Updates on Corneal Cross-Linking & Myopia Control

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Part 1: Objectives

- To clarify the underlying principles
- To critically review the scientific literature
- To provide an update on these technologies
- To guide selection of the appropriate candidates
- To assist in identifying and managing potential adverse events or loss of efficacy
- To guide the integration of these technologies into practice

Disclosures

- Dr. Fuller – provides statistical support for a non-funded, independent clinical evaluation of a CXL device
- Educational consultant to
  - Alcon,
  - Allergan,
  - B+L,
  - Cooper Vision and
  - JJV

What is CXL?

- Collagen fibrils branch and extend limbus to limbus
- Cross-linking occurs between fibrils in the same lamellar layer
- Provides biomechanical stability
Man-made

- Polymer chemistry uses – this is responsible for some of the differences in modulus in SiHy lenses
- Reduction in biodegradation – collagen-based bioprosthesis

Natural

- Advanced glycation end products (AGE’s) – age & DM (prevent or decrease severity of KCN)
- Photo-oxidative CXL – UV & ionizing radiation
- Enzymatic CXL – l-lysyl oxidase; a deficiency can lead to Ehlers-Danlos; maybe a gene defect in KCN
- Non-enzymatic CXL – glutaraldehyde; formaldehyde; diphenylphosphoryl; nitroalcohol; genipin

Initial Candidates

- Primary corneal ectasias
  - Keratoconus
  - Pellucid marginal degeneration
  - Must demonstrate progression
  - Age cut-off is arguable
- Secondary corneal ectasias
- LASIK/PRK

Potential Candidates

- Off-label
  - Combined procedures – with LASIK, INTACS, and cataract procedures
  - PiXL – treat low amounts of myopia without LASIK
  - Microbial keratitis – sterilize the wound
  - Sclera – to strengthen grafts or melts
- Corneal dystrophies – Fuch’s and other
Physical Properties

**CXL Process**
- Photochemical process
- Non-thermal
- Comparison to photocoagulation
  - Photocoagulation – 630 W/cm²
  - Photochemical – 3 mW/cm²
  - Maximum temp. increase of 2-3°C

**UV Spectrum**
- Ultraviolet spectrum
  - UVA – 320-400 nm
  - UVB – 280-320 nm
  - UVC – 180-280 nm

Absorption of UVA

- RF 0.1% sol.
  - Selected for an average KCN pach of 400 microns
  - Biomechanical effect is independent of concentration over a large area
  - Higher conc. actually reduce CXL effect
  - Produces a large absorption coefficient of 90% in the stroma protecting the endothelium, lens and retina.
  - 65% absorbed in the first 200 microns

Absorption of UVA/Emittance

- Riboflavin has two peak absorption maxima
  - 375nm
  - 445nm
- Emits fluorescence at 534nm

Tissue Changes

- Increase in modulus and firmness by a factor of 1.7x
- Increase in shrinkage temp. from 63°C to 70°C
- Decrease in swelling percentage
- Increase in collagen fibril thickness by 4.5% 
- Increased resistance to collagenase
- Creation of molecular aggregates with higher molecular weights
- Decrease in permeability
Cellular Changes

- **Epithelial cells**
  - Epi-off – cells grow back in 3-4 days
  - Normal thickness at 3 to 6 months
  - Intact epithelium protects limbal stem cells
- **Keratocytes**
  - Increases apoptosis in first 250-300 microns
  - New cells migrate from periphery
  - Alterations occur up to 36 mos.


Histological changes in human cornea after cross-linking with riboflavin and ultraviolet A

- **Endothelial cells**
  - Statistically non-significant reduction
  - Density and morphology unchanged at 1 year
  - Threshold for damage is 0.35 mW/cm²; exposure levels are 0.18 mW/cm²
  - Assuming a 400 micron thick or greater cornea

Cellular Changes

• Nerves
  • Subepithelial nerve plexus disappears
  • Regenerates after 7 days and is normal by 6 mos.

Riboflavin Used in the US Trials

• Riboflavin (vitamin B₂) 0.1% sol. – m.w. 376 gm/mol (Photrex 0.12% / Photrex Viscous 0.12% with Dextran 20% from Avedro)
  • Non-toxic
  • Absorbs UVA light
  • Used to create free radicals which cross-link the carbonyl groups within and between collagen fibrils in the same lamellae not between lamellae
  • There may be some inter-fibrillar bonds between proteoglycans

Cellular Changes

• Deeper structures
  • Lens – protected by the absorption of UVA by RF and cornea
  • Retina – also protected by absorption and lack of irradiation being focused in its plane

Riboflavin Overseas

<table>
<thead>
<tr>
<th>Riboflavin</th>
<th>Formula</th>
<th>Use</th>
<th>Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedioCROSS TE</td>
<td>0.25% Riboflavin, 1.2% HPMC, 0.01% BAC</td>
<td>Cross-linking for keratoconus and corneal ectasia</td>
<td>On</td>
</tr>
<tr>
<td>MedioCROSS M</td>
<td>0.1% Riboflavin, 1.1% HPMC</td>
<td>Cross-linking for keratoconus and corneal ectasia</td>
<td>Off</td>
</tr>
<tr>
<td>VibeX Xtra</td>
<td>0.22% Riboflavin, Saline, Isotonic</td>
<td>LASIK</td>
<td>Stromal Bed</td>
</tr>
<tr>
<td>VibeX Rapid</td>
<td>0.1% Riboflavin, Saline, HPMC</td>
<td>Accelerated CXL</td>
<td>Off</td>
</tr>
<tr>
<td>ParaCel</td>
<td>0.25% Riboflavin, HPMC, BAC</td>
<td>Accelerated CXL</td>
<td>On</td>
</tr>
</tbody>
</table>
Procedures: Dresden v. Athens
Bunsen-Roscoe Law (Intensity x Time = Exposition)

- **Dresden protocol**
  - Intensity is 3 mW/cm²
  - Treatment time 30 mins.
  - At 2 to 5 min. intervals
  - Applied over an 8 mm diameter area to protect limbus, sclera and goblet cells

- **Athens protocol**
  - Maximum intensity up to 43 mW/cm²; Treatment time 2 min.
  - Typical protocols (Kymionis et al.)
    - 9 mW/cm² for 14 min
    - 18 mW/cm² for 7 min
    - May pulse doses

Comparison of outcomes

- **Outcomes of treatment efficacy**
  - Accelerated CXL - shallower
  - Conventional CXL - deeper
  - Regression > with A-CXL

- **Problem**
  - Less available oxygen in accelerated CXL with epi-on.

- **Solution**
  - 30 mW Pulsed therapy at 1 s intervals of 3-8 min; allows O₂ more time to penetrate

Epithelium-off Delivery of Riboflavin

- RF 0.1% every 1 to 5 mins. for 30 mins.
- Eliminates the barrier to diffusion presented by the epithelium
- Diffusion achieves a maximum in the anterior stroma at 20 to 30 mins., protecting the endothelium/lens/retina

Epithelium-on (Transepithelial) Delivery of Riboflavin

- **Improving penetration**
  - Increase contact time (viscous sol. or ring application)
  - Change permeability (pilocarpine with either BAK and EDTA; tetracaine; hypo-osmotic riboflavin sol.)
  - Dextran inhibits conductance when added, whereas 0.01% BAC and 0.44% NaCl increase permeability.
  - Using a Daya disrupter you can pock-mark the epithelium improving permeability
Direct Application of Riboflavin

- Create a pocket as in Intacs
- Inject riboflavin into the pocket or after flap creation in LASIK

Iontophoresis Delivery of Riboflavin

- Riboflavin in negatively charged
- Current is delivered for 5 mins. across the intact epithelium
- CONCLUSION: I-CXL using 0.1% riboflavin halts keratoconus progression within 24mo, resulting in a significant improvement in visual and topographic parameters. Moreover, the depth of the demarcation line is similar to that previously reported in standard epithelium-off CXL procedures.

Devices

- **Overseas**
  - CBM VEGA X-linker (Constuzione Strumenti, Oftalmici, FL, IT)
  - CCL-365 (PESCHKE Meditrade GmbH, Huenberg, SW)
  - UV-X (IROC GmbH, Zurich, SW) acquired by Avedro

- **United States FDA Trials**
  - Avedro (Waltham, MA) KXL was the submission device but UVX used in trials
    - 30 min. induction every 2 mins. with Photrexa Viscous or until flare is observed in the AC continues throughout tx.
    - 3 mW/cm² for 30 mins.
    - 5.5 J/cm² maximum energy density

25 26 27 28
Devices

- United States FDA Trials
  - Selectable apertures deliver beams 7.5 mm, 9.5 mm & 11.5 mm
- Subjective alignment by fluorescence
- Touchscreen interface
- Internal battery
- Delivered through a gantry, upright or supine
- Software lockout ensures operators stay within allowable parameters

Case #1

- 17 y.o. w/m with decreasing vision and contact lens intolerance
- Dx with KCN Oct. 2012
- Cornea OD: Inf. Temp. scarring; Vogt’s striae; Fleischer’s ring
- Cornea OS: clear
- Rapid progression to PK OD Mar. 2015
- Referred for trans-epithelial CXL OS July 2015

<table>
<thead>
<tr>
<th>OD Lens History</th>
<th>Date</th>
<th>BCVA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose K</td>
<td>1/11/13</td>
<td>20/30</td>
<td></td>
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<tr>
<td>Synergeyes Clear Kone</td>
<td>1/18/13</td>
<td>20/30</td>
<td></td>
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<tr>
<td>Office visit</td>
<td>6/12/13</td>
<td></td>
<td>Corneal abrasion FTK</td>
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<tr>
<td>Essilor Jupiter</td>
<td>6/19/13</td>
<td>20/30</td>
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<tr>
<td>Surgery OD</td>
<td>5/14</td>
<td>20/30</td>
<td>PK</td>
</tr>
<tr>
<td>Synergeyes PS</td>
<td>9/14</td>
<td>20/15</td>
<td></td>
</tr>
<tr>
<td>Episode of rejection</td>
<td>3/15</td>
<td>20/20</td>
<td>PF 1% Maintenance</td>
</tr>
<tr>
<td>Switch to UltraHealth</td>
<td>6/15</td>
<td>20/20</td>
<td>Not tolerating PS/UH</td>
</tr>
<tr>
<td>Valley Contax Cust. Stable Elite</td>
<td>7/15</td>
<td>20/20</td>
<td></td>
</tr>
</tbody>
</table>
Case #2

- 21 y.o w/m; applying to the US Navy
- Dx: KCN in 2010
- Sx: CXL and Intacs Feb 2015
- Successfully fit with Custom Stable Elite (Valley Contax) scleral lenses

<table>
<thead>
<tr>
<th>MRE</th>
<th>BCVA</th>
<th>Sim K's</th>
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</thead>
<tbody>
<tr>
<td>-5.50-2.75 x070</td>
<td>20/25</td>
<td>46.6/52.0</td>
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<tr>
<td>-6.00-5.00 x170</td>
<td>20/100</td>
<td>31.60/37.50</td>
</tr>
<tr>
<td>CS Elite 7.85/15.8 -3.50</td>
<td>20/20-3</td>
<td></td>
</tr>
<tr>
<td>CS Elite 7.85/15.8 pl-2.00 x022</td>
<td>20/25+</td>
<td></td>
</tr>
</tbody>
</table>

Approval granted for the treatment of progressive keratoconus in April 2016

- The KXL system and the two photoenhancers,
- Photrex 0.146% (riboflavin 5'-phosphate ophthalmic solution)
- Photrex Viscous 0.146% (riboflavin 5'-phosphate in 20% dextran ophthalmic solution)
- 12 months results
  - Reduction in mean Kmax of 1 D in study 1 and 0.5 D in study 3 compared with increase of 1 D in study 1 and 0.5 D in study 3 in sham-controlled eyes.
  - Adverse events included corneal opacity, corneal epithelium defect, corneal striae, dry eye, eye pain, punctate keratitis, photophobia, reduced visual acuity and blurred vision.
Overseas Experience

Primary Keratoconus

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up (mos.)</th>
<th>Kmax dec. (D)</th>
<th>BCVA's Inc. lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wollensak et al. 2003</td>
<td>3-47</td>
<td>2.01D in 70%</td>
<td>1.26 lines in 65%</td>
</tr>
<tr>
<td>Raiskup-Wolf et al. 2008</td>
<td>6-72</td>
<td>2.68D in 62%</td>
<td>≥1 in 53%</td>
</tr>
<tr>
<td>Wittig-Silva et al. 2008</td>
<td>3-12</td>
<td>1.45D</td>
<td>0.17 LogMAR</td>
</tr>
<tr>
<td>Vinciguerra et al. 2009</td>
<td>12</td>
<td>1.35D</td>
<td>0.15 LogMAR</td>
</tr>
<tr>
<td>Hersh et al. 2011</td>
<td>48-60</td>
<td>2.00</td>
<td>≥2 in 21.1%</td>
</tr>
<tr>
<td>Asri et al. 2011</td>
<td>12</td>
<td>&gt;2.00 in 21.3%</td>
<td>40% improved</td>
</tr>
<tr>
<td>Poli et al. 2012</td>
<td>12.36</td>
<td>No significant trend</td>
<td>Significant Improvement</td>
</tr>
</tbody>
</table>

1998 – First CXL in C.G.suitUniversity Hospital Dresden, GE.

Overseas Experience

Secondary Ectasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up (mos.)</th>
<th>Kmax dec. (D)</th>
<th>BCVA's Inc. lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohlihas et al. 2005</td>
<td>18</td>
<td>Stable</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Hafezi et al. 2007</td>
<td>12-25</td>
<td>Dec. in all</td>
<td>Improved in 90%</td>
</tr>
<tr>
<td>Vinciguerra et al. 2010</td>
<td>12</td>
<td>2.02D</td>
<td>0.1 LogMAR</td>
</tr>
<tr>
<td>Kissner et al. 2011</td>
<td>96</td>
<td>Stable in 60%</td>
<td>Stable in 60%</td>
</tr>
<tr>
<td>Salgado et al. 2011</td>
<td>12</td>
<td>Not statistically significant</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>Hersh et al. 2011</td>
<td>12</td>
<td>1.6D</td>
<td>Significantly improved</td>
</tr>
</tbody>
</table>

Meta-Analysis

* Review of efficacy epi-off KCN or surgical ectasia

Analysis of epithelium-off CXL papers by study type

<table>
<thead>
<tr>
<th>Analysis of epithelium-off CXL papers by study type</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Prospective case series</td>
<td>25 (51%)</td>
</tr>
<tr>
<td>Prospective comparative case series</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Retrospective case series</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Case series</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>N= 49</strong></td>
</tr>
</tbody>
</table>


Final Data Included

* 39 of 49 papers graded as very low quality evidence
* Only 46 of 49 papers included efficacy & AE data
* Data included for analysis from 40 studies out of these 46 papers

49 papers

46 papers efficacy + AE

40 studies
Outcomes Assessed

- Time points 6, 12 and 24 months
- Topography – Mean, Max and Min K
- Visual acuity – corrected and uncorrected
- Refraction
- Central corneal thickness (CCT)

Results

Topography
- Changing up to 12 mo.
- Mean and Max K’s – Reduction of 1.00D
- Min K – reduction of 0.75 D

Visual Acuity Results
- Statistically significant improvement at all time periods
- UCVA improved more than BCVA Maintained over time

Summary Adverse Events

A Matter of Record from the Advisory Panel Report
(301) 890-4188

...“the most common adverse events for either indication (keratoconus or surgical ectasia) at greater than or equal to 10 percent are corneal epithelial defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following corneal epithelial debridement.”
Integration into Practice
- Understand criteria
- Look for progressing cones and surgical ectasias
- Younger patients without scarring are prime candidates
- Results are clinically and statistically significant
- Results are long lasting
- The safety profile based on the evidence is great
- Work with your state boards, this may be in your scope of practice already.
- Reimbursement varies

Part 2: Objectives
- To understand the scope of the epidemic of myopia progression
- To appreciate the impact on public health
- To provide an evidenced-based summary
- To review contact lens applications
- To guide practice implementation

Epidemic of Myopia Progression
- Worldwide prevalence – 22% or 1.5 B people
- United States (ages 12-54 years)
  - 1971-1972 – 25%
  - 1999-2004 – 41.6%
  - Myopes >8.00D increased 8x
- Varies with ethnicity
  - East Asia – 70-80%
  - Western countries – 25-40%
Global Prevalence of Myopia and High Myopia from 2000 through 2050

Graph showing the distribution of people estimated to have myopia across age groups in 2000 and 2050.


<table>
<thead>
<tr>
<th>SEX &amp; AGE</th>
<th>1971-1972 (%)</th>
<th>1999-2004 (%)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27.1</td>
<td>45.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>45.54</td>
<td>22.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>AGE</th>
<th>1971-1972 (%)</th>
<th>1999-2004 (%)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>31.4</td>
<td>42.6</td>
<td>0.004</td>
</tr>
<tr>
<td>25-34</td>
<td>32.3</td>
<td>51.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35-44</td>
<td>39.3</td>
<td>49.4</td>
<td>0.02</td>
</tr>
<tr>
<td>45-54</td>
<td>39.5</td>
<td>51.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Ocular Changes Associated with Myopia

Retinal/Posterior Complications3-11

- Chorioretinal atrophy
- Lattice degeneration
- Pigmentary degeneration
- Lacquer cracks
- Posterior staphyloma
- Fuch’s spot
- Myopic macular degeneration (leading cause of vision loss across the world)
- Rhegmatogenous defects
- Posterior vitreal detachment

High Myopia with rhegmatogenous detachment

Rhegmatogenous Detachment
Other Potential Complications

- Glaucoma\textsuperscript{12-14} – odd ratio of 1.5 to 3.3x greater risk
- Cataracts\textsuperscript{15} – nuclear and subcapsular
- Optic disc anomalies\textsuperscript{3,16}
  - Crescent
  - Tilted discs
  - Larger disc areas

Nature

- Genetics\textsuperscript{17-33}
  - Biometric components of myopic eye
    - Axial length (AL) – longer; heritability 40-94%
    - Anterior chamber depth (ACD) – deeper
    - Keratometry – flatter
    - Lens thickness – thinner

- If two parents myopic risk is 5x to 6x greater compared to no or one parent
  - Myopic children shown to spend more time indoors and reading than those of emmetropic parents
- If of east Asian ethnicity 8x risk
Nurture

- Environmental
  - Time outdoors seems to be protective regardless of race – BUT only prior to onset of myopia
  - Urban populations at higher risk
  - Myopia shown to progress during winter months
  - Sunlight exposure inversely related to myopia independent of activity level

Proposed mechanisms of action (MOA)

- Animal models from past 30 years – chickens, mice, monkeys, tree shrews
- Emmetropization process – matches AL to optical power
- Structural protein control defective – retina, RPE, choroid and/or sclera

MOA Takeaways

- Form deprivation – plus lens ↑ and minus lens AL ↓
- Peripheral focus – hyperopic ↑ and myopic ↓ AL
- Animal studies suggest association not causation
- CLEERE Study – excessive accommodation does not cause myopia
MOA Takeaways

- (Kang et al, 2010; Sng et al, 2011)
- Emmetropes & hyperopes exhibit peripheral myopia relative to central refraction and an oblate ocular shape
- Myopes exhibit more hyperopic peripheral defocus relative to central refraction and less oblate ocular shapes

MOA Limitations

- (Mutti et al, 2007, 2011) – Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE)
  - “A more negative refractive error, longer axial length, and more hyperopic relative peripheral refractive error in addition to faster rates of change in these variables may be useful for predicting the onset of myopia, but only within a span of 2 to 4 years before onset.”
  - The inconsistent link between retinal peripheral hyperopia and axial elongation suggests other mechanisms are in play

Comparative Overview of Treatments


Treatment Options

**Pharmacological**
- Atropine\(^{65-96}\) (ATOM Study)
  - Statistically and clinically significant decrease in progression over two years (77% reduction in myopia and no change in AL)
  - SE are significant
  - Rebound effect is concerning
  - Counter both with low dose (0.01%)
- Pirenzipine 2% gel bid\(^{82-85,88,89,92-102}\)
  - M1 selective antagonist (accommodation and mydriasis)

**Optical**
- Undercorrection\(^{85,86,92,94,96,103-107}\)
  - Seems to promote progression in humans but not animals
  - Human studies—more myopia in group treated with 0.75D under correction (Chung et al, 2002); no significant affect (Alder & Millodot, 2006)
- Bifocals\(^{84,85,88,92,96,108-123}\) (US, Finland and Denmark)
  - No significant slowing
- PAL (COMET Study) \(^{47,85,93,96,101,104,113,124-142}\)
  - Statistically but not clinically significant

**Contact lenses**\(^{56,84-86,88-96,102,103,105,138,143-186}\)
- GP lenses — Differing results but they do not slow progression in children\(^{92}\)
- Soft lenses — “myopic creep” not found in randomized studies and SCL do not prevent progression
- Comparing GP to SCL — lower amounts of myopia in GP wearers but no difference based on AL. Corneal flattening accounts for the difference

**Bifocals/Dual focus**\(^{85,86,91,92,94,163,165,173,180}\)
- Average reduction in myopic progression of 46% versus 43% for OK lenses
- Only center distance lenses investigated

<table>
<thead>
<tr>
<th>Author</th>
<th>Bifocal Design</th>
<th>Add Power</th>
<th>Study</th>
<th>Bifocal (D)</th>
<th>Single Vision Control (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anstice</td>
<td>Concentric</td>
<td>+2.00</td>
<td>Contralateral</td>
<td>-0.44±0.33</td>
<td>-0.69±0.38</td>
</tr>
<tr>
<td>Lam</td>
<td>Concentric</td>
<td>+2.50</td>
<td>Randomized</td>
<td>-0.59±0.49</td>
<td>-0.79±0.56</td>
</tr>
<tr>
<td>Sankaridurg</td>
<td>Progressive</td>
<td>+2.00</td>
<td>Prospective, historical control</td>
<td>-0.28±0.28</td>
<td>-0.84±0.47</td>
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<tr>
<td>Walline</td>
<td>Progressive</td>
<td>+2.00</td>
<td>Prospective, historical control</td>
<td>-0.51±0.06</td>
<td>-1.03±0.06</td>
</tr>
</tbody>
</table>

How they work

- **MOA**
  - Aspheric designs with center distance increase peripheral retinal SA in a positive direction (Atchison et al, 2006; Kang et al, 2013; Ticak et al, 2013)
  - (Walline et al, 2013) Compared aspheric dist. Center to spherical soft lens over 2 years
    - 50% reduction in progression
    - 29% reduction in AL

- **Challenges**
  - Power profiles for adds vary across spherical power ranges even in the same lens design (de la Jara et al, 2014)
  - Effects on accommodation were not considered
    - (Bickle and Walline, 2013) Add powers above +2.50 in center distance design may not be tolerated by myopic children

Dual-focus Soft Multifocals

- **Dual-Focus design (MiSight, Cooper Vision)**
  - Proclear material
  - +2.00 add; 3.36 mm OZ
  - MOA – center drives accommodation, treatment zones create myopic peripheral defocus

- **Dual-Focus design (MiSight, Cooper Vision)**
  - (Anstice and Phillips, 2011) Cross-over design
  - MiSight v. Spherical control
  - 10 month duration; N=34
  - 30% reduction in myopia in MiSight eye
  - No significant loss of CSF in this study, but......
Dual-focus Soft Multifocals

• Limitations
  • No significant loss of CSF in this study, but......
    • (Kollbaum et al, 2013) compared dual-focus & near centered designs against spectacle correction finding more ghosting for both and loss of one line of LogMAR VA in dual focus
  • Small sample size
  • Short duration
  • Paired-eye is not binocular as will be used
  • At cross-over the fellow eye has progressed and is not matched to the treated eye
  • Duration of effect and rebound issues are unknown

Aspheric Concentric Soft Multifocals

• Unnamed Myopia Control Lens (Alcon)
  • Air Optix (Lotrafilcon B)
  • 8.6/14.2
  • +0.25 in central 1.5mm progresses to +1.00 at 2.0 mm and +2.00 at edge of the 9.0 mm zone
  • Peripheral plus powered aspheric design
  • Not commercially available unlike the MiSight which is available overseas and Canada

Aspheric Concentric Soft Multifocals

• Alcon myopia control lens
  • Methods:
    • Chinese children (n = 45) aged 7 to 14 years,
    • −0.75 to −3.50 D and cylinder ≤1.00 D)
    • Followed up for 12 months
    • Control group (n = 40) matched for age, sex, refractive error, axial length, and parental myopia wearing single-vision spectacles.

Results:

• Progression in SER at 12 months was 34% less (−0.57 D) with the novel contact lenses (95% confidence interval [CI], −0.45 to −0.69 D) than (−0.86 D) SRx (95% CI, −0.74 to −0.99 D).
• Estimated increase in axial length (AL) was 33% less for CL group [0.27 mm (95% CI, 0.22–0.32 mm)] than SRx group [0.40 mm (95% CI, 0.35–0.45 mm)
EODF Soft Multifocals

• **EDOF** (Novel design, BHVI; NaturalVue, VTI)
  - Tilia et al, 2016
    • BHVI design compared against Air Optix MF (Hi, Med, Lo adds); N=52; prospective, randomized, cross-over design
  - Results:
    • No difference at 6m
    • EODF better in all other distances, better stereopsis, fewer complaints of glare and ghosting, preferred 5x more often

EODF Soft Multifocals

• **Tilia et al., 2016**
  • BHVI against Acuvue Oasys for Presbyopia; N=41; prospective, cross-over, randomized, single masked trial
  • Results: EODF lenses provided better intermediate and near vision without compromising the distance.

EODF Soft Multifocals

• Sha et al., 2018
  • BHVI design compared to 1-Day Acuvue Moist MF; N=57, double-masked, prospective, randomized, cross-over design.
  • Results: No difference in HCVA at dist or stereopsis. EODF better at intermediate and near with fewer photic complaints

EODF Soft Multifocals

• **EDOF for Myopia Control**
  • Cooper et al
    • VTI lens, retrospective, case series from 10 practices
    • Results: Reduction in annualized myopia progression by 95.4%-96.25%; 98.4% of children showed reduced progression, 81.25% showed complete halting; 6.25% showed regression of progression
  • Limitations: Numerous
Summary comparison of selected designs

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects Completing Study (n=)</th>
<th>Reduction in Myopia Progression (%)</th>
<th>Reduction in Axial Length (%)</th>
<th>Duration (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proclear® Multifocal (CooperVision, Pleasanton, CA)</td>
<td>Center-distance, aspheric, concentric</td>
<td>51</td>
<td>29</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Novel design (Brien Holden Vision Pt Ltd., Sydney, NSW, AU)</td>
<td>Center-distance, aspheric, concentric</td>
<td>34</td>
<td>32</td>
<td>12</td>
<td></td>
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<tr>
<td>MiSight (CooperVision, Pleasanton, CA)</td>
<td>Center-distance, concentric zones</td>
<td>54</td>
<td>80</td>
<td>20</td>
<td></td>
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<tr>
<td>Defocus Incorporated Soft Contact (Centre for Myopia Research, the Hong Kong Polytechnic University)</td>
<td>Center-distance, concentric zones</td>
<td>65</td>
<td>31</td>
<td>24</td>
<td></td>
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<tr>
<td>Acuvue Bifocal (JJV, Jacksonville, FL)</td>
<td>Distance-center zonular</td>
<td>72</td>
<td>79</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>NaturalVue Multifocal 1 Day® (VTI, Alpharetta, GA)</td>
<td>EODF</td>
<td>95 to 96</td>
<td>No data</td>
<td>6 to 25</td>
<td></td>
</tr>
</tbody>
</table>

Orthokeratology lenses

• Many players in this space (Paragon CRT, B+L Specialty Vision Products; Emerald, Euclid, etc.)
  • MOA
    • Myopic peripheral retinal defocus (Kang et al, 2011)
    • Increase in spherical aberration (Gifford et al, 2013)
    • Increase in amplitude of accommodation (Zhu et al, 2014)

Orthokeratology lenses

• Orthokeratology lenses
  • Average reduction in myopic progression of 43%
    • AL 0.36±0.24 mm OK v. 0.09±0.09 mm sph GP (Swarbrick et al, 2015)
  • ROMIO study – effective in children already with >5.00 DS myopia (Cho and Cheung, 2012)
    • AL for OK group 0.19±0.1 mm v. spectacles only 0.51±0.32 mm (P=0.005)

Orthokeratology lenses

• Rebound effect found (Swarbrick, 2015)
  • Design – Cross-over OK in one eye GP sphere in the other after 6 mos.
    • OK eye had less of an inc. in AL
    • Switching the GP lens to the OK eye caused AL growth rate to double until it caught up
    • Similar results seen in atropine v. placebo studies
  • Conclusion – slows progression up to 3 years but not clear how long treatment should be continued to maintain the effect. Rebound may be an issue.
Environmental options

- **Environmental**
  - Outdoor time (Jones et al, 2007)
    - Possibly reduces onset but not progression
    - Recommendations for 8-15 hours a week
    - Supported by human and animal studies as being protective

Summary

- **Take-aways**
  - Low dose atropine provides best effect
  - OK, Soft Dual Focus/BF contacts are second best effect but more practical
  - Center distance designs are preferred in DF/BF contact lenses or EDOF
  - Multiple profiles in lens designs are indicated (Cooper, Alcon and Essilor are players)
  - Combining low dose atropine with OK/DF/BF CL’s is likely additive

Implementation into Practice

- **FDA**
  - There are no FDA approved treatments for myopia control or prevention – all are off-label in the United States
  - Public Workshop - Controlling the Progression of Myopia: Contact Lenses and Future Medical Devices, September 30, 2016
  - Purpose was to discuss increasing prevalence and reach a consensus on best study designs for devices

  [Link to workshop](https://wayback.archive-it.org/7893/20170404181842/https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm500404.htm)

- **A 33% decrease in myopia progression could reduce myopia >-5.00D by 73% according to the Brien Holden Institute**

Implementation into Practice

- **FDA**
  - If a lens was submitted today it would likely take 7 years to approve (2017)
  - A 33% decrease in myopia progression could reduce myopia >-5.00D by 73% according to the Brien Holden Institute
 Doctrine of Informed Consent Applies

• Risks-Benefits-Alternatives
  • Must tread lightly
    • Must inform parents/patient this is an off-label treatment
    • The science of underlying cause is not definitively established
    • The MOA of various devices is not completely understood
  • Study the evidence, attend major meetings (e.g. AAO, AOA, GSLS, IAO, AAOMC)

 Fee Agreements

• Vary widely
• Global fee
• Fee per visit
• Should disclose approach clearly
• Parents/Patients must be committed to the long haul

 Equipment

• Topographers, Tomographers and Swiss Army knives
• Axial length biometry
• Cycloplegic refractions