Overview of Dry Eye Disease for Eye Care Professionals in Canada

Clara C. Chan, MD, FRCSC, FACS
Department of Ophthalmology & Vision Sciences, University of Toronto

Mahshad Darvish-Zargar, MDCM, MBA, FRCSC
Department of Ophthalmology, McGill University

Jitendra Gohill, MD, PhD, FRCSC
Cumming School of Medicine, University of Calgary

Setareh Ziai, MD
Department of Ophthalmology, University of Ottawa

Abstract

Dry eye disease (DED) is a highly prevalent, often chronic, multifactorial ocular surface condition that carries a significant burden. The 2017 report from the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) is an in-depth look at all aspects of DED. Although TFOS DEWS II comprehensively defined and classified the disease and summarized the current DED literature on a global scale, it did not highlight country-specific aspects of DED diagnosis and treatment options. In this review, we provide an overview of DED in the Canadian context, with an emphasis on DED identification, diagnosis, and treatment options available in Canada. In addition, we discuss needs and opportunities within the Canadian ophthalmic community regarding DED.

KEY WORDS:
Dry eye disease, TFOS DEWS II, inflammation, Canada

ABBREVIATIONS
AC, air conditioning; ADDE, aqueous-deficient dry eye; BC, British Columbia; BID, twice a day; DED, dry eye disease; DREAM, Dry Eye Assessment and Management; EDE, evaporative dry eye; HRQoL, health-related quality of life; LFA-1, lymphocyte function–associated antigen 1; MGD, Meibomian gland dysfunction; MMP-9, matrix metalloproteinase 9; OCT, optical coherence tomography; OSD, ocular surface disease; OTC, over-the-counter; TFOS DEWS II, Tear Film & Ocular Surface Society Dry Eye Workshop II; TMH, tear meniscus height.

INTRODUCTION

The 2017 report from the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) provided a comprehensive overview of our current understanding of dry eye disease (DED).[1] However, a country-by-country focus on all aspects of DED was beyond the scope of TFOS DEWS II. Country-specific information is important because geographical, environmental, and cultural differences influence DED occurrence, severity, and response to treatment. As Canada is a large multicultural country with an extreme climate, it is relevant to apply TFOS DEWS II knowledge to Canadian eye care professionals and their patients. The most recent Canadian review on DED management was published in 2009.[2] Hence, this review represents a Canadian adaptation of the salient points from the TFOS DEWS II report and describes DED epidemiology and pathophysiology before discussing diagnostics and treatment options.

PREVALENCE AND BURDEN OF DISEASE

The evidence-based re-definition of DED created by the TFOS DEWS II subcommittee was as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".[1] Consequently, the prevalence of DED according to this new definition has not yet been estimated. Historical estimates of global DED range from 5–50% depending on the study methodology.[3] In Canada, the prevalence of DED among patients attending optometric practices was 29% in 1994.[4] A more recent population-based study conducted in 2016 in Ontario estimated that the prevalence of DED was 22%.[5] In both Canadian studies, the prevalence of DED was highest in older patients and females,[4,5] which is consistent with global reports cited in TFOS DEWS II.[3]

DED causes ocular pain and irritation, stinging, dryness, ocular fatigue, and reduced perception of visual function and visual performance, which negatively affects the patient's health-related quality of life (HRQoL).[3] Consequently, patients are more likely to report difficulties with driving, reading, performing professional work (i.e., reduced productivity), using computers, and watching TV.[3,6] In the US-based Beaver Dam Offspring Study, DED was associated with significantly lower quality of life according to HRQoL instruments and a vision-specific questionnaire.[7] There are no published studies on the impact of DED on HRQoL in Canada.

Similarly, there are no DED-specific cost data in Canada. However, it should be informative to review robust DED-specific cost data collected from US studies. Rough estimates of DED-specific costs in Canada may be derived from US-based data if the same prevalence and severity of DED in the two countries, along with the same age and gender mix, are assumed. Overall, the economic burden of managing eye disease in Canada is estimated to be $US15 billion per year,[8] which compares favorably with the $US139 billion estimated annual economic burden of eye disease in the US, after normalizing for population size.[9] If a decision-tree analysis conducted in the US is applied to Canada, then the total annual direct cost (2008 values) to the healthcare system for DED management is $US420 million (US-specific estimate, $US3.84 billion).[10] The cost for Canada is likely an underestimate because the prevalence of DED used in the US-based decision-tree analysis was about 6%,[10-12] whereas the estimated prevalence of DED in the Ontario population-based study was 22%.[5] In 2008, the average annual indirect cost related to a reduction in work productivity due to DED-related absenteeism (i.e., days missed) and presenteeism (i.e., reduced functioning at the workplace) was substantial ($US11,302 per person),[10] and likely to affect Canadians with DED to a similar extent. Productivity loss (mostly due to reduced effectiveness in the workplace) in the US was estimated to be $US55.4 billion per year (approximately $US6 billion per year in Canada), which exceeds direct costs to society (including the cost of treatment).[10] Given the high propensity for many dry eye sufferers to self-treat with over-the-counter (OTC) artificial tears, the US-based estimates likely underestimate the economic burden of DED.

The under-estimate is potentially greater in Canada because of provincial minor ailment programs that cover DED treatment.[13] For instance, in some provinces, discount cards are available from the manufacturers of cyclosporine and lifitegrast. Quebec patients have increased access to cyclosporine and lifitegrast through the patient d'exception program. Ontario offers a limited-use code 49 for patients who have severe corneal staining which provides partial coverage for artificial tears. Provincial differences in the economic burden for patients should be taken into consideration by clinicians as they recommend therapeutic options to patients. Sometimes, the least expensive option to give a patient quick relief is a topical corticosteroid as required (e.g., loteprednol or fluorometholone).

PATHOPHYSIOLOGY AND CLASSIFICATION

Several ocular mechanisms are in place to achieve tear film homeostasis. Constant tear film replenishment through blinking and tear secretion maintains tear film stability and optical quality. The tear film is a dynamic and interactive two-layered model (a mucin-rich aqueous layer [mucoaqueous subphase] and an overlying lipid layer).[14] The eyelids pull apart and the lipid layer simultaneously drifts apart across the aqueous layer, pulling aqueous tears with it across the ocular surface.[14] Conditions such as poor blink quality/quantity and lid abnormalities disrupt this system and can worsen dry eye symptoms.[1,14]

Loss of tear film homeostasis is the unifying characteristic of DED.[1] Two key factors that contribute to DED pathogenesis are tear film break-up and hyperosmolarity.[14] Tear hyperosmolarity is caused by a cycle of increased evaporation and/or insufficient tear production, resulting in tear film instability and increased friction on the ocular surface (Figure 1).[15] These conditions, in turn, drive ocular surface inflammation, which amplifies hyperosmolarity. This hyperosmolar inflammatory environment promotes (1) apoptosis (programmed cell death) of the corneal, conjunctival epithelial, and goblet cells, further contributing to tear film instability; (2) abnormal differentiation and accelerated desquamation and activation of proteolytic enzymes that disrupt intercellular epithelial tight junctions, resulting in breakdown of the epithelial barrier; and (3) neurogenic inflammation and increased disease severity. Environmental factors such as humidity and airflow over the ocular surface also increase evaporation. Patients are classified as having evaporative dry eye (EDE) caused by excessive tear evaporation, aqueous-deficient dry eye (ADDE) caused by inadequate tear production, or mixed-mechanism dry eye (EDE + ADDE).[1]

DIAGNOSIS

Diagnosis of DED should be based on symptoms and at least one positive homeostasis test result.[16] Patients suspected of DED are identified through a classification scheme (Figure 2) outlined by TFOS DEWS II.[1] Step 1 of a 4-step evaluation process (Figure 3) begins with a series of triaging questions to rule out other ocular surface diseases (OSDs; Table 1).[1,16] Clinical signs of DED without symptoms indicate a predisposition to DED or dysfunctional sen-

sation due to neurotrophic conditions (e.g., DED-induced corneal nerve damage or diabetic neuropathy) (Figure 2).[1] Symptoms without signs indicate preclinical DED or neuropathic pain due to non-OSD.[1] The classification scheme caters to various clinical scenarios of neuropathic pain (such as a lesion or somatosensory system disease) in which the burden of ocular pain symptoms outweighs the clinical signs of DED.[1]

Step 2 is a risk-factor analysis for making informed decisions about DED management options. DED risk factors are categorized according to the probability of DED development and can vary from country to country (Table 2 and Figure 3).[3,23] The demographic risk factors of increased age and female sex are most consistently cited.[3] In 2014, >6 million Canadians were aged ≥65 years, representing 16% of Canada's population.[17] By 2030, >9.5 million Canadians, which represents 23% of the population, will be aged ≥65.[17] All Canadians are exposed to lifestyle and environmental factors that have been consistently associated with an increased risk of DED (i.e., electronic device use, contact lens wear, pollution, and low humidity).[3] Electronic device usage in Canada is one of the highest in the world; the total number of mobile phone subscribers in Canada exceeded 30 million in 2018.[18] Based on US estimates, >4 million Canadians wear contact lenses.[19] Although Canada has good air quality,[20] perennial low relative humidity levels in some provinces and cold winters countrywide necessitate the use of drying heating systems that predispose individuals to DED.[21,22]

Step 3 encompasses diagnostic tests to confirm symptoms and signs of DED (Figure 3).[16] Symptoms can be assessed most readily in clinical practice using the 5-Item Dry Eye Questionnaire[24] and OSD Index.[25-27] If the score from either of these evaluations suggests DED, detailed diagnostic tests of clinical signs should be performed.[16] Tear osmolarity should be tested before instilling any other eye drops (fluorescein, topical anesthetic, vital dye staining). Subsequent tests should be sequenced from the least to the most invasive to provide the most consistent results.[16] These include tear break-up time and ocular surface staining (with fluorescein, rose bengal, or lissamine green [commercially unavailable in Canada]).[16] The TFOS DEWS II recommends non-invasive tear break-up time initially, if available, but due to the expense and limited access to devices such as the keratograph, at a minimum, tear break-up time should be checked with fluorescein.[16] Consistent technique when using fluorescein is important, as too much or too little will create inconsistent results.

Diagnostic challenges include a weak correlation between DED signs and symptoms.[28] As the severity of DED worsens, the ocular surface becomes neurotrophic and DED signs can predominate over symptoms.[1]

Step 4 classifies DED as aqueous deficient, evaporative, or mixed, and assesses severity.[16] Further investigations of the Meibomian glands (using meibography and lipid interferometry) and tear volume assessment (using tear meniscus height [TMH]) may be used to determine the etiology and severity of DED and guide treatment. ADDE is observed in conditions affecting the lacrimal gland.[16] EDE is observed in conditions affecting the eyelid (Meibomian gland dysfunction [MGD], blink abnormalities) or the ocular surface (mucin deficiency, contact lens wear). ADDE and EDE are not distinct etiologies but exist on a continuum: most patients have variable combinations of both forms. Classification seeks to assess which form predominates, to enable targeted therapy.

MANAGEMENT

DED management aims to restore homeostasis of the ocular surface and tear film. In Canada, a stepwise approach to managing DED is followed, similar to that described in the TFOS DEWS II.[29] Rather than giving strict guidelines, TFOS DEWS II recommends a staged DED management algorithm to help select therapies based on patient needs and available options.[29] This algorithm presents a series of management and treatment steps, with progression to the next level recommended in case of nonresponse to treatment or increase in DED severity. Unfortunately, palliative symptom relief may be the final resort in advanced/severe cases. Management begins with education and lifestyle adjustments (dietary modifications, management of risk factors), and progresses to tear supplementation or lid hygiene and anti-inflammatory therapies (Table 3).[29] Additional management such as devices (scleral contact lenses) or surgical procedures are considered for more severe or recalcitrant presentations.[29]

Few new interventions for DED are approved because of the mismatch between patient signs and symptoms as well as limitations in clinical trial design due to our incomplete understanding of the pathophysiology of DED.[45] Dietary modifications, including increased whole-body hydration, and supplementation with vitamins, omega-3 and/or omega-6 fatty acids, and lactoferrin may have potential in ameliorating DED, but further levels of evidence are required before clinical practice recommendations can be developed.[29] Omega-3 fatty acids, the best studied dietary intervention, was shown to improve signs and symptoms of DED in a meta-analysis of 17 randomized clinical trials involving 3363 patients with DED.[46] The improvement was weighted toward studies conducted in India relative to

other countries.[46] Recent results from a large, randomized, double-blind trial, the Dry Eye Assessment and Management (DREAM) study conducted at 27 sites in the US, showed that a daily omega-3 fatty acid supplement of 3000 mg did not produce better outcomes than olive oil placebo (delivering n–9 oleic acid) over 12 months.[47] However, it should be noted that patients were allowed to continue their current treatments for DED in this 'real world' clinical trial, which may have had a bearing on the results, including the considerable placebo effect and improved compliance with other dry eye therapeutics.[47] In that study, patients did not appear to be clinically improved, but felt that their symptoms of dry eye were better.[47] Frequent visits with the study team were also thought to be related to the improved patient symptoms.[47] Given these equivocal efficacy data, cornea specialists in Canada and elsewhere suggest increased omega-3 fatty acid intake as a reasonable option over the long term, providing there is adequate monitoring for evidence of disease improvement and control. The precise omega-3 fatty acid composition and dosage regimen for optimizing management of DED are unknown. Regular consumption of fatty fish, a Mediterranean diet, or intake of OTC supplements containing eicosapentaenoic acid and docosahexaenoic acid is advisable to increase systemic exposure to omega-3 fatty acids. Prospective data indicate that supplementation with oral lactoferrin, an endogenous tear glycoprotein, improves signs and symptoms of dry eye in patients with Sjögren's syndrome and after small incision cataract surgery.[48,49] However, lactoferrin is not commonly prescribed and additional studies are required to understand its mechanism of action, efficacy, and optimal therapeutic dosage regimen.

As stated in TFOS DEWS II, management of DED risk factors involves the appropriate use of systemic and topical medications, and mitigation of harmful environmental factors (Table 2).[29] It is worth reiterating that preservative-free ocular formulations for glaucoma treatment are preferred in patients with comorbid DED.[50] The Canadian Centre for Occupational Health and Safety provide 'thermal comfort' recommendations for office work,[21] which may be extended to residential living conditions. Optimum room temperatures in summer and winter are 24.5°C and 22°C, respectively, with a relative humidity of 50%.[21] A humidifier may be useful when the relative humidity is low, as is often the case in the Canadian prairies and Rocky Mountains.

Treatments for tear insufficiency cited in the TFOS DEWS II recommendations are tear replacement therapy, and approaches that conserve and stimulate tears (Table 3).[29] Recommended tear supplementation options include OTC artificial tears, gels, ointments, and biological tear substitutes (autologous serum, adult allogenic serum, umbilical cord serum, and platelet preparations).[29] Autologous and allogeneic sera are compositionally more similar to human tears than artificial tears, but their use is limited by production, storage and regulatory issues. Allogeneic serum has an advantage over autologous serum in that it is derived from individuals without active disease, but there remains a risk of an immune response to foreign antigens.[29] Recent data on the biological tear substitute amniotic fluid extract for the treatment of DED shows beneficial ocular effects.[51] Presently, patients can purchase amniotic fluid extract from some eye care provider offices or can obtain a prescription to procure the product at distributing pharmacies. Amniotic fluid extract is used once to twice a day and appears to be a good option for patients who do not want to have their blood drawn to have serum tears made or who cannot have their blood drawn due to other issues (e.g., anemia, fainting). Also, for some patients, the protein in serum tears can cause irritation, so amniotic fluid extract is an alternative. Both serum tears and amniotic fluid extract work best for patients with severe dry eye, for example, as a result of Sjögren's disease, neurotrophic corneal disease or a persistent epithelial defect.

Tear conservation by temporarily blocking tear outflow via punctal occlusion (punctal plugs) was shown to improve tear retention, but a recent meta-analysis determined that improvements in DED signs and symptoms with punctal plugs are inconclusive.[52] When punctal plugs are used to improve ocular surface tear retention and wetting, the clinician should be mindful that blocking the outflow of tears containing excess inflammatory mediators can result in worsening red eye, a papillary reaction, and worse dry eye symptoms. Concurrent or prior treatment of ocular surface inflammation is advisable. Tear stimulation therapy uses pharmacological agents (oral/topical secretagogues) or devices that stimulate aqueous, mucin, or lipid secretion. Most are currently under development or available outside Canada, notwithstanding the use of the oral secretagogue pilocarpine for patients with severe Sjögren's syndrome. Other recommended agents—such as the topical aqueous secretagogue diquafosol tetrasodium and the mucin secretagogue rebamipide—are unavailable in Canada.[29] Testosterone ophthalmic solution (unavailable commercially in Canada) has been demonstrated to have lipid-stimulating effects in an early clinical study, but additional research on its use as a treatment strategy is required.[53] An intranasal device that increases tear production through neurostimulation (US Food and Drug Administration–approved TrueTear®[54]) is unavailable in Canada.

TFOS DEWS II recommends treatments for lid abnormalities such as blepharitis, MGD, and blinking abnormalities that cause dry eye (Table 3).[29] Anterior blepharitis treatment aims to improve lid hygiene through the use of lid cleansers in combination with omega-3 fatty acids, natural products (e.g., tea tree oil), antibiotics, and antipara-

sitic agents (metronidazole and ivermectin).[32,33] Topical products containing tea tree oil can reduce counts of, and even eradicate, ocular *Demodex*.[29] Oral ivermectin had positive results in patients with *Demodex* blepharitis[55] but requires co-management with an infectious disease specialist due to the potential for severe systemic side effects. Options for MGD treatment include lipid-containing ocular lubricants, manual or mechanical therapies (e.g., an ocular heating mask is more effective than a warm compress[56]), thermal pulsation, or intense pulsed light (used off-label in Canada for EDE due to MGD).[29,35,57] Use of intraductal probing has been reported but may induce additional scarring. Debridement of the lid margin to reduce biofilm build up and hyperkeratinization also requires further investigation.[29] Incomplete blinking or incomplete eyelid closure during sleep can dry the ocular surface.[29] Corneal exposure can be managed by temporary or permanent eyelid closure (patch/tape), eye moisture chamber goggles, Op-site patches, or therapeutic contact lenses (Table 3). Surgical procedures are needed to repair entropion or ectropion and re-establish the lid anatomy.

Anti-inflammatory therapy using topical glucocorticoids can help reduce DED-associated inflammation. Corticosteroids inhibit the expression of pro-inflammatory molecules, promote the expression of anti-inflammatory molecules, and stimulate lymphocyte apoptosis, all of which contribute to an immediate anti-inflammatory effect.[58] In patients with moderate-to-severe DED, short pulse treatments of repeated corticosteroid use may be needed to control ocular surface inflammation as long-term continuous use increases the risk of steroid-associated complications (e.g., ocular hypertension, cataracts, opportunistic infections).[29] In Canada, the corticosteroid ophthalmic suspension loteprednol etabonate[36] is indicated for short-term relief of signs and symptoms of seasonal allergic conjunctivitis. Loteprednol etabonate is also available in gel form and is indicated for treatment of inflammation and pain following cataract surgery.[37] Unlike other ophthalmic corticosteroids, loteprednol etabonate contains an ester rather than a ketone at the C-20 position, thus minimizing intraocular penetration and reducing the potential for side effects such as intraocular pressure elevation and cataract formation.[59] Non-glucocorticoid immunomodulators block T-lymphocyte activity, which reduces inflammatory markers on the ocular surface; a cyclosporine ophthalmic emulsion[38] is available in Canada for the treatment of moderate to moderately severe ADDE. Topical tacrolimus improved dry eye symptoms in patients intolerant to cyclosporine with severe DED and graft-versus-host disease;[60] topical tacrolimus is indicated in Canada for treatment of atopic dermatitis.[39] TFOS DEWS II suggests nonsteroidal anti-inflammatory drug treatment, but cases of corneal melting in patients with severe DED have been observed. Antibiotics are thought to improve DED-associated MGD clinical parameters and anterior blepharitis by decreasing meibomian lipid breakdown. Oral tetracycline[40] and its analogues (e.g., doxycycline[41]) have been used to treat rosacea and chronic blepharitis, but their use for DED management is poorly understood, and optimal dosing schedules remain undefined.[29] A few studies have demonstrated that topical azithromycin (unavailable commercially in Canada) and oral azithromycin[42] were effective in the management of MGD and DED.[29] The lymphocyte function–associated antigen 1 (LFA-1) antagonist lifitegrast,[43] indicated in Canada for DED treatment, blocks binding between LFA-1 and intercellular adhesion molecule 1, inhibiting DED-associated inflammation.

When all else fails, surgery can be considered.[29] Permanent surgical closure of the punctum is generally reserved for cases where punctal plugs are not retained or tolerated. Tarsorrhaphy can help individuals with severely dry eyes due to severe or persistent corneal exposure.[29] Other surgical procedures are outlined in Table 3.

CONCLUSIONS

The evidence-based 2017 TFOS DEWS II report provides reference points along the entire continuum of the clinical management of DED, from detection and diagnosis to treatment and future research. The clinical aspects of the report represent a guide for eye care professionals caring for patients with DED who then have to make evaluations and judgements based on a patient's individual circumstances. Since demographic, cultural, geographical, environmental, and lifestyle factors influence DED epidemiology and response to treatment, it is important to consider TFOS DEWS II recommendations on a country-by-country and regional basis. Interpreting and applying TFOS DEWS II recommendations is particularly relevant for Canada due to this country's diverse ethnocultural make-up and expansive geography.

Management of DED in Canadian clinical practice is undergoing significant change because of current and future challenges and opportunities. The latest estimated prevalence of DED in Ontario (22%) lies in the middle of the global range.[3,5] A major challenge is that the prevalence of DED will increase as the Canadian population continues to age, since DED disproportionately affects older individuals. Given that more than 4500 optometrists practice in Canada, increased awareness of diagnosis and management strategies will help patients with DED to access care. The involvement of optometrists may help to overcome some of the challenges associated with Canada's significant regional variation in the distribution of ophthalmologists.[61] An interdisciplinary approach could facilitate

earlier diagnosis and initiation of preventive measures and treatments. Co-management by eye care professionals (optometrists and ophthalmologists) is especially important for cases of advanced DED or cases requiring surgical intervention, and when addressing DED management for ocular surgery candidates (i.e., refractive surgery, cataract surgery). The availability of new diagnostic tools and emerging technologies in Canada should further aid our ability to identify clinical signs of DED.

Practices unique to Canada that affect the management of environmental and other DED risk factors (e.g., contact lens use, electronic device screen time) warrant further investigation before country-specific guidelines can be developed. The complex and progressive nature of DED along with the high inter-individual difference in response to some treatments require elucidation. Filling these knowledge gaps may engender the better use and development of etiology-directed therapies. For the moment, promoting tear film homeostasis by delivering holistic patient-centered care plans that encourage adherence is crucial for effectively managing DED and improving quality of life. ●

FUNDING

Preparation of the manuscript was supported by Takeda and Novartis. Takeda and Novartis reviewed the manuscript for medical accuracy only.

ACKNOWLEDGEMENTS

The authors thank Daniella Babu, PhD, and Ira Probodh, PhD, of Excel Scientific Solutions, who assisted with preparing the manuscript, supported by Takeda and Novartis.

AUTHOR CONTRIBUTIONS

All authors participated equally in the development of the intellectual content, provided important critique for each revision, and approved the final version of this manuscript.

AUTHOR DISCLOSURES

Clara C. Chan has been a consultant for Alcon, Allergan, Bausch & Lomb, Santen, Shire,* and TearScience, and has received research support from Allergan, Bausch & Lomb, and TearLab. Mahshad Darvish-Zargar has received grant/research support from Bayer, and has received honoraria/consulting fees from Allergan, J&J, Santen, and Shire.* Jitendra Gohill has received grant/research support from Pfizer, Alcon, and AMO; has received honoraria/consulting fees from Alcon and Shire;* and has participated in a company-sponsored speaker's bureau for Alcon. Setareh Ziai has received grant/research support from Shire* and honoraria/consulting fees from Allergan, Labtician, J&J, and Shire.*

*A Takeda company.

CORRESPONDING AUTHOR

Clara C. Chan, MD, FRCSC, FACS, Department of Ophthalmology & Vision Sciences, University of Toronto, 601-600 Sherbourne St, Toronto, ON M4X 1W4, Canada, Tel: +1 (416) 960 5007, E-mail: clarachanmd@gmail.com

Figure 1: *Vicious cycle of DED. Tear hyperosmolarity, cell damage and apoptosis, inflammation, and loss of goblet cells are the main factors that contribute to the pathophysiology of DED and tear film instability*[1,14]

Adapted with permission from Craig et al.1 .

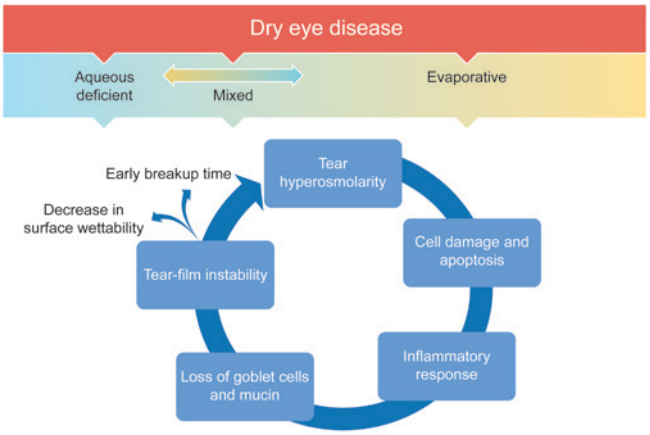

Figure 2: *Access to DED care and clinical decision algorithm in Canada for patients suspected of having DED*

BID, twice a day; DED, dry eye disease; OSD, ocular surface disease; OTC, over-the-counter; TFOS DEWS II, Tear Film & Ocular Surface Society Dry Eye Workshop II

Adapted with permission from Craig et al.1 .

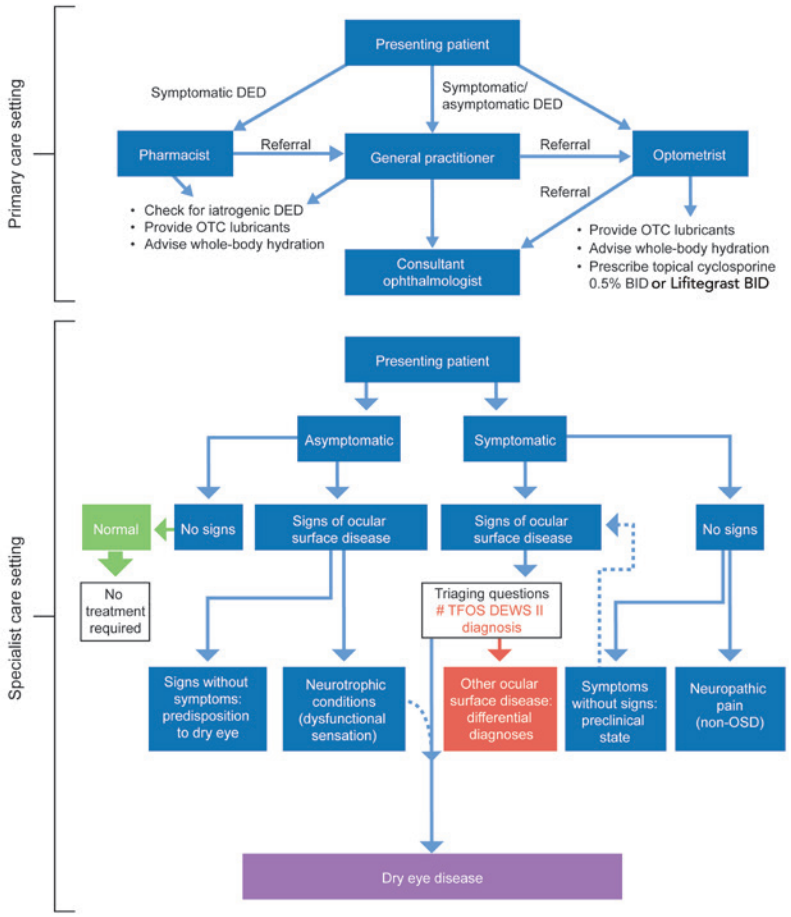

Figure 3: *Steps for DED evaluation from the Canadian perspective*[16,17-22]

AC, air conditioning; BC, British Columbia; DED, dry eye disease; MGD, Meibomian gland dysfunction; MMP-9, matrix metalloproteinase 9; OCT, optical coherence tomography; TMH, tear meniscus height.

Reproduced with permission from Wolffsohn JS, et al.16.

*Based on US data and assuming similar socio-demographic characteristics with Canada.

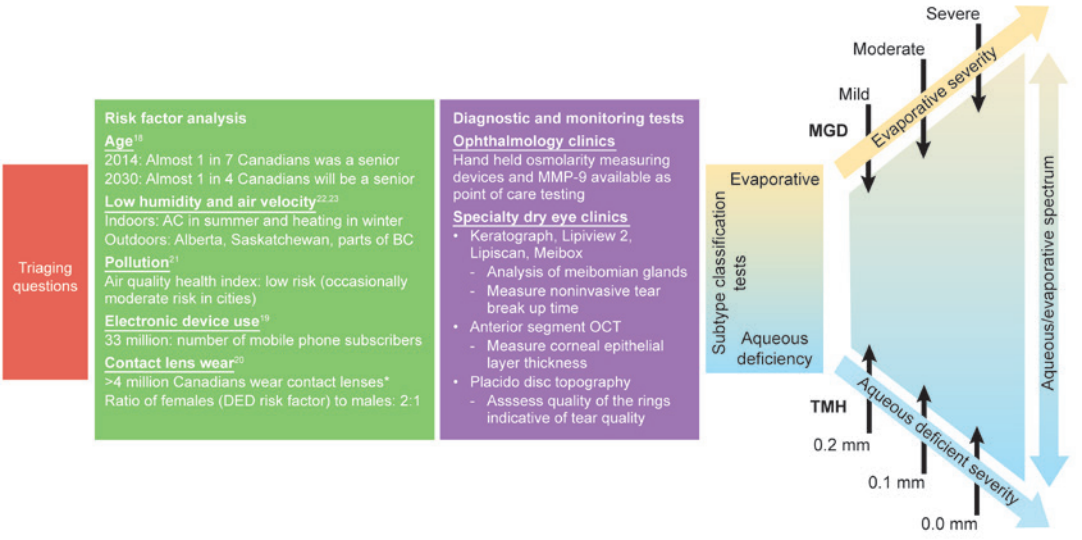

Table 1: *Questions to rule out other conditions that overlap dry eye disease*

How severe is the eye discomfort?	Unless severe, dry eye presents with signs of irritation such as dryness and grittiness rather than "pain." If pain is present, investigate for signs of trauma, infection, and ulceration.
Do you have any mouth dryness or enlarged glands?	Triggers a Sjögren's syndrome investigation.
How long have your symptoms lasted and was there any triggering event?	Dry eye is a chronic condition present from morning to evening, but generally worse at the end of the day; so, if sudden onset or linked to an event, examine for trauma, infection, and ulceration.
Is your vision affected and does it clear on blinking?	Vision is generally impaired with prolonged staring, but should largely recover after blinking; a reduction in vision that does not improve with blinking, particularly with sudden onset, requires an urgent eye examination.
Are the symptoms or any redness much worse in one eye than the other?	Dry eye is generally a bilateral condition; so, if symptoms or redness are much greater in one eye than the other, a detailed eye examination is required to exclude trauma and infection.
Do the eyes itch? Are they swollen or crusty, or have they given off any discharge?	Itching is usually associated with allergies while a mucopurulent discharge is associated with ocular infection.
Do you wear contact lenses?	Contact lenses can induce dry eye signs and symptoms, and appropriate management strategies should be used by the contact lens prescriber.
Have you been diagnosed with any general health conditions (including recent respiratory infections) or are you taking any medications?	Patients should be advised to mention their symptoms to the health professionals managing their condition, as modified treatment may minimize or alleviate their dry eye.

Adapted with permission from Wolffsohn JS, et al.[16]

Table 2: *Risk factors for dry eye disease*[3,23]

Factors consistently associated with DED across studies*			
Demographic	*Lifestyle/Environment*	*Medical Conditions/Procedures*	*Medications*
Age Female sex Asian race	Use of computers and portable electronic devices Contact lens wear Pollution Low humidity Sick building syndrome	Sjögren's syndrome MGD Hematopoietic stem cell transplantation Connective tissue disease Androgen deficiency	Antihistamines Antidepressants Anxiolytics Isotretinoin Hormone replacement therapy
Probable risk factors for DED†			
Demographic	*Lifestyle/Environment*	*Medical Conditions/Procedures*	*Medications*
None	None	Diabetes Rosacea Viral infection Thyroid disease Psychiatric conditions Pterygium Low fatty acid intake Refractive surgery Allergic conjunctivitis	Anticholinergics Diuretics Beta blockers
Inconclusive risk factors for DED§			
Demographic	*Lifestyle/Environment*	*Medical Conditions/Procedures*	*Medications*
Hispanic ethnicity	Smoking Alcohol	Menopause Acne Sarcoidosis Pregnancy *Demodex* infestation Botulinum toxin infection	Multivitamins Oral contraceptives

MGD, Meibomian gland dysfunction

*Existence of ≥1 adequately powered and otherwise well-conducted studies along with a plausible biological rationale and corroborating basic research or clinical data.

†Inconclusive/limited information to support the association.

§Directly conflicting information or inconclusive information but with some basis for a biological rationale.

Table 3: *Summary of DED management and treatment strategies*[29]

Strategy	Care options	Available/applicable in Canada
Dietary modifications	• Improve whole-body hydration • Omega-3 and/or omega-6 fatty acids supplements • Lactoferrin	Yes
Management of risk factors	• Iatrogenic (systemic and topical medications) o Use preservative-free ophthalmic formulations o Switch suspected medication route of administration from oral to topical o Adjust drug dose o Change medication o Use more aggressive treatment of drug-induced DED • Environmental o Avoid exposure to pollutants and dry air conditions o Reduce exposure to visual displays and portable electronic devices o Use appropriate contact lenses	Yes
Treatments for tear insufficiency	• Artificial tears • Biological tear substitutes o Autologous serum o Adult allogenic serum o Umbilical cord serum o Platelet preparations • Punctal occlusion (nonsurgical) • Topical secretagogues o Oral secretagogues o Aqueous secretagogues	• Yes • Yes, limited (a prescription-only amniotic fluid extract is available as Regener-Eyes® from select ophthalmologist/ optometrist offices) • Yes • Yes o Pilocarpine[30] off-label o LACRISERT®[31]
Treatment for lid abnormalities	• Anterior blepharitis o Lid cleansing o Topical antibiotics o Broad-spectrum antiparasitics o Tea tree oil o Omega-3 fatty acid supplements • MGD o Lipid-based ocular lubricants o Ocular heating mask and warm compress o Manual lid massage or thermal pulsation o Intense pulsed light • Blinking abnormalities or ocular exposure o Temporary eyelid closure (with patch/tape) o Eye moisture chamber goggles o Thin polymer films o Therapeutic contact lenses • Surgical procedures to manage entropion and ectropion	• Yes o Metronidazole[32] and ivermectin[33] available off-label • Yes o Systane Balance and Systane Complete, Refresh Optive Advanced and Refresh Optive Mega-3, Soothe XP, and Retaine MGD o Yes (LipiFlow®[34]) o Yes o Used off-label for EDE due to MGD[35] • Yes o Yes (plastic food wrap) o Yes (bandage, scleral lenses) • Yes
Anti-inflammatory therapy	• Topical glucocorticoids • Non-glucocorticoid immunomodulators • Systemic and topical antibiotics • LFA-1 antagonist	• Loteprednol (off-label)[36,37] • Cyclosporine[38] and tacrolimus[39] (both off-label) • Tetracycline,[40] doxycycline[41] (off-label), azithromycin (off-label)[42]* • Lifitegrast[43]
Surgical approaches	• Punctal occlusion • Tarsorrhaphy • Surgical conjunctivochalasis treatment • Botulinum toxin A injections (for essential blepharospasm) • Lid corrections • Amniotic membrane • Salivary gland transplantation • Parotid duct transposition • Microvascular submandibular gland transplantation	• Yes • Yes • Yes • Yes • Yes • Yes, PROKERA®[44] • Yes • Yes • Yes

*While there is no commercial topical azithromycin available in Canada, formulations may be manufactured at compounding pharmacies to treat MGD. Oral azithromycin is used in patients with tetracycline allergy or those unable to tolerate the gastrointestinal side effects related to doxycycline.
DED, dry eye disease; LFA-1, lymphocyte function–associated antigen 1; MGD, Meibomian gland dysfunction; PRO, prosthetics

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf Jul 2017;15(3):276–83.
2. Jackson WB. Management of dysfunctional tear syndrome: a Canadian consensus. Can J Ophthalmol 2009 Aug;44(4):385-94 Aug 2009;44(4):385–94.
3. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. Ocul Surf Jul 2017;15(3):334–65.
4. Doughty MJ, Fonn D, Richter D, Simpson T, Caffery B, Gordon K. A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. Optom Vis Sci 1997 Aug;74(8):624-31.
5. Caffery B, Srinivasan S, Reaume CJ, et al. Prevalence of dry eye disease in Ontario, Canada: a population-based survey. Ocul Surf 2019 Jul;17(3):526-31.
6. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol 2007 Mar;143(3):409-15.
7. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the Beaver Dam Offspring Study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol Apr 2014;157(4):799–806.
8. Campbell RJ, El-Defrawy SR. Shaping the future of ophthalmology in Canada. Can J Ophthalmol 2016 Dec;51(6):397-99.
9. National Eye Institute. Eye disease statistics. 2014. Available at: https://www.nei.nih.gov/sites/default/files/2019-04/NEI_Eye_Disease_Statistics_Factsheet_2014_V10.pdf [Accessed August 17, 2019].
10. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea Apr 2011;30(4):379–87.
11. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol Jun 2009;127(6):763–8.
12. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol Aug 2003;136(2):318–26.
13. Taylor JG, Joubert R. Pharmacist-led minor ailment programs: a Canadian perspective. Int J Gen Med 2016;9:291-302.
14. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. Ocul Surf Jul 2017;15(3):438–510.
15. Baudouin C, Messmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of Meibomian gland dysfunction. Br J Ophthalmol Mar 2016;100(3):300–6.
16. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf Jul 2017;15(3):539–74.
17. Government of Canada. Action for Seniors report. 2014. Available at: https://www.canada.ca/en/employment-social-development/programs/seniors-action-report.html [Accessed August 2019].
18. Statista. Mobile usage in Canada - Statistics & Facts. 2019. Available at: https://www.statista.com/topics/3529/mobile-usage-in-canada/ [Accessed August 20, 2019].
19. Statistic Brain Research Institute. Corrective lenses statistics. Available at: https://www.statisticbrain.com/corrective-lenses-statistics/ [Accessed August 20, 2019].
20. Government of Canada. Air Quality Health Index. Available at: https://weather.gc.ca/airquality/pages/index_e.html [Accessed August 20, 2019].
21. Canadian Centre for Occupational Health and Safety. OSH Answers Fact Sheets. Thermal Comfort for Office Work. Available at: https://www.ccohs.ca/oshanswers/phys_agents/thermal_comfort.html [Accessed August 20, 2019].
22. Government of Canada. North America - Relative Humidity. Available at: https://weather.gc.ca/astro/meteo_animation_e.html?id=hr&utc=00 [Accessed August 20, 2019].
23. Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. Ocul Surf Jul 2017;15(3):511–38.
24. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. Cont Lens Anterior Eye 2010 Apr;33(2):55-60.
25. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol Jan 2010;128(1):94-101.
26. Ozcura F, Aydin S, Helvaci MR. Ocular surface disease index for the diagnosis of dry eye syndrome. Ocul Immunol Inflamm Sep-Oct 2007;15(5):389-93.
27. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol May 2000;118(5):615-21.
28. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. Clin Ophthalmol 2015;9:1719–30.
29. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf Jul 2017;15(3):575–628.
30. Pfizer Canada Inc. SALAGEN® (pilocarpine HCl 5 mg tablets) [product monograph]. 2014; https://pdf.hres.ca/dpd_pm/00031208.PDF. Accessed 10/10/2018.
31. Bausch & Lomb I. LACRISERT® (hydroxypropyl cellulose ophthalmic insert) [package insert]. https://www.bausch.com/Portals/69/-/m/BL/United%20States/USFiles/Downloads/Consumer/Pharma/lacrisert-patient-instruction-sheet.pdf. Accessed 10/10/2018.
32. Sanofi-Aventis Canada. FLAGYL® (metronidazole) [product monograph]. 2018; http://products.sanofi.ca/en/flagyl.pdf. Accessed 10/10/2018.
33. Galderma Canada Inc. Rosiver™ (ivermectin cream, 1% w/w) [product monograph]. 2017; https://www.nestleskinhealth.com/sites/g/files/jcdfhc196/files/inline-files/Rosiver-PM-E.pdf. Accessed 10/10/2018.
34. TearScience. LipiFlow® thermal pulsation system. https://www.jnjvisionpro.ca/products/lipiflow-treatment. Accessed 10/10/2018.
35. Rennick S, Adcock L. Intense pulsed light therapy for meibomian gland dysfunction: a review of clinical effectiveness and guidelines. Ottawa: CADTH; 2018 Feb. (CADTH rapid response report: summary with critical appraisal). Available at: https://www.ncbi.nlm.nih.gov/books/NBK531789/pdf/Bookshelf_NBK531789.pdf [Accessed August 25, 2019].
36. Bausch & Lomb I. ALREX® (loteprednol etabonate opthalmic suspension 0.2% w/v) [product monograph]. 2012; https://www.bausch.ca/wp-content/uploads/2019/12/Alrex-PM-EN.pdf. Accessed 10/10/2018.
37. Bausch & Lomb I. LOTEMAX® gel (loteprednol etabonate ophthalmic gel 0.5 % w/w) [product monograph]. 2014; http://www.bausch.ca/Portals/59/Files/Monograph/Pharma/Lotemax-gel-pm.pdf. Accessed 10/10/2018.
38. Allergan Inc. Restasis MultiDose™ (cyclosporine ophthalmic emulsion 0.05% w/v) [product monograph]. https://allergan-web-cdn-prod.azureedge.net/allergancanadaspecialty/allergan-canadaspecialty/media/actavis-canada-specialty/en/products/pms/9054xmd-2018jun01-en-restasis-multidose_1.pdf. Accessed 10/10/2018.
39. Astellas Pharma Canada, Inc. PROTOPIC® (tacrolimus ointment) [product monograph]. https://www.astellas.com/us/system/files/PROTOPIC%20OINTMENT.pdf. Accessed 10/10/2018.
40. Government of Canada. Product information: tetracycline. https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=5293. Accessed 10/10/2018.
41. Teva Canada Limited. Teva-Doxycycline capsules (doxycycline hyclate) Teva-Doxycycline tablets (doxycyline hyclate) [package insert]. 2018; https://pdf.hres.ca/dpd_pm/00042598.PDF. Accessed 4/9/2019.
42. Altamed Pharma. Azithromycin (azithromycin dihydrate) tablets [product monograph]. https://pdf.hres.ca/dpd_pm/00046156.PDF. Accessed 10/10/2018.
43. Shire Pharma Canada ULC. XIIDRA® (lifitegrast ophthalmic solution 5% (w/v)) [product monograph]. 2017; https://www.shirecanada.com/-/media/shire/shireglobal/shirecanada/pdffiles/product%20information/xiidra-pm-en.pdf. Accessed 10/10/2018.
44. Bio-Tissue. PROKERA®. https://www.biotissue.com/patients/our-products/patients-prokera.aspx. Accessed 03/19/2019.
45. Novack GD, Asbell P, Barabino S, et al. TFOS DEWS II clinical trial design report. Ocul Surf Jul 2017;15(3):629-49.
46. Giannaccare G, Pellegrini M, Sebastiani S, et al. Efficacy of omega-3 fatty acid supplementation for treatment of dry eye disease: A meta-analysis of randomized clinical trials. Cornea May 2019;38(5):565-73.

47. Asbell PA, Maguire MG, Pistilli M, et al. n–3 Fatty acid supplementation for the treatment of dry eye disease. N Engl J Med May 3 2018;378(18):1681–90.
48. Devendra J, Singh S. Effect of oral lactoferrin on cataract surgery induced dry eye: A randomised controlled trial. J Clin Diagn Res 2015 Oct;9(10):NC06-9.
49. Dogru M, Matsumoto Y, Yamamoto Y, et al. Lactoferrin in Sjogren's syndrome. Ophthalmology Dec 2007;114(12):2366-7.
50. Aguayo Bonniard A, Yeung JY, Chan CC, Birt CM. Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK). Expert Opin Drug Metab Toxicol Jul 18 2016:1–11.
51. Yeu E, Goldberg DF, Mah FS, et al. Safety and efficacy of amniotic cytokine extract in the treatment of dry eye disease. Clin Ophthalmol 2019;13:887-94.
52. Ervin AM, Law A, Pucker AD. Punctal occlusion for dry eye syndrome: summary of a Cochrane systematic review. Br J Ophthalmol Mar 2019;103(3):301-6.
53. Schiffman R, Bradford R, Bunnell B, Lai F, Bernstein P, Whitcup S. A multicenter, double-masked, randomized, vehicle-controlled, parallel group study to evaluate the safety and efficacy of testosterone ophthalmic solution in patients with meibomian gland dysfunction [ARVO e-abstract #5608]. Invest Ophthalmol Vis Sci 2006;47.
54. Allergan Inc. TrueTear® https://www.truetear.com/. Accessed 10/10/2018.
55. Salem DA, El-Shazly A, Nabih N, El-Bayoumy Y, Saleh S. Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of Demodex folliculorum. Int J Infect Dis May 2013;17(5):e343–7.
56. Bitton E, Lacroix Z, Léger S. In-vivo heat retention comparison of eyelid warming masks. Cont Lens Anterior Eye Aug 2016;39(4):311–5.
57. Gupta PK, Vora GK, Matossian C, Kim M, Stinnett S. Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Can J Ophthalmol 2016 Aug;51(4):249-53
58. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol Jan 2012;130(1):90–100.
59. Comstock TL, Sheppard JD. Loteprednol etabonate for inflammatory conditions of the anterior segment of the eye: twenty years of clinical experience with a retrometabolically designed corticosteroid. Expert Opin Pharmacother 2018 Mar;19(4):337-53.
60. Sanz-Marco E, Udaondo P, Garcia-Delpech S, Vazquez A, Diaz-Llopis M. Treatment of refractory dry eye associated with graft versus host disease with 0.03% tacrolimus eyedrops. J Ocul Pharmacol Ther Oct 2013;29(8):776–83.
61. Bellan L, Buske L, Wang S, Buys YM. The landscape of ophthalmologists in Canada: present and future. Can J Ophthalmol 2013 Jun;48(3):160-6.