Myopia Control: City Lights, Blood, Antagonist Action
Part I

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For this two-part article, let's take a not-so-quick look at some of the recent research on myopia causes and therapeutics including atropine, caffeine, the choroid, and public policy. In part II, the contemporary light spectrum is covered and we point out the links between ocular pathologies and neural health and function.

Prelude: Considerations for Myopia Control

Overall: It's still not easy. Some methods rely on a great deal of practitioner skill and experience. More challenges are posed by patient tolerance and compliance, which determines dilligent use and clinical outcomes. A big chunk of the intervention window (~5-17 years old) comprises childhood, where comfort and trust are major factors in method selection, adherence, and progression. When increasingly young children are referred for eye check-ups due to earlier ages of myopia onset, adverse or frightening experiences in the clinic and from devices are very influential. As awareness of lifelong risks and clinical interventions is still low, especially beyond East Asia, negative experiences can drastically shift attitudes in the household away from myopia control.

Aside from lifestyle management, addition to the toolkit of high-impact treatment techniques is limited, but new endpoints such as axial length, and choroid thickness and response have been introduced. Research over the past few decades has expanded to cover factors like polygenic risk, epigenetics, obesity, educational systems, and even iris

colour, with nutritional, cellular signalling, vascular, mechanical, photoperiod, and eye-brain neural plasticity forces in the mix.

High Myopia versus Myopia

High myopia is defined by most professionals as ≤−5.00 Dioptres, occasionally ≤−6.00 Dioptres. There seems to be a ceiling effect at approximately 90% for myopia in the population, with the rates of high myopia lower, but more variable due to contextual factors. The percentage affected by high myopia and its attendant risks can be attenuated with timely and effective interventions. Estimates of this cohort range from 10% to as high as 28.9% in a Japanese study (Ishiko *et al.*, 2021).

Some high myopia cases may be aetiologically distinct from myopia that progresses rapidly, for example if specific gene variants are involved. It is unclear whether or not categories for myopia will be altered in future to reflect causal mechanisms and cell/tissue damage risks as opposed to syndromic status, axial length measurements, and dioptre. Furthermore, as some studies have pointed out, there are prenatal forces involved that could serve as potential medical or parent-behavioural intervention windows (Seow *et al.*, 2019; Jackson & Moosajee, 2023).

In terms of the largest risk factors for myopia progression calculated in Manoharan *et al.* (2023) by an algorithm, these included change in dioptre, age at presentation, dioptre at presentation, and age of onset. As research findings become even more multifactorial and complex, with therapeutics progressively proved and invalidated, what matters most for practitioners is how parents receive information and perceive the treatment or therapeutic in terms of medical and financial value (See Yang *et al.*, 2022).

However, this is not just an issue to be managed by clinicians, parents, and children. Beyond industry regulation and top-down national initiatives, government policy has a great deal of power in terms of forging the dominant ocular environment through economic and educational policies, along with urban design.

Part I: Genes, Choroid, Antagonist Action

Anticholinergics, Monoamines, & ADOR Antagonists

Atropine

As of June 2023, no pharmacologic therapy is approved for treating childhood myopia progression in the United States, though off-label atropine (anti-muscarinic) use was permitted in 2017. In contrast, daily atropine drops have been used since the 1990s at concentrations of 0.1% by the Singapore National Eye Centre. After the 2012 ATOM 2 trials and out of concern for side effects, the dosage was reduced to 0.01% with a 60% slowdown of myopia progression recorded. Currently and in part to reduce dose-related adverse effects, delivery in a mist format is being trialled as part of a treatment package that includes a proprietary microdose formula, child-friendly dispenser, and in-built Bluetooth function to monitor compliance.

Another way to minimise side effects is through mitigating certain aspects of atropine's off-label production and use, therefore suboptimal (non-pharmaceutical) composition of the therapeutic, which includes preservatives that acts as

toxins and corneal irritants. Utilising this method, the 3-year CHAMP trial showed higher responder portion via 0.01% atropine over 3 years, in terms of reducing myopia progression and axial elongation (Zadnik *et al.*, 2023).

There is some 'bad' news for the US atropine market, though. The 2.5 year MTS1 trial by Vanderbilt Eye Institute recently concluded, with contradictory results to those obtained in the Singaporean ATOM studies for control of myopia progression via low-dose (0.01%) atropine. The difference was attributed to different genetic backgrounds affecting responsiveness to the anti-muscarinic, with more well-designed trials required to determine optimal doses that limit rebound and adverse effects like muscle spasms, allergic reactions, photophobia, and near blur for non-Asian child cohorts in the United States. Some additional recommendations were combination treatments and plans, with attention to different age-based intervention windows for efficacy of each substance / device.

There seem to be impactful safety and efficacy tradeoffs, and therefore atropine treatment dosage concerns, that are particular to different ethnic groups. This is important for crafting effective policy, research design, and prevention protocols in multiracial populations, as the prevalence of myopia and high myopia in the United States has been increasing, to estimates of 11.8% in Asian and 5.4% in White ethnic groups, with Hispanics the least affected (1.8%). In their review, Banashefski *et al.*, (2023) note a paucity of data and studies on the topic and thus the reliance on a high myopia definition of ≤−5.00 dioptres instead of ≤-6.00 for their study inclusions.

Another big category for comparative analysis is in terms of urban vs. rural populations. Using data from a recent census in the USA, urban prevalence of myopia was estimated at 41%, and rural at 15.7% (Fortin & Kwan, 2022). This urban-rural difference is less wide, but still present in Asian populations highly affected by myopia including China, Japan, Korea, and Singapore. The last is considered lushly-landscaped but 100% urbanised. Some of the reasons suggested include outdoor time factors, typical viewing postures, and the academic environment including near work. More controversially there is the screen time factor, and pertinent to urban planning and design, perhaps quantity of vegetation and green space. In future, this may include consideration of 500m green buffers around schools that seemed to reduce Beijing's school-level myopia prevalence by 15% (Zhang *et al.*, 2023).

Covered later and expanding on earlier explorations in photoperiod and birth season, the light spectrum that urban populations are exposed to may be a culprit to disentangle from the arrayed complexities of modern life and its associated population characteristics. In fact, even things like higher BMIs and obesity may be protective factors as uncovered in a Korean study (Lee, Lee & Kim, 2018), with the proposed mechanism being fatty deposits in orbital space that limited axial elongation. This applied to Chinese but not Israeli subjects in the same context.

In light of all this, another atropine for myopia control trial (AIM) is ongoing in Germany that will include only Caucasian heritage children to compare effects of 0.02% versus 0.01% in terms of cyclopegic refraction and axial length (Farassat *et al.*, 2023). Dose minimisation seems to be the approach for this cohort on account of significant side effects found at a concentration of 0.05% in a study (n=19) by Joachimsen *et al.* (2021). This is contrary to safety and efficacy results from a Hong Kong-based cohort, and likely to compromise acceptance and compliance of Caucasian children according to the authors.

It is also worth mentioning that atropine drops are administered at the ocular surface, and have broad cross-reactivity as well as a long, unpredictable route to the cells and tissues at the back of the eye. This may depend on anatomy, but potentially also genetically-mediated biochemistry of the patient. The higher the dose, the more off-target effects there will be on function of nicotinic, adrenergic, and serotonergic, and other systems (See Thomson *et al.*, 2023).

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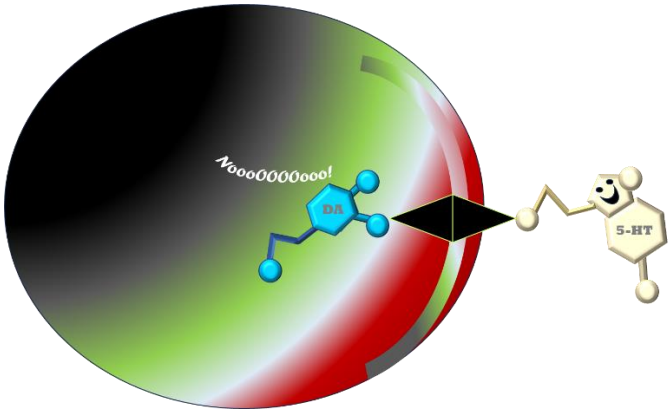
Maybe you're born with it. Maybe it's 5-HT

The primacy of retinal dopamine (level, D1 and D2 receptors, nitric oxide regulation) in myopia explanations now faces several contenders. Although light-related increase in retinal dopamine does act as a stop signal for ocular growth, this is not the only determinant of myopia development. In fact, candidates with attention deficit hyperactivity disorder (ADHD) exhibit hypo-dopaminergic states in the retina, but there is no association between ADHD and myopia, only other refractive errors. While many other molecular candidates inhabiting and stimuli affecting the posterior eyeball are undergoing scrutiny (Reviews in Yang *et al.*, 2022; Shinojima *et al.*, 2022; Huang *et al.*, 2022), research shows that serotonin may be a retinal-stretching culprit, and is poised to steal some of the limelight from dopamine and atropine.



Retinal dopamine, serotonin, and axial elongation

Another anti-muscarinic, pirenzepine, has dropped out of favour since the first decade of the 2000s. However, an abstract presented at ARVO 2023 demonstrated that the protective effects of both anti-muscarinics on myopic refractive shift can be disrupted by serotonergic activity (Hoffmann *et al.*, 2023). The experiment was on chicks, with drug administration as 4 days of morning vitreous chamber injections. While they're really getting into the posterior molecular stew of myopia, that's not ideal for human drug delivery, especially not in young children.

A paper published in Biomedicine & Pharmacotherapy, November (Thomson *et al.*, 2023) explained that atropine's anti-myopic effects were due to serotonergic receptor antagonism along with other cholinergic and non-cholinergic mechanisms. This was proven when administered serotonergic agonists were able to block the protective effects of atropine over the experimental period. Important to note: this was in animal experimental myopia, and has had inconsistent results across methods and agents. Serotonin levels did not change, so pharmaceutical intake of serotonin (which does have adverse effects on visual clarity), may or may not affect myopia development and treatment. As a consideration, even though children are not typically prescribed SSRIs (selective serotonin reuptake inhibitors), there may be alternative exposure routes and developmental pathways affected.

In Masson's 2019 article on retinal serotonin, the role of 5-HT in retinal maturation as well as neurodegeneration was pointed out, indicating timing, receptor activity and distribution, and intercellular signalling processes are more

influential for eye growth and retinal health than adult levels. Thomson et al. (2023) also considered melatonin, a serotonin metabolite and heteromer involved in sleep patterns, as an alternative cause of anti-myopic effects, though tests in chickens have not shown any association between myopia development and melatonin levels.

There have been no conclusive results on studies exploring the relationship between sleep and myopia. Swtiching to a molecular focus on the serotonin-melatonin and dopamine aspects of a naturalistic circadian photoperiod (Huang *et al.*, 2022), biorhythms, and daily shifts in ocular shape and properties might yield more direct mechanisms, association, and insight. The mysterious role of MAOA, the enzyme that breaks down both dopamine and serotonin, remains obscure, but it seems to have higher expression levels in lens-induced myopia according to Landis et al. (2021). The role of rod photoreceptor function and a broad range of light levels is also described in this paper as anti-myopic, and will be touched on in part II.

ADOR Antagonists: Caffeine & 7-Methylxanthine (7-MX)

There have been calls to seek pharmaceutical alternatives to atropine. While it has many strong advocates, results are not so strong, partially due to variation in effect on different age groups and now we know also, ethnic phenotypes. As a derivative of deadly nightshade, it is also technically toxic, in high doses a molecule of murder, hence the drive to keep concentrations as low as possible with imposed legal-professional requirements for its use. Given these efficacy and safety issues, in order to limit the global prevalence and high degrees of myopia with attendant risk of blindness-causing conditions in later life, some other compounds like caffeine and one its metabolites, 7-methylxanthine, are being investigated.

Caffeine at very high doses is also toxic. Did you know that the lethal dose 50 (LD50) of caffeine for rats is around 367mg/kg? Therefore:

To exterminate the average half-kilo Norway rat, one would require at least two double espressos presented as fatal temptations.

Humans are more likely to caffeine overdose through supplements, powders, or capsules, as purchasing 50 – 100 coffees is inadvisable and generally unaffordable.

Photo: Mariam Antadze (Pexels)

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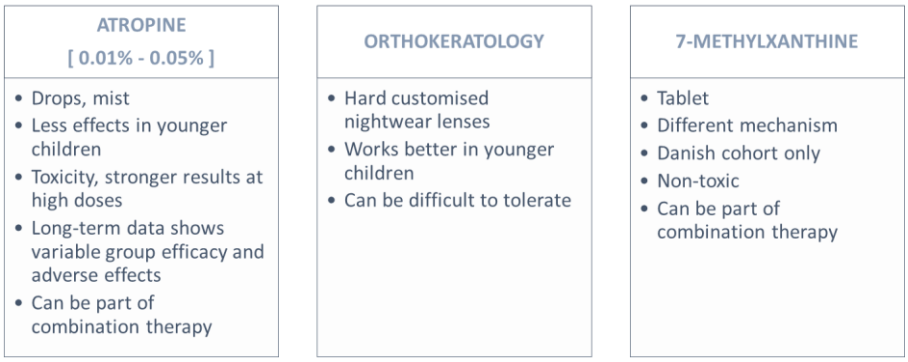
In a review of literature published up to February 2022, Lawrenson *et al.* (2023) noted that only *high dose* atropine was a near-competitor to orthokeratology, but had rebound as well as side effects. This isn't an ideal situation for the industry. Although ortho-k is often successful, the process can be expensive. It also requires a higher degree of practitioner experience, skill, and equipment to fit and monitor. Furthermore, the night-wear lenses remain difficult for many children to tolerate. Ortho-k is not immune to interference from age-related developmental forces either, having a greater impact on myopia progression for younger children.



Sources: Lai et al. (2023); Lawrenson et al. (2023)

Perhaps the task falls to the non-toxic 7-methylxanthine. The non-selective ADOR antagonist 7-MX in tablet form was approved in 2009 by the Danish Medical Agency for myopia control, with no reported side effects from long-term use as a kind of supplement according to a mini-review by Lai et al. (2023). There is some difficulty in comparing therapeutics due to a shortage of long-term placebo-controlled myopia control trials. However, a long-term Danich clinical trial using 7-MX in tablet form showed comparable one-year efficacy in terms of axial growth (-0.07 mm) of taking 1000 mg/d, which "seems comparable to that of 0.01% atropine eyedrops or multifocal soft contact lenses of various designs" (Lai *et al.*, 2023: 971). The mechanism seems to be increased expression of type 2 dopamine receptors (DRD2), and unlike other methods, does not rely on choroidal thickening. As such, authors suggest that effects could be additive, or part of a combination approach.

Choroid: Imaging and Axial Elongation

The retina is demanding in terms of dominating sensory-neural pathways and the metabolic requirements of its many millions of cells. They are nourished by a dense network of blood vessels, supplying oxygen and nutrients that affect cellular function and repair. All this necessitates general support of the many-layered and multifunctional choroid, a tissue that is responsive to an array of short-term stimuli including caffeine and light properties (See Ostrin *et al.*, 2023). There is also a general association of thicker choroids with less myopic eyes, but directionality and causation is uncertain. Observations from administered caffeine and 7-MX complicates things, as the response is typically choroidal thinning, but the two have associations with inhibition of axial elongation. Perhaps greater precision in imaging will shed more light on the tissues and pathways involved?

Visualisation of the teeny tiny blood vessels using vascular casts, scanning electron micrograph, and Optical Coherence Tomography (OCT) has just been supplemented by recent advances in spatio-temporal OCT (STOC-T). This technology requires less than a second for hundreds of laser patterns to visualise the posterior ocular surface at depth, permitting clinician eyes on living tissue in reaction to therapeutics such as light and pharmacological products (Poweska for ICTER, ICHF, 2023).

The creators note several advantages including greater axial range, compact machine size, non-invasive method, speed versus traditional OCT scans that require several minutes, and the ability to see eye function as opposed to structure which is critical for early detection of pathology. Image quality is not yet perfect, but the single-cell level at various depths is made possible, with "high transverse resolution at different depths, making the differentiation of morphology visible for the first time within the Sattler, Haller, and choriocapillaris layers," (BioPhotonics, 2023).

In future, this may have relevance for experiments on choroid thickness and function. However, even if imagining resolution increases, there are still substantial differences in design of short-term experiments on myopia mechanisms. According to a recent White Paper by the International Myopia Institute (Ostrin *et al.*, 2023), although evidence remains insufficient, results from animal studies hint at significance of choroid health and action for eye growth regulation.

Part 1 Conclusion

Research and policy enthusiasm to reduce incidence and burden of myopia is certainly a positive, but that doesn't mean we should jump the gun when it comes to implementation. Opting for extremes instead of cautious claims and adjustment can result in waste or negative outcomes for eye health and beyond.

Here's a media management example: According to personal correspondence, after the landmark study (Rose *et al.*, 2008) comparing myopia in Chinese children from Sydney and Singapore, parents had to be cautioned to not make their child stare at the sun as a preventive. At the policy level, decades of initiatives in schools based on numerous near-work theories did nothing to slow the rates in Taiwanese children (Katwala, 2023), until the roles of outdoor daylight and retinal dopamine were uncovered. Even understanding of atropine has undergone several theoretical revisions, to implicate non-accommodative pathways, then dopamine, then cholinergic agonists, then serotonergic receptor antagonism, potentially also glycine, and impact on the scleral matrix instead (Kaiti *et al.*, 2022). Time outdoors matters, so do genes and natural views, and so does duration and intensity of schooling. Switch to a pressure-free Yutori educational system in Japan (2002-2011) did successfully slow myopia progression, but the hit to the nation's international academic standing killed support for the policy. It was officially abandoned by 2012 (Ishiko *et al.*, 2021).

As a jump-the-gun example, China's National Myopia Prevention Plan includes several pieces of advice that are not (yet?) scientifically validated, and neither are policies and products based on screen time reduction according to Morgan et al. (2021). Being complacent about myopia is certainly not viable either. First on the basis of retinal detachment risks alone. Second, the fact that effectiveness of current therapeutics varies significantly by genetics, age, anti-depressant use, and delivery, straining against the ecological force of corporeal, corporate, and digital lifestyles.

Economies transition and cultural trends prevail. Formats and priorities like cram schools and high-pressure labour markets means a sacrifice of our long-distance vision, even as experts warn of the ticking time bomb of secondary

blindness. Despite not fully understanding of the mechanisms, we know that our urban post-industrial lifestyle, somehow, is the culprit, and the developing human body is reacting to it with near-vision adaptation and eyeball elongation.

So what can we really do if therapeutics are expensive, imperfect, or fix the consequences as opposed to the problem? If the ocular exercise, nutrition and supplementation routes are dubious, perhaps supermarkets could participate in public vision training by making patrons hunt like terrestrial eagles and sharp-eyed tyrannosaurs for fleeing snack items. Perhaps beyond tactical use of shortwave radio to avoid detection by budding Skynet programmes and enemy forces, frequencies against the cheek could double as a therapeutic for brain tissue. That's not a recommendation, but the skittering snack packets would at least make for a dynamic shopping experience.

More scientifically on the basis of ongoing research about the choroid, altering nitric oxide levels and improving circulation are some other strategies proposed for myopia control and lifelong retinal health, and that may involve light therapy, covered in *Part II: City Lights and Brain States.*

Disclaimer: *The material presented is for informational and entertainment purposes only, in summary of recent news and events. It neither reflects the views nor constitutes professional advice of the organisation. The major sources used are referenced below.*

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