%
In-office Intense Pulsed Light (IPL) therapy	[20%] 4%	[40%] 16%	[20%] 7%	[70%] 34%	[16%] 8%	[33%] 14%
Topical antibiotics	[29%] 28%	[94%] 72%	[71%] 64%	[77%] 45%	[46%] 41%	[63%] 50%
Topical azithromycin	[22%] 17%	[77%] 44%	[54%] 38%	[40%] 4%	[31%] 22%	[45%] 25%
Systemic azithromycin	[20%] 13%	[66%] 31%	[50%] 37%	[34%] 30%	[35%] 20%	[41%] 26%
Oral antibiotics (e.g. doxycycline)	[27%] 26%	[75%] 60%	[61%] 63%	[35%] 30%	[44%] 38%	[48%] 43%
Topical corticosteriods	[28%] 28%	[97%] 88%	[71%] 71%	[77%] 55%	[47%] 41%	[64%] 57%

Topical secretagogues	[11%] 3%	[50%] 15%	[34%] 17%	[16%] 2%	[34%] 27%	[29%] 13%
Oral secretagogues	[11%] 3%	[34%] 9%	[29%] 11%	[10%] 1%	[24%] 9%	[22%] 7%
Topical cyclosporine	[23%] 23%	[96%] 87%	[68%] 63%	[22%] 8%	[42%] 36%	[50%] 43%
Topical tacrolimus	[10%] 5%	[41%] 10%	[43%] 26%	[10%] 6%	[20%] 13%	[25%] 12%
Topical lifitegrast	[7%] 2%	[67%] 52%	[22%] 5%	[6%] 1%	[10%] 3%	[23%] 12%
Autologous/allogeneic serum	[16%] 15%	[50%] 25%	[58%] 50%	[10%] 10%	[32%] 27%	[33%] 25%
Therapeutic contact lens approaches	[40%] 30%	[87%] 49%	[72%] 52%	[70%] 37%	[47%] 35%	[63%] 41%
Amniotic membrane	[13%] 9%	[58%] 39%	[44%] 30%	[7%] 4%	[32%] 26%	[31%] 22%
Intraductal probing	[13%] 6%	[40%] 10%	[28%] 14%	[19%] 6%	[17%] 8%	[23%] 9%
Other surgical approaches	[8%] 4%	[13%] 6%	[30%] 17%	[4%] 4%	[23%] 13%	[16%] 9%

Differences in management approaches were identified globally. Artificial tears with low viscosity were more commonly prescribed by practitioners than high viscosity products (by 1.06 times; n=817 vs 768) and unpreserved prescribed by more practitioners than preserved (by 1.27 times; n=697 vs 888). Ointments were prescribed by more practitioners (by 1.13 times; 762 vs 672) than lipid containing lubricants, but high viscosity lubricants were recommended by a similar number of practitioners as ointments (by 1.01 times; n=768 vs 762). The number of practitioners who recommended the use of general lid wipes/scrubs outnumbered those recommending specific demodex cleansing wipes (by 1.89 times; 860 vs 454). Demodex lid cleansing with wipes for home use were recommended by more practitioners than those that applied in-office treatment (by 1.55 times; 454 vs 293). Home-made warm lid compresses (such as using a facecloth) are still recommended more commonly by practitioners than commercially available warm lid compresses/face masks (by 1.14 times; n=702 vs 603). When it comes to performing in-office treatments for eyelid management such as Blephex or debridement, the latter is used by more practitioners (by 1.27 times; n=403 vs 323), as is therapeutic meibomian gland expression (by 1.59 times; n=514 vs 323). For tear preservation, more practitioners used punctal occlusion than moisture chamber spectacles/goggles (by 1.35 times; n=409 vs 302). LipiFlow and intense pulsed light therapy were used by similar numbers of practitioners (n=116 vs 108). More practitioners prescribed topical than oral antibiotics (by 1.14 times; n=471 vs 415). Azithromycin was used by a similar number of practitioners in both oral and topical form, with a slight preference for topical use (by 1.05:1; n=248 vs 235). Secretagogues were prescribed by more practitioners topically rather than orally (by 1.97 times; n=134 vs 68). Topical immunomodulators such as tacrolimus were prescribed slightly more frequently than lifitegrast (by 1.22 times; n=110 vs 90), but corticosteroids were much more frequently prescribed than tacrolimus (by 4.63 times; n=510 vs 110). Practitioners tend to prescribe therapeutic contact lenses more commonly than either autologous/allogenic serum (by 1.62 times; n=406 vs250) or

amniotic membrane (by 1.94 times; n=406 vs 209). Autologous/allogenic serum was reported to be used more abundantly than amniotic membrane (by 1.20 times; n=250 vs 209). Intraductal probing and other surgical approaches were reported to be performed by equal number of practitioners 1:1 (n=90 vs 90).

Sub-categories of management therapies identified in Table 2 were used to reduce the data to make it easier to visualise in Figure 1. Of those that prescribed:

- Artificial tears, 832 (73%) reported prescribing both low and high viscosity, with and without preservatives.
- Lid hygiene, 360 (32%) reported using the lid hygiene options listed in Table 2.
- Warm compress, 408 (36%) noted working with in office thermal pulsation of lids as well as prescribing home use warm compresses.
- Antibiotics, 372 (33%) reported using both topical and oral azithromycin.
- Topical anti-inflammatory/immunosuppressants, 408 (36%) prescribe two anti-inflammatory options.
- Secretagogues, 197 (19%) used both topical and oral forms.
- Biologic products, 243 (21%) used both serum and membranes.
- Surgical approaches, 145, (13%) performed intraductal probing as well as other surgical approaches.

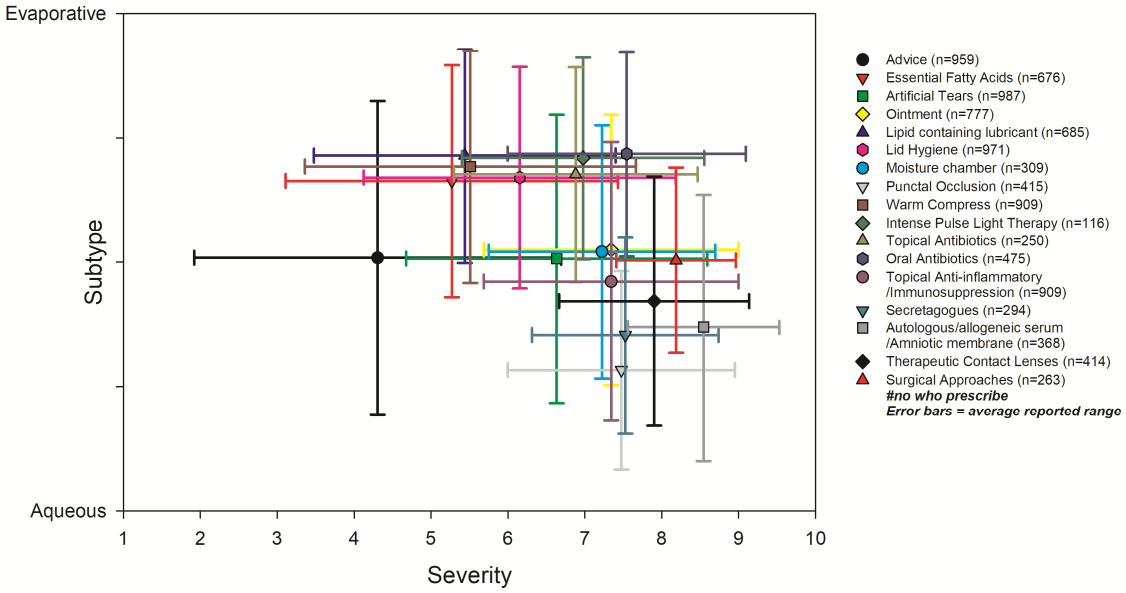

Figure 2: The median severity and subtype for which each DED management is prescribed (symbol) and the average reported range ('error' bars). n = number of practitioners reporting prescribing each management.

Severity

The range of treatments offered at different disease severities are shown in Table 4. Some treatments were prescribed across all severity levels, such as artificial tears (by ~80% of practitioners) and nutritional supplements (by ~45%). Others, were prescribed more frequently with increasing disease severity, for instance, in-office lid management, which increased from ~29% for mild DED to ~57% for moderate to severe disease, and topical antibiotics (which increased from ~8 to ~38%). Oral antibiotics were more commonly prescribed by practitioners as the severity of disease increased (from ~4% for mild DED to ~43% for severe DED), as were punctal occlusion (from ~5 to 4~8%), topical anti-inflammatories/immunosupressants (from ~4 to ~24%), biologics (from ~2 to ~47%), therapeutic contact lenses (from ~5 to ~43%) and surgical approaches (from ~3 to ~27%).

Table 4. Proportion of practitioners therapy prescribing for each level of DED severity that they examine

	Mild	Moderate	Severe
Essential fatty acids	43.2%	49.4%	40.2%
Artificial tears	84.1%	88.0%	74.2%
Ointments	34.9%	47.2%	31.1%
Lipid-based products	54.4%	73.1%	50.2%
Lid hygiene	11.8%	26.6%	25.0%
Moisture chamber googles	8.4%	22.8%	38.4%
Punctal occlusion	4.7%	24.5%	47.9%
Warm compresses	55.1%	64.5%	44.3%
In-office treatments	28.6%	56.8%	56.7%
Topical antibiotics	7.5%	31.9%	37.6%
Oral antibiotics	4.0%	26.9%	43.2%
Topical anti-inflammatories/immunomodulators	4.4%	13.3%	24.4%
Secretagogues	10.5%	41.1%	56.2%
Biologics	1.7%	12.6%	46.5%
Therapeutic contact lenses	4.5%	16.0%	42.9%
Surgical approaches	2.9%	7.2%	26.7%

Analysis of the percentage of practitioners choosing a specific management approach according to the different severity levels, identified statistically significant differences between continents and within continents (Table 5). Between continents, the main differences were the use of pharmaceuticals at lower levels of severity in North America and Asia/Middle East, as well as the use of unpreserved lubricants and homemade warm compresses at higher severities in Latin America compared to other continents (Table 5). Within continents, the main differences were: lid hygiene, topical corticosteroids, topical and oral secretagogues and autologous/allogeneic serum were prescribed at lower severities in Romania than in the UK, as was oral secretagogues in Spain compared to the UK; pharmaceuticals are prescribed at lower severities in the USA than Canada; commercially available warm lid compresses/face masks are prescribed at lower severities in Mexico than Argentina; and preserved/lipid containing lubricants are prescribed for lower severities in Thailand than Hong Kong; yet moisture chamber spectacles/goggles and surgery are prescribed for lower severities in Hong Kong than Thailand; in addition, in office Demodex treatment is prescribed at lower severities in Russia than Hong Kong (Table 5).

Table 5. Statistically significant differences in the severity at which therapies were prescribed between continents and between countries within these continents with sufficient data.

	Europe/UK Scandinavia (EU)	North America (NA)	Latin America (LA)	Australasia (AA)	Asia/Middle East (AME)
Europe/UK Scandinavia	LVUL Spain ↑11% UK (p=0.006) OLH UK ↑19% Romania (p=0.009) HWC Spain ↑16% UK (p=0.016); Romania ↑22% UK (p=0.001) Tco UK ↑16% Romania (p=0.005) TS UK ↑52% Romania (p=0.005) OS UK ↑35% Spain (p=0.014); UK ↑63% Romania (p=0.006) AAS UK ↑23% Romania (p=0.05)				
North America	Advice NA ↑8% EU (p=0.001) LVUL NA ↑8% CSA (p=0.001) Tco EU ↑7 NA (p=0.001) TCy EU ↑11% NA (p=0.001) LF EU ↑1% NA (p=0.001) AM NA ↑4% EU (p=0.001)	CAM Canada ↑9% USA (p=0.009) OLH Canada ↑10% USA (p=0.012) OTP Canada ↑13% USA (p=0.001) Tcy Canada ↑12% USA (p=0.001) LF Canada ↑17% USA (p=0.001) AAS Canada ↑9% USA (p=0.010) AM Canada ↑9% USA (p=0.001)			
Latin America	Advice LA ↑8% EU (p=0.002) LVUL LA ↑12% EU (p=0.001) HVUL LA ↑7% EU (p=0.001) HWC LA ↑12% EU (p=0.001) Tco EU ↑7% LA (p=0.002) TCy EU ↑13% LA (p=0.001)	HVUL LA ↑7% NA (p=0.003) HWC LA ↑22% NA (p=0.001)	CAM Argentina ↑23% Mexico (p=0.011)		
Australasia	LcL EU ↑8% AA (p=0.001) HWC EU ↑1% AA (p=0.003)	LVUL NA ↑8% AA (p=0.001) Tco AA ↑8% NA (p=0.001) TCy AA ↑18% NA (p=0.001) LF AA ↑22% NA (p=0.001) AM AA ↑10% NA (p=0.001)	LVUL LA ↑13% AA (p=0.001) HVUL LA ↑8% AA (p=0.001) LcL LA ↑11% AA (p=0.001) HWC LA ↑20% AA (p=0.001) Tco AA ↑9% LA (p=0.001) TCy AA ↑20% LA (p=0.001)	No significant differences	
Asia/Middle East	TS EU ↑7% AME (p=0.001) TCy EU ↑10% AME (p=0.001)	HWC AME ↑11% AA (p=0.002) TS NA ↑11% AME (p=0.003)	LVUL LA ↑11% AME (p=0.001) HVUL LA ↑6% AME (p=0.002) HWC LA ↑11% AME (p=0.001)	LcL AME ↑15% AA (p=0.001) HWC AME ↑9% AA (p=0.001) TS AA ↑20% AME (p=0.001) TCy AA ↑17% AME (p=0.001) LF AA ↑23% AME (p=0.001)	LVPL HK ↑14% Thailand (p=0.001) HVPL HK ↑17% Thailand (p=0.001) LcL HK ↑17% Thailand (p=0.003) ODC HK ↑26% Russia (p=0.006) MCG Thailand ↑17% HK (p=0.011) OSA Thailand ↑17% HK (p=0.006)

Notes: Amniotic membranes (AM), autologous/allogeneic serum (AAS), commercially available warm lid compress/face mask (CAM),essential fatty acids (EFA), high viscosity enhancing preserved lubricants (HVPL), high viscosity enhancing unpreserved lubricants (HVUL), homemade warm lid compress (HWC), intraductal probing (IP), intense pulsed light (IPL), lipid containing lubricants (LcL), lid margin debridement (LMD), lid wipes/scrubs (LwS), low viscosity enhancing preserved lubricants (LVPL), low viscosity enhancing unpreserved lubricants (LVUL), moisture chamber spectacle/goggles (MCG), therapeutic meibomian gland expression (MGE), oral antibiotics (OAb), in office demodex lid control (ODC), ointment (OI), in office lid hygiene (OLH), oral secretagogues (OS), other surgical approaches (OSA), in office thermal pulsation of lids (OTP), punctal occlusion (PO), oral azythromicin (SAz), topical antibiotic (TAb), topical azythromicin (TAz), therapeutic contact lenses (TCl), topical corticosteroids (TCo), topical cyclosporine (TCy), topical lifitegrast (TLF), topical secretagogues (TS), topical tacrolimus (TT). HK = Hong Kong. **↑ = prescribed at higher severity, ↓ = prescribed at lower severity**

Subtype

Globally, practitioners seem to have a well-defined management behaviour when treating DED patients according to their subtype. While a similar number of practitioners seems to prescribe ointments for each subtype, the principal reported approach for aqueous deficient DED was punctal occlusion by most practitioners, on the other hand, the use of product-containing lipids is the preferred management choice for EDE (Table 6). On the spectrum from aqueous deficient to evaporative DED, essential fatty acids, lipid based products, lid hygiene, warm compresses, in office treatments such as IPL and antibiotics (topical or oral) were more commonly prescribed for evaporative DED, while punctal occlusion, secretagogues, biologics, therapeutic contact lenses, artificial tears, moister chamber goggles, topical anti-inflammatories/Immunosupressants and surgical approaches were more typically prescribed for aqueous deficient DED (Figure 2).

Table 6. Proportion of practitioners that specifically use each therapy for a particular subtype of DED

	ADDE	EDE
Essential fatty acids	9.3%	7.9%
Artificial tears	6.7%	26.4%
Ointments	26.9%	9.9%
Lipid based products	18.8%	16.5%
Lid hygiene	5.7%	32.8%
Moisture chamber goggles	4.2%	20.5%
Punctal occlusion	24.4%	16.3%
Warm compresses	66.2%	6.4%
In office treatments	4.2%	26.4%
Top antibiotics	5.3%	31.6%
Oral antibiotics	3.5%	22.9%
Topical anti-inflammatories/Immunosupressants	3.5%	31.9%
Secretagogues	20.3%	5.2%
Biologics	52.3%	8.3%
Therapeutic contact lenses	41.0%	4.3%
Other surgical approaches	34.6%	10.5%

Notes: Aqueous deficient dry eye (ADDE); evaporative dry eye (EDE)

Few differences were identified between continents, with high viscosity lubricants more commonly prescribed for predominantly aqueous deficient DED in Australiasia than in North America or Europe and EFAs are more frequently prescribed for DED that is predominantly aqueous deficient DED in Asia/Middle East than in Latin America. Within continents autologous/allogeneic serum is more commonly used for managing evaporative DED in the Romania than in Spain; in Argentina, antidemodex wipes, topical antibiotics/azythromicin are prescribed for more evaporative DED than in Mexico; lid hygiene with wipes/scrubs is more frequently recommended for aqueous deficient DED in Russia than in Thailand or Hong Kong; antidemodex wipes and topical antibiotics are used more for evaporative DED in Thailand than Russia; and topical/systemic azythromicon are more commonly used for the evaporative subtype patients in Thailand than Hong Kong (Table).

Table 7. Statistically significant differences in prescribing therapies for aqueous deficient (ADDE) and evaporative (EDE) dry eye subtypes between continents and between countries within these continents with sufficient data.

	Europe/UK Scandinavia (EU)	North America (NA)	Latin America (LA)	Australasia (AA)	Asia/Middle East (AME)
Europe/UK Scandinavia	AAS Romania ↑29% Spain (p=0.008)				
North America	No differences	No differences			
Latin America	No differences	No differences	ADW Argentina ↑26% Mexico (p=0.009) Tab Argentina ↑17% Mexico (p=0.006) Taz Argentina ↑17% Mexico (p=0.007)		
Australasia	HVUL EU ↑5% AA (p=0.003)	HVUL NA ↑9% AA (p=0.001)	No differences	No differences	
Asia/ Middle East	No differences	No differences	EFA LA ↑12% AME (p=0.001)	No differences	LwS Thailand ↑18% Russia (p=0.001) LwS HK ↑17% Russia (p=0.008) ADW Thailand ↑23% Russia (p=.004) Tab Thailand ↑14% Russia (p=0.006) Taz Thailand ↑11% HK (p=0.011) Saz Thailand ↑16% HK (p=0.001)

Notes: Autologous/allogeneic serum (AAS), Essential Fatty Acids (EFA), unpreserved high-viscosity enhancing lubricants (HVUL), lid wipes/scrubs (LwS), oral azythromycin (SAz), topical antibiotic (TAb), topical azythromycin (TAz).

↑ = prescribed more towards the evaporative end of the dry eye spectrum EDE, ↓ = towards the aqueous deficient end of the spectrum ADDE.

Discussion

The aim of this study was to determine how clinical DED management patterns differed by disease severity and subtype. Data collected from practitioners across the globe has also allowed differences in dry eye management approaches between continents and countries within continents to be identified.

Although previous studies have compared clinical patterns of DED management, this has been limited to comparisons between two countries [16], between professions [22] or exploring the trends within one or two countries only [17-20]. The only previous global study had responses from 115 mainly corneal specialists and focused on aqueous deficient DED management [21]. Hence, to our knowledge, this is the first study to have compared the current management patterns of eye care professionals across the world in the context of severity and subtype of DED.

The survey respondents are largely reflective of the balance of eye care professions across the globe, in each region (http://atlas.iapb.org/global-action-plan/gap-indicators/), with data from over 50 countries. The online delivery of the survey facilitated the response from eye care professionals with a range of clinical experience from 1 to 21 years.

Globally, eye care practitioners reported predominantly seeing patients with mild symptoms and least commonly those with severe DED. Overall, 85% of the surveyed practitioners were managing DED with a broad range of strategies, and almost all (96%) were providing patient education about dietary modification, local/office environment, and hydration. Some practitioners indicated they were not licenced even to offer advice, perhaps because they were working as part of a multi-disciplinary team and this was not their role. Environmental and iatrogenic factors can disrupt the homeostasis of the tear film, hence advice is critical with all levels of DED severity, as identified in the TFOS DEWS II Management and Therapy paper [3].

Patient education/advice, dietary advice, artificial tears and warm compress, artificial tears, are classified as “Step 1” interventions in the TFOS DEWS II management

algorithm [3] (i.e. they are conventional, low risk, and commonly available management approaches for early stage disease); this study identifies these are the most commonly recommended management approaches, as reported also in other studies [16, 18-20]. A slightly higher preference for the use of low viscosity preserved lubricants was noted in this study, which could be related to the overall more milder nature of the DED the respondent reported treating and the greater perceived blurring of vision on instillation with ointments [23]. No differences were found between the frequency of use of high viscosity drops and ointments. Among treatments recommended for demodex infestation, less practitioners (by ~1.5x) treat the patient in-office at their consultation, instead preferring to prescribe demodex cleansing lid wipes for at-home use. Also, general lid wipes/scrubs are prescribed by almost twice (~1.9x) as many practitioners as those specifically for treating demodex, despite the high prevalence of these mites, particularly in the elderly [24]. Therapeutic contact lenses are more used than biologic products when treating advanced DED (x1.6 autologous/allogenic serum and x1.92amniotic membranes), presumably due to its availability and difficulty to produce.

Management patterns according to the severity level of dry eye disease were similar across the different continents. Low severity DED is predominantly managed by advice, while mild dry eye is managed by artificial tear drops and sprays, warm compresses lipid-containing products and nutritional supplements. Practitioners use pharmaceutical approaches, ointments, punctal occlusion, in-office treatments and secretagogues for more moderate DED, while only more severe dry eye is managed with blood/tissue products, therapeutic contact lenses and surgical approaches. This follows the stepwise approach that is recommended by the TFOS DEWS II management algorithm.[3] For the most severe dry eye cases, autologous/allogenic serum is used slightly more commonly (by ~1.2x) than amniotic membranes, perhaps due to their relative availability. Severe dry eye is less commonly managed than mild to moderate dry eye. There is a consistent drop in the number of practitioners managing DED as the severity of patients increases which reflects the number of patients dropping with the severity of most disease. The North American and Asia/Middle East regions seemed to

differ from other continents due to their tendency for a more pharmacological approach at lower levels of DED severity (especially in the USA). The notable difference within continents was in the use of home-made warm compresses across Europe. The continued use of face-cloths to heat the eyelids is surprising, since they are less effective at heat retention [25] resulting in reduced efficacy [26] relative to commercial products.

On the spectrum from aqueous deficient to evaporative DED, nutritional supplements, lipid drops/sprays, lid hygiene, lid warming therapies and antibiotics (topical or oral) were reportedly used more commonly for evaporative subtypes, while artificial tears, moisture chamber goggles, punctal occlusion, therapeutic contact lenses, secretagogues and biologics were used preferentially for aqueous deficient DED (Figure 2). As identified in the introduction, there is currently limited research investigating the efficacy of management therapies by DED subtypes, but there is some evidence that liposome containing sprays are more beneficial for patients with evaporative DED [14]. More research is needed to explore whether biomarkers and clinical tests can better inform the optimum choice of DED management strategy for a patient.

To our knowledge, this is the largest international survey of DED prescribing practices to date and the first to explore how the severity and subtype might influence management choices. Surveys always are subject to selection bias as they are likely to attract practitioners who are more involved in the condition being examined and therefore may be biased to more severe disease management and more actively involved in DED management than the ‘average’ practitioner. Country and region were based on where respondents were practicing, which may not be where they trained. However, in the absence of comparative and prognostic clinical studies, the results allow clinicians to benchmark their practice against their peers, highlight areas of disparate practice where further research is warranted to ensure optimised patient

management, and may be useful in informing industry on how best to target product development.

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