Ophthalmology MANAGEMENT Article

Clues to DTS may lurk on meds list

Systemic drugs from many classes may provoke severity.

By By Laura Periman, MD March 1, 2015

Safeguarding the Cornea

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My understanding of dysfunctional tear syndrome (DTS), or ocular surface disease (OSD), has evolved from years of clinical practice, a research and development background in immunopathophysiology and an avid interest in reading new research. In residency and fellowship, I thought of DTS as a simple problem of insufficient aqueous production, insufficient evaporative protection or both, for which we had limited treatment options.

But in 2002, the introduction of the steroid-sparing immunomodulator cyclosporine (Restasis, Allergan), gave us the first commercially available medication that specifically and effectively treats the inflammatory nature of keratoconjunctivitis sicca associated with DTS. Cyclosporine has become the long-term, steroid-sparing and macrophage-function sparing foundational therapy in treating the underlying immunopathophysiology of DTS.[1,2]

A new view

With publication of the DEWS Report in 2007, my view expanded to a new appreciation of the ocular surface as a fully-integrated, multi-faceted, truly elegant system, known as the Lacrimal Functional Unit (LFU), designed to maintain homeostasis despite various exogenous and endogenous stressors. DTS results from the chronic, self-perpetuating inflammatory cycle consequent to the loss of homeostatic regulatory control.

Today, the DEWS Report, the MGD Report and the International Task Force (ITF) guidelines on DTS management are the roadmaps that I use to navigate the DTS patient. Updates on the horizon will give us a clearer, expert and consensus-based roadmap of how to successfully navigate our patients' OSD with the new diagnostic and treatment modalities. The DEWS and MGD reports teach us that the key underlying mechanisms of DTS are desiccating stress and hyperosmolarity[1,3] which can result from myriad causes including: age, hormone status, lifestyle, environmental exposures and medications.

A new stressor to eliminate

The medications aspect is an increasingly important component of my assessment — and recommendations — for the DTS patient. My approach stems from a 2011 paper in which the authors elegantly summarized and organized those medications that most exacerbate DTS.[4] I laminated the table, placed a copy in each exam room and still refer to it when needed.

'Non-responding' or 'progressing' DTS patients referred to our practice will often have one or more of these desiccating stress-inducing medications on their lists. The patient's primary medical physician can often substitute a less exacerbating medication (such as switching a hypertension patient from a diuretic or beta blocker to a generic calcium channel blocker or ACE inhibitor, which are inherently less drying to the lacrimal functional unit). The patient usually will notice symptom improvements within one to three months provided the appropriate prescribed ITF level interventions are continued.

As a patient improves from a level 3 to a level 2 (very rewarding to see clinically), the maintenance therapies can be simplified accordingly.

The following summaries of three case reports illustrate how interesting and varied the effect of systemic medications on the ocular surface can be.

Table 1: Systemic Medication Classification

COMMON SYSTEMIC MEDICATIONS THAT PROBABLY CAUSE DTS				
		Generic Name	**Trade Name**	**DTS Mechanism**
Medication class: Listed by most exacerbating to least exacerbating within each class	Antidepressants			Muscarinic receptor antagonism decreases lacrimal gland output. SSRIs have fewer severe anticholinergic effects than TCAs
	TCAs	amitriptyline	Elavil	
		nortriptyline	Pamelor	
		doxepin	Sinequan	
	SSRIs	fluoxetine	Prozac	
		fluvoxamine	Luvox	
		sertraline	Zoloft	
		paroxetine	Paxil	
		citalopram	Celexa	
		escitalopram	Lexapro	
	NDRI	bupropion	Wellbutrin	
	NaSSAs	mirtazapine	Remeron	Remeron shows lower incidence of dry mouth than TCAs and SSRIs
				Anticholinergic profile limits lacrimal gland output
	Anxiolytics	diazepam	Valium	
		alprazolam	Xanax	
		lorazepam	Ativan	
	Benzodiazepine	zolpidem	Ambien	
	Hypnotics	zopiclone	Imovane	
		eszopiclone	Lunesta	
	Antihypertensives	hydrochlorothiazide (HCTZ) metoprolol and other beta blockers		Decreased intravascular volume limits tear production by lacrimal gland
	Hormone manipulators	leuprolide	Lupron	LHRH analog that decreases sex hormones (especially testosterone), impacting meibum production, leading to increased evaporative tear losses

Neuromuscular junction blockade	botulinum toxin	Botox, Xeomin	Decreased blink forces may limit tear spread and meibum delivery
Anticholinergics and dopaminergics for Parkinson's disease	benzhexol	Artane (anticholinergic)	Anticholinergics and anticholinergic profiles of dopaminergic agonists decrease lacrimal gland output
	pramipexole	Mirapex (dopamine agonist with anticholinergic effects)	
	levodopa	Sinemet	
	benztropine	Cogentin	
Antipsychotics			
Typical	chlorpromazine	Thorazine	Anticholinergic profile limits lacrimal gland output
	thioridazine	Melleril	
	haloperidol	Haldol	
Atypical	clozapine	Clozaril	
	risperidone	Risperdal	
	quetiapine	Seroquel	
	aripiprazole	Clozaril	
Antihistamines			Oral antihistamines have M3 receptor activity that directly limits lacrimal gland output and directly decreases mucin output from goblet cells. Cetirizine and fexofenadine have the least M3 receptor affinity
First generation:	diphenhydramine	Benadryl	
	hydroxyzine	Atarax, Vistaril	
Second generation:	desloratadine	Clarinex	
	loratadine	Claritin	
	cetirizine	Zyrtec	Topical antihistamine/mast-cell stabilizers have markedly less muscarinic receptor activity and are therefore less drying to the ocular surface
	fexofenadine	Allegra	
Anticholinergics for overactive bladder	propantheline	Propantheline	Bladder has M2 and M3 receptors; meds' effects help the bladder but limit lacrimal gland & goblet cell functions. Ranking of drying effects: propantheline>oxybutynin> tolterodine, propiverene
	oxybutynin	Ditropan	
	tolterodine	Detrol	
	propiverine	Detrunorm	
	solifenacin	Vesicare	

Table 2

Dry Eye Severity	**Level 1**	**Level 2**	**Level 3**	**Level 4**
Discomfort/Severity /Frequency	Mild-Occurs under environmental stress	Moderate-Occurs with and without stress	Severe-Frequent/constant without stress	Severe-Disabling and constant
Visual Symptoms	None or mild with fatigue	Annoying and/or activity limiting	Annoying, chronic and/or constant limiting of activity	Constant and/or possibly disabling
Conjunctival Injection	None to Mild	None to Mild	1+	2+
Conjunctival Staining	Mild to trace	1+ to 2+	3+	4+
Corneal Staining	None	1+ to 2+	Marked central	Severe punctate erosions
Corneal/Tear Signs	None to mild	Mild debris	Filamentary/mucous clumping	Ulceration
Lids/Glands	Variable presentation 8% MGD	Variable presentation 53% MGD	Frequent	Trichiasis, keratinization, symblepharon
TBUT	Variable presentation	<10	<5	<2
Treatment	**Level 1**	**Level 2**	**Level 3**	**Level 4**
	Education of systemic medications and environmental modifications	Education of systemic medications and environmental modifications	Education of systemic medications and environmental modifications	Education of systemic medications and environmental modifications
	Control Allergies	Control Allergies	Control Allergies	Control Allergies
	Preservative Free artificial tears/gels /ointment	Preservative Free artificial tears/gels /ointment	Preservative Free artificial tears/gels /ointment	Preservative Free artificial tears/gels /ointment
		Oral Omega 3 supplement	Oral Omega 3 supplement	Oral Omega 3 supplement
		Rx anti-inflammatories (Restasis, Lotemax)	Rx anti-inflammatories (Restasis, Lotemax)	Rx anti-inflammatories (Restasis, Lotemax)
			Doxycycline	Doxycycline
			Scleral Contact Lenses	Scleral Contact Lenses
			Moisture Chambers	Moisture Chambers

	Autologous serum	Autologous serum
	Amniotic Membrane	Amniotic Membrane
	Punctal Plugs	Punctal Plugs
		Surgery

Case Report 1

PL is a 73-year-old Asian female referred to us with a 15-year history of chronic DTS with frequent exacerbations. Her short medication list included metoprolol x 12 years (Lopressor, Novartis) for mild essential hypertension. She reported bothersome DTS symptoms with overlying exacerbations three to four times per year. The patient's symptoms and clinical signs indicated ITF-level 3 DTS and marked meibomian gland loss.

External examination revealed a grossly incomplete blink and incomplete lid seal. (Incomplete lid seal is measured as light leaking through the interpalpebral fissure as tested in a darkened room by placing an inferonasally directed muscle light on the superotemporal aspect of the superior tarsus of each upper lid with the patient's eyes closed in a relaxed facial position).[5]

Her moderate incomplete lid closure and significant MGD prompted questions regarding past oculoplastic surgery and concurrent use of neuromuscular junction-blocking injectables (botulinum toxin) around the eyes.

The patient reported a bilateral upper eyelid blepharoplasty (excellent result) 20 years prior. She also had been receiving neuromuscular junction-blocking injectables in the forehead, glabellum and orbicularis muscles three to four times per year for the past decade. We pointed this out, and the patient realized that her symptoms were significantly exacerbated two months after starting metoprolol and one to two weeks after each administration of the injections. The patient's identifiable and modifiable desiccating stresses were the beta blocker metoprolol and the botulinum toxin injections. Systemic beta blockers directly limit lacrimal gland output and may affect the sympathetic innervation of the meibomian glands.[6] Neuromuscular junction blockade injectables to the temporal orbicularis muscle likely weaken blink forces and lid wiper function.[7] We asked her primary medical physician to switch to a less exacerbating anti-hypertensive and we asked the patient to stop receiving cosmetic injections around her eyes. We anticipate that her DTS symptoms will improve within two to five months after meeting these requests and maintaining the full ITF level 3 interventions necessary to control the chronic inflammatory cycle generated by the desiccating stresses. The patient's age, hormone status, reduced blink forces secondary to the BoTox and the systemic beta blocker's neurobiochemical feedback effects have compromised her meibomian gland health significantly. Once we have inflammation under control (a negative InflammaDry test, Rapid Pathogen Screening, Inc.), she will be a candidate for in-office thermal meibomian gland pulsation therapy (LipiFlow, TearScience) to stimulate the remaining meibomian gland tissue to optimal performance.

Case Report 2

AB is a 53-year-old healthy female with essential hypertension and a 15-year history of chronic DTS. She was well maintained on topical cyclosporine (Restasis, Allergan) twice a day for 10 years until two years prior to presentation. Review of the medication list revealed a past history of SSRI use, lisinopril (Prinivil, Merck) for the hypertension and hydrochlorothiazide (HCTZ) for management of hypertension and chronic lower extremity edema (LEE). Review of systems (ROS) was positive for low energy, low metabolism, slow wound healing, chronic constipation and temporal eye brow hair loss. ROS was negative for cardiovascular disease (except the hypertension); however, a history of multiple joint arthropathy was elucidated. The patient reported a normal thyroid-stimulating hormone test (but not T3 and T4 testing), last checked more than a year ago. When we pointed out the timing of symptom onset and SSRI administration, the patient realized her disease started shortly after she began taking SSRIs and it was exacerbated again shortly after starting HCTZ.

Slit lamp exam revealed incomplete blinking, ITF early level 3 disease and moderate MGD loss on retroillumination. Physical exam revealed thin temporal eyebrow cilia and mild to moderate pretibial pitting edema.

Full thyroid panel testing and Sjo testing (Nicox) was recommended to rule out hypothyroidism and autoimmune disease as contributors to the underlying cause of her LEE and DTS.

In this case, the patient's identifiable desiccating stresses were prior SSRI use, HCTZ use and incomplete blinking. Since her inflammation was controlled on topical cyclosporine (negative InflammaDry test, Rapid Pathogen Screening, Inc.), she received LipiFlow (TearScience) treatment and blink-retraining exercises. Four weeks later,

she reported that her symptoms had improved. We emphasized that continued progress depended upon correction of the underlying causes and exacerbating medications.

Case Report 3

AM is a 28-year-old healthy oncology fellow with a two-year history of marked soft contact lens intolerance and red, irritated eyes. ROS was negative for systemic autoimmune disease. Medication history revealed chronic self-administration of diphenhydramine (Benadryl, McNeil Consumer) for the past two years as a sleep aid given her work and call schedule. DTS symptom onset correlated with starting this OTC medication. Diphenhydramine is well known to have muscarinic (M3) receptor promiscuity that directly limits lacrimal gland output (aqueous) and goblet cell output (mucin). Exam revealed early ITF level 2 DTS; she was started on ITF level 2 interventions.

One year later, after she eliminated the offending desiccating stress medication, followed the level 2 interventions and also decreased the hours of soft contact lens wear in the hospital, the patient improved to an ITF level 1. She also found her eyes could better tolerate the low-humidity, turbulent air conditions in the hospital and ICU.

Case Report 4

CR is a 59-year-old female with a 20-year-history of DTS symptoms. The patient's medical history revealed chronic migraine headache disorder, controlled to one to two episodes per month on low-dose amitriptyline. This information prompted more detailed questions; we asked about Raynaud's phenomenon. The patient reported not only severe Raynaud's phenomenon of the hands and feet, but that she also suffered migratory arthralgias and myalgias along with visible, painful nodules on the pads of her toes in the winter. Upon closer questioning, the patient reported that every time she tried to decrease her dose of amitriptyline, the frequency of severe migraine headaches increased. The patient also had received isotretinoin decades earlier for chronic cystic acne. She reported doing well with her DTS on topical cyclosporine for 3 years, but was lost to follow-up and had used only nutraceuticals (fish oil and flax seed oil) and PF AFT for the past 2 years. Her symptoms had notably worsened during that time, as expected, without immunomodulatory therapy 7.[8] SLE revealed ITF level 2 DTS. We reinitiated topical immunomodulatory therapy consistent with level 2 ITF guidelines and requested lab testing for cryoglobulins and autoimmune disease (Sjo test).

Table 3: Algorithm for Assessment and Management of OSD Patients on Systemic Medications

Step 1 Any comorbid OSD conditions? **Step 1. If yes,** treat comorbid OSD conditions (including but not limited to blepharitis, MGD, allergy) **If no,** go to Step 2.
Step 2 Any systemic medications? **Step 2. If yes,** obtain a complete list of patient's prescriptions, OTCs, herbals and supplements. If no, go to Step 3.
Step 3 Can the medication safely be decreased or discontinued? **Step 3. If yes,** discuss with primary care physician. If no, go to Step 4.
Step 4 Can the medication be switched to a less desiccating alternative? **Step 4. If yes,** discuss with primary care physician. If no, increase OSD interventions (e.g. escalate from ITF level 2 to ITF level 3 interventions) and go to Step 5.
Step 5 Update and review medication list at each visit for new or discontinued medications

Discussion and Summary

Prescription and OTC medications used for a specific diagnosis or purpose impact the whole body and its organ systems more than we routinely consider. This article's intent is to remind us to consider how common systemic medications impact the ocular surface.

I ask myself if a medication on the list limits normal physiologic function (such as decreased tear, mucin or meibum production), normal mechanical function (such as reduced blink force or blink frequency) or both. DTS is a chronic, self-perpetuating inflammatory cycle. Treatment is initiated to prevent its progression. Once the suspected desiccating stress-inducing medications are identified, they can often be stopped, decreased or switched to a less offending class.

In my clinical experience, once these clear desiccating stress exacerbators have been identified and adjusted, the topical therapies and nutraceuticals we recommend have an even greater impact on preventing DTS progression

and improving each patient's ocular surface disease.

Look at your OSD patient's systemic medication list: Rewarding clues await discovery. **OM**

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