Pain Without Stain: Managing Neuropathic Corneal Pain

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Financial disclosure

- Speaker – Novartis Pharmaceuticals

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DED Revisited – DEWS II Report

- Incidence – estimate that nearly 30 million people have DED, underestimated, increasing in prevalence with diets poor in omega-3s, increased screen time activities/contact lenses/laser and cataract surgery
  - Dry eye remains one of the most searched terms on the internet
- "Given the improving diagnostics and therapeutics, waiving our hands and making conjectures as to the etiology of this disease while throwing the next brand of artificial tears at these patients is no longer acceptable" – Marjan Farid, MD Irvine CA

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DEWS-I Report 2007 Pearls

- Corneal tests and symptoms DO NOT correlate with disease
- 30% of DE patients are ASYMPTOMATIC
  - Took 7 times for FDA to clear Restasis
- MGD most common cause of DE
  - Mucin is everywhere in the three layers of tear film
- Hyperosmolarity is common thread in DED
  - Tear Osmolarity in Diagnosis & Management of Dry Eye, Lemp,M AmJOphth 2011;151:792-798
  - Objective Approach to Dry Eye Disease Severity, Sullivan,B InvestOphthVisScience Dec 2010 Vol 51 No 12
- Asymmetry in osmolarity (and clinical presentation) is pathognomonic of DED
  - Difference of 6-8 mm is diagnostic

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DED Revisited – DEWS II Report

- New definition – "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which the tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities play etiological roles"
- The recognition of the multiple etiological elements involved in DED is a key difference between this new definition and the one in the original DEWS report
  - Core mechanisms are hyperosmolarity, thinning, destabilization of tear film and inflammation of surface
    - Hyperosmolarity is the central pathogenic element

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DED Revisited – DEWS II Report

- Classification scheme
  - Symptomatic with signs
  - **Symptomatic without signs**
  - Asymptomatic with signs
  - Asymptomatic without signs
- Initial diagnosis of DED can be made with symptoms (DEQ-5>6 or OSDI >13) and one positive test out of three
  - TBUT
  - Osmolarity
  - Ocular surface staining

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DED Revisited – DEWS II Report

- "New" Tear Film
  - 2-6 u thick and major refracting surface of the eye
  - Traditional model described 3 distinct layers
  - TFOS DEWS II established that these layers are less discrete
- Two later system
  - Mucoaqueous combination layer – decreasing concentration of mucins moving anteriorly
    - Apical epithelial cell of conjunctiva and cornea are covered in transmembrane mucins (MU-C5AC) Reduce friction, barrier func
  - Overlying lipid layer – derived from meibum, distributed over surface with each blink
    - TFLL reduced evaporation by only up to 10%

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DED Revisited – DEWS II Report

- Pathophysiology – initiated by numerous intrinsic & extrinsic factors that promote hyperosmolar tear film. This leads to inflammatory cycle causing ocular surface epithelial disease and neural stimulation. Desiccation activates stress signaling pathways, activating innate inflammatory mediators that stimulate production of MMP, T cell recruitment, dendritic cell maturation. Corneal barrier disruption develops by protease-mediated lysis of epithelial tight junctions, accelerated cell death, desquamation, irregular and poorly lubricated surface, exposure and sensitization of epithelial nociceptors.

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DED Revisited – DEWS II Report

- Pathophysiology – conjunctival goblet cell dysfunction and death are promoted by T helper 1 cytokine interferon gamma. These epithelial changes further destabilize the tear film, amplify inflammation, and create a vicious cycle. Next to the intestine, the conjunctival epithelium has the second highest concentration of mucous producing goblet cells such as killer cell, dendritic cells, macrophages, and CD4 and CD8 T cells that function in antimicrobial defense but may participate in dry eye pathogenesis

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DED Revisited – DEWS II Report

- Pathophysiology – hyperosmolarity is at the core of DED and is primarily driven by tear film breakup
  - Increased expression of inflammatory mediators, recruitment of inflammatory cells, further inflammation, apoptosis of cornea and conjunctival epithelial cells, decreased surface glycocalyx, decreased goblet cell density
    - A "vicious circle of inflammation"
- Lacrimal functional unit
  - Lacrimal and accessory lacrimal glands – aqueous tear film
  - Conjunctival goblet cells – production of mucin
  - Meibomian glands – production of meibum
  - Disrupt any of these components – instability / hyperosm

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DED Revisited – DEWS II Report

- Pathophysiology – tear homeostasis is achieved by reflex arc of the LFU
  - Afferent limb provided by trigeminal innervation of cornea/conjunctiva
  - Sensory drive provided by parasymapathetic secretomotor innervation
  - Sensory drive for secretion of each component is stimulated by corneal thermoreceptors
    - Sense cold and hyperosmolarity
    - When stimulated reflexive increase in lacrimation, blink rate, and ocular discomfort

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DED Revisited – DEWS II Report

- New definition – DED can be classified into two primary categories
  - Aqueous deficient dry eye (ADDE)
  - Evaporative dry eye (EDE)
- ADDE & EDE exist in a continuum, often overlap
  - Majority of DED atients have the combination type disease
- In DED it is COMMON that signs do not correspond with patient reported symptoms
  - The absence of symptoms or overt clinical signs does not exclude the diagnosis of DED
- A validated symptom questionnaire is a useful tool

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Why Treat DED?

- It is chronic and progressive (Ngo W Cornea 2013; 32)
- Prevalence is continuing to increase
- Affects Refractive surgery and cataract surgery outcomes, biometric measurements
  - Premium channel IOLs especially sensitive to OSD
    - Diffractive eschellet designs more optically dependent on tear film
  - ASCRS 2017 data showed 55% of pre-operative cataract surgery examinations had abnormalities in BOTH osmolarity & MMP-9 testing, and had minimal or no symptomatology
    - Brissett AR et al. Paper ASCRS 2017; May 9, 2017; Los Angeles CA
  - Remains undermanaged in these groups

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Multifactorial Nature of DED

- Age – strongest correlated DED risk factor
- Female, connective tissue disease, Sjogrens
- Post-menopausal state
- Medications – beta blockers, diuretics, antihistamines, antidepressants (SSRI), anxiolytics, isotretinoin
- Systemic diseases – RA, DM, Thyroid, migraine, GVHD, Sarcoid, rosacea, allergic conj, refractive sx
- Environmental, pollution, low humidity
- Previous eye surgery – LASIK, corneal procedures
- Blepharitis/MGD

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InflammaDry (Rapid Pathogen Screening)

- Matrix Metalloproteinase (MMP-9) is the best biomarker for ocular surface disease & dry eye
- Developed as a simple in office test to predict and prevent problems after LASIK and other surface surgery
- Also as a test for dry eye disease
- Available as ***InflammaDry***

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InflammaDry Testing 83516

- Unilateral, modifiers –RT, -LT
- CMS requires modifier –QW for CLIA waived
- Immunoassay for analyte other than infectious agent antigen; qualitative or semi-quantitative method
- Many diagnosis codes associated with dry eye payable
- Applies to InflammaDry Device (Quidel)
  - CLIA waiver granted
- Requires Interpretation & report Fee $15.82

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Tear Lab

- "Lab on a Chip"
  - We have a test!
    - Analogy of treating DM without BG, HA1c etc
  - No longer needs CLIA, COLA, inspection, etc
- Gold cartridge draws nl of fluid and processes
- Osmolarity is the global marker of Dry Eye (DEWS Report)
  - Least variable test for DE
  - Central mechanism in pathogenesis of DED
  - More variable results seen in more advanced disease
  - Large differences between eyes noted, increasing with disease severity
  - 308mosmsl = Dry Eye
  - Sensitivity 72.8%/Specificty 92%
    - No other clinical sign or test is better than 62%

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Osmolarity Severity Scale

- 280-300 Normal
- 308-320 Mild
- 320-340 Moderate
- 340+ Severe

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Osmolarity Highest Positive Predictive Value of DED

- Osmolarity 87%
- Schirmer's 31%
- TBUT 25%
- Staining 31%
- Meniscus height 33%
- Dry Eye Workshop Report 2007 OculSurf 2007;5:2 Tomlinson A, et al IOVS. 47(10) 2006

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Tear Osmolarity Testing 83861

- Unilateral, modifiers –RT, -LT
- CMS requires modifier –QW for CLIA waived
- Microfluidic analysis, tear osmolarity
- No defined diagnosis code list
- Applies to TearLab's Osmolarity Device
  - Novel "Lab-on-a-chip"
  - Point of care, 50nl sample of tear fluid
  - Sample-to-answer in less than 30sec
  - CLIA waiver granted
- Requires Interpretation & report Fee $23.25

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Tear Osmolarity Testing - IPEN

- Canadian company I-MED Pharma
- Developed the first hand-held platform for measuring osmolarity – I-PEN
- Reliably screens for DED
- Pending FDA 510(k) clearance it will begin distribution
- Exclusive agreement signed with OcuSoft Inc to distribute in USA

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New Dry Eye Disease Diagnosis

- Evolving diagnostic algorithm
  - Objective signs
    - Stains, TBUT, Meibomian gland expressions, Tear meniscus height/area/volume, lactoferrin levels, aberrometry, VA quality, osmolarity, MMP-9, meibography
  - Identify the subtype if DED present
  - Grade the severity
- Treat based on 1-4 above
- ***Simplified*** DED Protocol (before any drops)
  - History & examination
  - Osmolarity (308, 8 difference)
  - MMP-9
  - Meibography +/-

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Non-Dry Eye Disease OSD

- Osmolarity normal & MMP-9 normal
  - Blepharitis
  - Allergic conjunctivitis
  - EBMD
  - CL intolerance
  - Conjunctivochalasis
  - Keratoneuralgia
  - Computer vision syndrome

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Non-Dry Eye Disease OSD

- Osmolarity normal & MMP-9 elevated = Inflammation
  - Blepharitis
  - Allergic conjunctivitis
  - EBMD
  - RCE
  - Pterygium
  - Rosacea

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Dry Eye Center of Excellence

- Diagnostic Testing Center of Excellence
  - Tear Osmolarity (Tear Lab)
  - MMP-9 for inflammation (InflammaDry / RPS)
  - Meibomian Gland imaging (Tear Science)
  - Sjo Test (Nicox/B&L)
- Putting the pieces of the diagnostic puzzle together
  - High osmolarity (>320, diff of 12) = Rxs & hypotonic aft's
  - Low osmolarity = lid margins, oil based tears ex.retaine MGD
  - +InflammaDry = Anti-inflammatory, Loteprednol
  - +InflammaDry & High Osmolarity = restasis or Xiidra
    - Highly sensitive for DED and with aqueous deficiency R/O Sjogrens
  - +InflammaDry & Low Osmolarity = steroids, loteprednol

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DED Revisited – DEWS II Report

- Neurosensory abnormalities have emerged as the fastest growing area in DED
- Surface inflammation causes sensitization or abnormally increased activity of some sensory nerve terminals evoking dryness sensation and pain
  - Cold thermoreceptors, polymodal nociceptors, mechano-nociceptors
- This dysfunction of sensory neurons may account for the lack of consistency between signs and symptoms
- Puzzling cases of patients with a minimum of clinical signs but with severe symptoms may be suffering from chronic neuropathic pain ("pain without stain")

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Neuropathic Corneal Pain (NCP)

- NCP may have a peripheral origin (ocular surgery, HZV)
- NCP may have systemic origin (small fiber polyneuropathy, fibromyalgia, trigeminal neuralgia, chemotherapy)
- Additional underlying causes are infectious keratitis, RCE, radiation keratopathy, CL wear
- Proparacaine Challenge Test – abolished peripheral pain but has no effect on central pain
  - Many patients achieve ***partial relief*** from topical anesthesia
  - Suggests that ***both central and peripheral*** sensitization are at play

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Neuropathic Corneal Pain (NCP)

- NCP can occur in the most richly innervated tissue of the body, perceived as pain, discomfort, irritation, dryness, burning, grittiness
- Can result from peripheral nerve injury and systemic etiologies
- Peripheral pain signaling over time can result in central sensitization, w central neurons becoming highly responsive
- Hallmark of central sensitization is pain that is disconnected from ongoing peripheral signs

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Neuropathic Corneal Pain (NCP)

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Neuropathic Corneal Pain (NCP)

- In-vivo Laser Confocal Microscopy (ILCM) – non-invasive, high resolution device allowing real time visualization at cellular level (1u resolution-HRT3 RCM)
  - Demonstrates decreased nerve density, increased tortuosity, reflectivity, and beading
  - Presence of microneuromas reflect sudden swelling of injured nerves at terminal endings and are specific for NCP (diagnostic)
  - Recent RCT demonstrated that patients with near normal corneal nerve density showed improvement in signs & symptoms after DE therapy; low nerve density showed no change providing further rationale for the notorious variability of responses observed with therapies

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Neuropathic Corneal Pain - Treatments

- Neuroregenerative Therapy – target neuronal regeneration with autologous serum tears (AST)
  - Recovery of corneal nerve topography has been demonstrated!
  - AST 20% 8 times daily until symptom resolution achieved
    - Typically 3-4 months if peripheral origin
  - Follow by slow taper over 9-12 months to prevent rebound
- Topical corticosteroidsTherapy – RCT demonstrated significant symptom reduction with Loteprednol 0.5% drop or gel qid for 2 weeks, bid for 2 weeks, qd for 12 wk
  - Loteprednol 0.5% gel has much lower concentration of neurotoxic preservative benzalkonium chloride (0.003%) compared to other steroids (0.05-0.01%)

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Overarching Treatment Approach

- Label the condition as a nerve problem rather than an eye problem
- Reassure the patient that there is no blinding process occurring with pain
- A combination approach to therapy is most beneficial
  - Local ocular
  - Systemic
  - Psychological
  - Collaborate with other clinicians
    - Neurologists / Dentists / psychiatrists / Pain management / Anesthesiologist

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Overarching Treatment Approach

- Goal of treatment is to reduce pain
  - For the patient
  - To prevent peripheral signaling from converting to centralized pain
- Recommendations are anecdotal, scientific, and preliminary clinical trial data as well as evidence based approaches from other neuropathic pain syndromes
  - Particularly true of systemic recommendations
  - Most ECPs are not comfortable prescribing the best systemic treatments
  - Some tertiary corneal specialists are experienced in this area

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NCP – Local Ocular Therapies

- First step is to provide local ocular support for the ocular surface and nerves
  - Lubricants
  - Punctal occlusions
  - Bandage soft contact lenses
  - Scleral lenses
- Second step is suppression of inflammation
  - Lotepredrnol (only steroid) / Restasis / Xiidra / CEQUA
- Topical anesthetics – have never proven effective long term but can provide relief short term
- Autologous serum tears, amniotic membrane

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NCP - Systemic Therapies

- No RCT available, data is scarce but extrapolate from from treatments of PHN and neuropathic pain elsewhere
- Tricyclic antidepressants – first line agents acting on pre-synaptic norepinephrine & serotonin, cholinergic blocking, histaminergic, and sodium channels
  - Nortriptyline (Pamelor) 10-25mg hs increased q3-7 D to 25-100mg hs
- Anti-convulsant Carbamazepine – first line agent, Na channel blocker for TGN
  - CBZ (Tegretol, Carbacol) started at 200mg hs, increased by 200mg q7D to final dose 400-1200mg divided in 2-3 doses/day

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NCP Systemic Therapies

- Low Dose Naltrexone (LDN) – second line agent is opioid antagonist to toll-like receptor 4 that is linked to neuropathic pain
  - Indicated for alcohol and drug abuse
  - Off label effective use in chronic neuropathic pain syndrome, low back pain, fibromyalgia, complex regional pain syndrome and painful diabetic neuropathy
    - LDN (Vivitrol/Revia) 1.5mg hs gradual biweekly increase of 1.5mg to final max dose of 4.5mg hs
- Tramadol – weak opioid agonist with norepinephrine and serotonin inhibition, indicated for pain (narcotic)
  - Tramadol (Ultram) 50mg qd or bid gradual increase to max dose of 400mg qd

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NCP Systemic Therapies

- Calcium channel a2g ligands – third line agents gabapentin (Neurontin) and pregabalin (Lyrica) widely used for PHN, central neuropathic pain, diabetic neuralgia, stabilizing neurons, inhibiting substance-P, glutamate, norepinephrine
  - Gabapentin (Neurontin) 900 mg resulted in 66% decrease in pain in RCT
    - Initiate with 600mg single dose on day 1 and increase q3D to dose of 1800mg divided in 3 doses
  - Pregabalin (Lyrica) 75mg bid increased over one week to 150mg bid
    - Can increase to 300mg bid if tolerated

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NCP Systemic Therapies

- Serotonin-norepinephrine inhibitors – Duloxetine (Cymbalta) 20-120mg/D and venlafaxine (EffexorXR) 75mg-225mg have central analgesic properties
  - Indications are Depression, general anxiety disorder, social anxiety disorder, pain
- Sodium Channel Blocker – Mexilentine 225-675mg/D orally active local anesthetic similar to lidocaine for refractory pain only
  - Many adverse events so limited use

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Future of DED – Pipeline

- Autologous Serum tears – more common in moderate to severe DED in treatment failures
- Include growth factors (TNF stimulated gene/protein 6, anti-TNFa, anti-IL-17), Chemokines (CCR1 CCR2 CCR5CXCR3), vitamins, fibronectin which promote proliferation and maturation of corneal epithelial cells
  - Comparable concentration of immunoglobins in healthy tears
- Antiprotease a2 macroglobin responsible for inhibiting collagenase – cases of alkaline burns
- Neuropeptide substance P and insulin like growth factors in serum which replenish deficiencies seen in

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Future of DED – Pipeline

- Amniotic tears / Human amniotic fluid (HAF) – topical suspension elicits same healing affects as AMT
  - Anti-inflammatory, antiangiogenic & anti-scarring effects derived without the discomfort and visual impairment of available AMT grafts
- Contact lenses – two type are used and helpful!!
  - Soft bandage lenses effective in providing relief (daily or extended wear) with antibiotic prophylaxis in refractory cases
  - Scleral lenses are the most effective in severe DED (92%)
    - Fluid filled / Vault the cornea / Rest on the limbus / Provide constant lubrication
    - Use remains limited by availability / cost and provider awareness of benefit
    - Downside – require more training to use, not all are candidates

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Microbiome and Immunoregulation

- Microbial community that inhabits the human body has immunoregulatory functions
  - Yet cultures of conjunctiva are often negative
  - In sharp contrast to cultures of the lid margin and perioc skin
  - Ocular surface biome is the lowest biomass of any tissue in the body (Ozan/IOVS)
    - Mice with 5 oral antibiotic cocktail prior to dessication had significantly worse dry eye than controls
      - Suggesting intestinal microbiome can modulate ocular surface inflammation and severity of dry eye
  - Intestinal dysbiosis has been found as risk factor for SS DED
  - Supplementation with commensal microbiota have shown anti-inflammatory effects in autoimmune conditions (IBS, DM)
    - Possible benefit from commensal bacteria metabolites or probiotics

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Cenergermin 0.002% for NK

- Indicated in treatment of moderate-severe neurotrophic keratitis
  - Sight threatening, non-validated treatments which often fail
- Recombinant form of human nerve growth factor (hNGF)
  - Deficient in eyes NK
  - Important in maintaining corneal homeostasis and healing
- Produced from E. coli bacteria
- Dose – 6 times per day for 8 weeksDose form – multi-dose bottle
- Adverse events – eye pain, hyperemia
- Available as – Oxervate / Dompe Farmaceutici SpA

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Thank you

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