Background

- Some reports in ophthalmological journals favor 0.01% atropine treatment for myopia control while giving little credence to soft lens options.1,2
- Previously, efficacy of myopia control interventions has been expressed as percentage or absolute reduction in myopic progression over a given time frame.
- Longer term estimates of efficacy fail to address two important considerations:
  1. **TREATMENT EFFECT IS ABSOLUTE RATHER THAN RELATIVE ACROSS THE PROGRESSION RANGE**
  2. **EFFICACY DECREASES OVER TIME ON BOTH AN ABSOLUTE AND RELATIVE BASIS**

Method

- **Systematic literature review:**
  - Myopia control interventions currently of interest
  - Included relevant peer-reviewed conference abstracts
  - 33 studies identified

- **Levels of Evidence**
  - Quality of investigations based on adherence to evidence-based principles for study design were categorized.
  - Maximum Efficacy
    - The only indisputable metric that can be used is data-driven estimates of cumulative absolute reduction in progression rather than absolute annual or relative rates.
    - The primary variable should be reduction in axial elongation because of its assumed relevance to disease development but refractive error serves as an important secondary endpoint.
    - Maximum efficacy outcomes of each category of intervention by reported values was assessed.
  - Likely maximum efficacy from available data for some interventions was also modeled.

Results

- Table 2 shows classification of 33 identified studies according to quality of evidence. Study design to the left in the table represent more rigorous levels of evidence.
- Despite the popularity of low-dose (0.01%) atropine, there is no direct evidence of a significant reduction in axial elongation with this intervention.
- Orthokeratology (as a cohort study) and spectacles (in a randomized controlled study, controlled, randomized with selective inclusion principles for study design were categorized.)
- Soft, multifocal lenses have the greatest weight of evidence but do not demonstrate superior performance possibly because of insufficient study periods.
- Increased time outdoors alone does not provide a large treatment effect but may be a useful adjunct therapy.
- Modelled data support the supposition of maximum potential efficacy over time. Figure 3 presents an example of the expected treatment efficacy based on this analysis.
- Rebound has been observed with atropine treatments and orthokeratology (see figure 4). No intervention with sizeable treatment effect has been shown to be free of rebound.

Conclusions

- **The maximum treatment effect that can currently be directly supported by data is 0.43mm for axial elongation (orthokeratology) and 1.05D (spectacles) for refractive error.**
- Quality of evidence is highest for soft multifocal lenses.
- Such efficacy may be restricted to a subset of patients and rebound cannot be ruled out.
- Greater efficacy may occur but requires evidence. Projected percentage treatment effects commonly reported are speculative and not evidence-based.
- This analysis establishes a precedent for evidence-based reporting of myopia control interventions.

References

5. Brennan Int Myopia CoV 2017; Birmingham, UK

Figure 1: Standardized cumulative frequency of 6 and 12 month axial elongations for non and control less populations from Cheng et al.16 The parallel nature of the lines shows absolute rather than relative cumulative frequency across the progression range.

Table 1: Percentage and absolute treatment effects from Figure 1 across progression deciles.

<table>
<thead>
<tr>
<th>Progression Percentile</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Treatment Effect (mm)</th>
<th>Control Effect (mm)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>0.78</td>
<td>0.94</td>
<td>0.16</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>20%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>30%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>40%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>50%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>60%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>70%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
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<tr>
<td>80%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
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<tr>
<td>90%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>100%</td>
<td>0.78</td>
<td>1.02</td>
<td>-0.24</td>
<td>0.10</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 2: Levels of evidence and maximum demonstrated efficacy for a set of myopia control interventions of current interest and higher doses of atropine and various bi/multifocal spectacles are not included.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reported (Patients)</th>
<th>Classification</th>
<th>Levels of Evidence</th>
<th>Max Efficacy (mm)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>0.01% (0.01%)</td>
<td>Adjuvant</td>
<td>Class I</td>
<td>0.43</td>
<td>1.2,13</td>
</tr>
<tr>
<td>Orthokeratology</td>
<td>0.01% (0.01%)</td>
<td>Adjuvant</td>
<td>Class II</td>
<td>1.05</td>
<td>1.2</td>
</tr>
<tr>
<td>Soft multifocal lens</td>
<td>0.01% (0.01%)</td>
<td>Adjuvant</td>
<td>Class III</td>
<td>1.05</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Figure 2: Logarithmic curve fit cumulative treatment efficacy for data on available interventions for orthokeratology and multifocal lens data. Data was not available for all interventions.

Figure 3: Example plot showing projected progression for an individual with 1D of myopia untreated when treated using the interpretation of the current analysis and 1% atropine is assumed.

Figure 4: Rebound with orthokeratology: A. Original graph from Chia et al14 “Atrial elongation in orthokeratology” 2018; B. Data generated from a rebound regression that accounts for superimposed growth while controlling for the intercept and trend in growth. Figure 3 presents an example of the expected treatment efficacy based on this analysis. Rebound has been observed with atropine treatments and orthokeratology. No intervention with sizeable treatment effect has been shown to be free of rebound.

Figure 8: Cumulative treatment efficacy at different levels of evidence for interventions of current interest (higher doses of atropine and various bi/multifocal spectacles are not included).

THE ILLUSION OF GREAT SUCCESS

A myopia control intervention in an individual (A) identified as a fast progressor will likely seem to have immediate and substantial success. But long term success can easily be falsely asserted. A number of factors contribute to the illusion.

1. **Myopia progression is fastest at diagnosis and tends to slow thereafter.** In an unanalysed sample of 185 untreated myopic eyes in children, 45 showed greater than 0.4mm axial elongation in the first year of follow-up. All but one eye (99%) showed less progression in the second year with an average reduction in progression of 35%.
2. **Regression to the mean is a powerful effect.** A difference between two refractive error measurements will likely have a standard deviation in excess of 0.35D. More extreme values (that is, those deemed to be fast progressors, who are thus more likely to be treated) on first measurement tend to the average on second measurement.
3. **Treatment efficacy is greatest initially and subsequently reduces over time as shown in this postcard.**


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