Evidence-based Efficacy of Myopia Control Interventions

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Background

- Some reports in ophthalmological journals favor 0.01% atropine treatment for myopia control while giving little credence to soft lens options.[1-3]
- Previously, efficacy of myopia control interventions has been expressed as percentage or absolute reduction in myopia 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

Figure 1: Standardized cumulative frequency of 6 and 12 month axial elongation for test and control lens populations from Cheng et al. (2016).[4] The parallel nature of the lines shows absolute rather than relative treatment effect across the progression range.

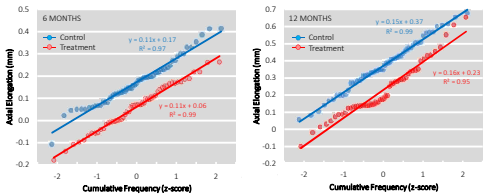


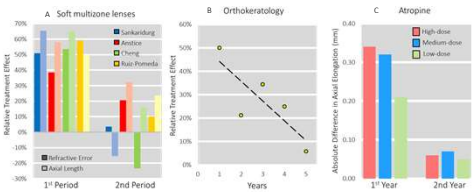
Table 1: Percentage and absolute treatment effects from Figure 1 across progression deciles.

6 MONTHS					12 MONTHS				
Progression Percentile	Control Group (mm)	Treated Group (mm)	Percentage Treatment	Absolute Treatment (mm)	Progression Percentile	Control Group (mm)	Treated Group (mm)	Percentage Treatment	Absolute Treatment (mm)
10%	0.06	-0.07	217%	0.12	10%	0.19	0.07	60%	0.11
20%	0.08	-0.03	135%	0.11	20%	0.27	0.12	54%	0.14
30%	0.12	0.00	102%	0.12	30%	0.31	0.14	56%	0.17
40%	0.14	0.03	75%	0.10	40%	0.33	0.15	56%	0.18
50%	0.17	0.07	60%	0.10	50%	0.35	0.18	49%	0.17
60%	0.19	0.10	50%	0.10	60%	0.41	0.27	35%	0.14
70%	0.21	0.12	44%	0.09	70%	0.44	0.29	34%	0.15
80%	0.24	0.16	33%	0.08	80%	0.50	0.34	32%	0.16
90%	0.31	0.18	41%	0.12	90%	0.57	0.43	24%	0.13

- This effect is consistent across interventions.[5]

2. EFFICACY DECREASES OVER TIME ON BOTH AN ABSOLUTE AND RELATIVE BASIS[6]

A. Relative treatment efficacy of investigational myopia-control soft lenses during 1st and 2nd periods of study.[4,7-9]
B. Relative myopia control efficacy across 5 years in an orthokeratology investigation with yearly efficacy plotted.[63]
C. Absolute difference in elongation between treatment and control groups for high-dose, medium-dose and low-dose atropine in the first and second years of treatment using data from the sub-group analysis of Huang et al.[33]



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Method

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

0.01% Atropine
Chia et al *Ophthalmol* 2014;157:451
Clark & Clark *J Ocul Pharm Ther* 2015;31:541
Yam et al *Ophthalmol* 2018; In press
Diaz-Llopis et al *Arch Soc Esp Oftalmol* 2018; 93: 182

Spectacles
Cheng et al *JAMA Ophthalmol* 2014;132:258
Lam et al *Int Myopia Conf* 2017, Birmingham, UK
Kanda et al *Jpn J Ophthalmol* 2018;62:537

Orthokeratology
8 studies reported by Li et al *Curr Eye Res* 2016;41:600
Paune et al *Biomed Res Int* 2015:507572
He et al *BMCOphthalmol* 2016;16:126
Li et al *Contact Lens Ant Eye* 2017;40:417

Outdoor time
Yi & Li *Zhonggua Dang Dai Er Ke Za Zhi* 2011;13:32
Parsinnen et al *Acta Ophthalmol* 2014;92:730
Hsu et al *Br J Ophthalmol* 2017;101:1611
Wu et al *Ophthalmol* 2018;125:1239

Soft multifocal contact lenses
8 studies reported by Li et al *Ophthalmic Physiol Opt* 2017;37:51
Chamberlain et al *Optom Vis Sci* 2017; e-abstract 170075
Ruiz-Pomeda et al *Graefe's Arch Clin Exp Oph* 2018;256:1011
Cooper et al *Eye Contact Lens* 2018:44(5);e16
Cheng et al *IOVS (ARVO abstracts)* 2018; 59(9):3927

- 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 modelled.

Results

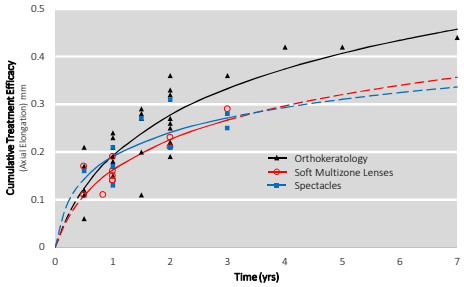
- Table 2 shows classification of 33 identified studies according to quality of evidence. Study designs to the left in the table represent more rigorous levels of evidence.
- Despite the popularity of low-dose (0.01%) atropine, there is no direct evidence of a significant reduction in axial elongation with this intervention.
- Orthokeratology (in a cohort study) and spectacles (in a controlled, randomized study with selective inclusion criteria) have provided the largest recorded cumulative treatment effects.
- 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 proposition of maximum potential efficacy over time. Figure 3 presents an example of 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.

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

Intervention	Regulatory Clearance (globally)	Metric	Study design: Controlled Randomized Masked	Controlled Randomized	Cohort/ Other	Maximum efficacy (D)
0.01% Atropine	—	Refractive	2	—	2	0.79D
		Axial	1	—	1	0.05mm*
Orthokeratology	—	Refractive	—	—	—	—
		Axial	—	2	10	0.43mm
Soft Multifocal Lens	2	Refractive	4	3	4	0.69D*
		Axial	4	3	3	0.29mm*
Spectacles (E-line, DIMS)	—/NA	Refractive	—	3	—	1.05D*
		Axial	—	3	—	0.31mm*
Increased outdoor time	NA	Refractive	—	2	2	0.61D
		Axial	—	1	—	0.15mm*

* indicates results from randomized, controlled studies

Figure 2: Logarithmic curves fit to cumulative treatment efficacy data for selected modalities. For soft multifocal and spectacle lens data, only studies showing over 50% initial treatment efficacy were included. After 7 years, the different interventions are projected to have modest treatment effects. Differences between modalities are unlikely to be significant based on these data.



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

1. Leo SW *Curr Opin Ophthalmol* 2017, 28:267
2. Modjtahedi et al *Ophthalmol* 2018;125:628
3. Zloto et al *Graefe's Arch Clin Exp Oph* 2018;256:2015
4. Cheng et al *Optom Vis Sci* 2016;93:353
5. Brennan *Int Myopia Conf* 2017, Birmingham, UK
6. Brennan & Cheng *Eye Contact Lens* 2018: in press
7. Sankaridurg et al *IOVS* 2011;52:9362
8. Anstice et al *Ophthalmol* 2011;118:1152
9. Ruiz-Pomeda et al *Graefes Arch Clin Exp Ophthalmol* 2018;256:1011
10. Hiraoka et al *IOVS* 2012;53:3913
11. Huang et al *Ophthalmol* 2016;123:697
12. Cho et al *Contact Lens Anterior Eye* 2017;40:82

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 if 50% efficacy is assumed.

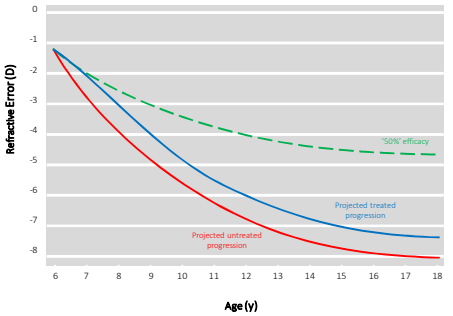
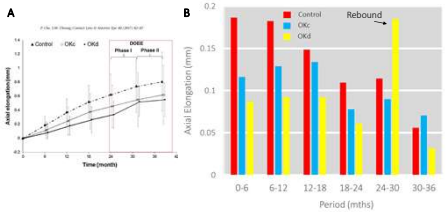


Figure 4: Rebound with orthokeratology: A. Original graph from Cho et al.[12] B. Axial elongation divided into time segments. OKc and OKd refer to orthokeratology subjects who continued wear and ceased wear between 24 and 30 months respectively. Rebound is observed during the 6 months of discontinuation of orthokeratology.



THE ILLUSION OF GREAT SUCCESS

A myopia control intervention in an individual child 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:
(i) Myopia progression is fastest at diagnosis and tends to slow thereafter. In an unpublished analysis of 186 untreated myopic eyes in children, 45 showed greater than 0.4mm axial elongation in the first year of follow-up. All but one eye (98%) showed less progression in the second year with an average reduction in progression of 35%.
(ii) Regression to the mean is a powerful effect. A difference between two refractive error measures 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.
(iii) Treatment efficacy is greatest initially and subsequently reduces over time as shown in this poster.

Content in this poster refers specifically to experimental trials of investigational product and is presented to analyze advances in the science of myopia control. There are no products currently cleared by the FDA for marketing in the USA for myopia control. Johnson & Johnson Vision Care, Inc. does not endorse off-label usage of any products.

Disclosure: Noel Brennan, Xu Cheng are employees of Johnson & Johnson Vision. Mark Bullimore consults for Johnson & Johnson Vision, Acucela, Inc., Alcon Research, Amorphex Therapeutics, LLC, Apellis Pharmaceuticals, Inc., CooperVision, Inc., Eyenovia, Inc., Genentech, Inc., Novartis Pharma AG, Tear Film Innovations, Inc.

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