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Are we doing enough for the patient with myopia? A literature review

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Abstract

Aim: **Myopia is one of the most common eye conditions and often has a progressive nature. With higher degrees come greater risks of visual disability; however, typically no treatment is offered clinically to tackle myopic progression. This review aims to determine whether it is possible to predict future high myopia, review the available treatments to slow myopic progression and consider their role in clinical practice.**
Methods: **A literature search was undertaken using the Web of Knowledge and PubMed databases.**
Results: **Progressive addition lenses (PALs) are effective in slowing myopic progression in those with larger accommodative lag, and bifocals with base-in prisms have been found effective in progressing myopia with both high and low accommodative lag. However, the reduced progression gained from these treatments is small (treatment effects: 0.28–0.33D/3 years, 0.61D/18 months and 0.85D/2 years). Atropine and pirenzepine instillation are consistent in slowing myopic progression in most cases (treatment effect 0.14–1.25D/year); however, accelerated myopic progression in treated eyes has been observed after atropine treatment.**
Conclusions: **None of the discussed treatments warrant widespread use. Atropine and pirenzepine appear to be the most effective options at present for slowing myopic progression. However, there is doubt as to whether their effects are maintained post-treatment. As it stands PALs have little effect clinically, though they may be beneficial for susceptible groups. Further research is required before clinicians can create evidence-based guidleines for these treatments, if their use is recommended at all.**

Key words: Accommodative lag, Aetiology, Atropine, Bifocals, Myopia, Pirenzepine, Progression, Progressive addition lenses, Treatment

Introduction

Myopia is one of the most common eye conditions, with a prevalence of 25–33% in the United States and up to 84% in some Asian populations.[1,2] It is often progressive, with gradual increases in severity until stabilisation in the late teens or early twenties.[3] In high myopia (>6.00D) the eye is at increased risk of diseases such as glaucoma, retinal detachment and cataract;[4] and the prevalence of myopic retinopathy increases with the severity of myopia.[5] In high myopia under the age of 10 years, amblyopia and reduced best-corrected visual acuity is present in 76%.[6]

There is currently no cure for myopia, nor a universally effective way to arrest its progression. The present debate is, rather, whether there is more we could do for myopic patients. The pathological consequences tend to present in high severities; however, the progressive nature of myopia suggests that intervention could also prevent less significant errors reaching greater levels.

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Methods

The Web of Knowledge and PubMed databases were searched for the key words listed above, and further studies sourced through the citations of those found. Only articles written in English were included. There is extensive literature surrounding myopia, therefore only three treatments are discussed: progressive addition lenses (PALs), atropine and pirenzepine. Other treatment options, for example undercorrecting single vision lenses (SVLs), orthokeratology, contact lenses and biofeedback,[6,7] were not included in view of limited or inconclusive research, or because of their method of flattening the cornea rather than acting on axial length.[7–9] Conversely, PALs were chosen (despite mixed conclusions as to their effectiveness) as there is evidence they could be more effective in subsets of myopia.[8]

Classification of myopia

Myopia has been classified by aetiology (simple, hereditary, degenerative), age of onset (juvenile-onset, adult-onset), severity (low, medium, high) and with or without degenerative changes (physiological, pathological),[3,10,11] but no well-accepted, well-defined classification of myopia exists. For the purpose of this review only the term 'common' myopia will be used. This would describe the bulk of myopia cases, encompassing types that may in other literature be termed 'school/adult-onset' or 'physiological' myopia.[3] It would be seemingly idiopathic, with onset typically from 7 years to adulthood,[3] and would be expected to stabilise at levels of 3.00–4.00D in the late teens or early twenties.[12]

Alternative to this would be myopia that does not quite follow the same pattern; is not quite as 'stable'. Due to either genetics or other factors, it reaches high degrees ($\geqslant$6.00D), incorporating cases (or future cases) of what has previously been described as 'pathological' myopia, i.e. myopia that is accompanied with pathological changes or visual dysfunction.[10] This review aims to explore whether there is any way we could better predict the normal (common myopia) or the alternative.

Causes of high myopia ($\geqslant$5.00D)

Not all myopia is seemingly idiopathic. Early-onset, high and/or progressive myopia is known to occur with other conditions.

Myopia sometimes occurs in conjunction with congenital or infantile obstructions to the visual pathway.[13–16] Most visually impaired children show significant ametropia (range -20.75D to $+21.75$D),[13] with few (23–30%) exhibiting refractive errors within $\pm$1.00D.[13,16] Pathology that has been associated with myopia includes ptosis, infantile haemangioma, retinopathy of prematurity (ROP) and aniridia.[13–16] The severity of myopia seen in children with these condiions is, however, variable. For example, the mean refraction $\pm$ standard deviation seen in ROP has been reported as -5.36 ± 3.92D[16] and -5.02 ± 6.04D,[13] and in retinitis pigmentosa, -4.33 ± 15.90D,[16] and -0.97 ± 5.63D.[13]

There is also 'syndromic' myopia.[17] This occurs in clearly inherited syndromes, such as Stickler, Marfan and Knobloch.[17–19] This myopia is generally high and of congenital or infantile onset, due to mutated genes affecting connective tissue.[17–19]

High myopia ($\geqslant$6.00D) may also be caused by genetics, for which some X-linked and autosomal dominant loci have been identified.[20–22] These were discovered through studies of families with high myopia, and the loci have not been found in common myopia.[23,24] An example of the nature of this myopia comes from a study by Young and colleagues.[21] The average age of myopia onset was 6.8 years (range 1.5–9.5 years) and there was no clinical evidence of connective tissue anomalies. The average severity of myopia was -9.48D (range 6.00–21.00D); however, there was a range of participant ages when assessed (2–84 years old), therefore these were not all final degrees of myopia and little can be concluded about the nature of myopic progression in these families.

In the absense of a syndrome it could be difficult to predict future high myopia in an otherwise healthy child. In the families with the identified genetic loci, the age of onset was often earlier than would be expected for 'common' myopia;[3] however, this was not so in all cases.[21] Therefore, in children who develop myopia at a later age, further clues of their likelihood of developing high myopia may come from family history. One longitudinal study, COMET (Correction of Myopia Evaluation Trial),[25] followed 469 children (from 6–11 years old) for 7 years, at which point 22% had developed myopia $>$6.00D. These children were more likely to have two myopic parents ($p = 0.008$). However, there is a hereditary element to almost all forms of myopia and the presence of two myopic parents would not necessarily differentiate between common and future high myopia.[26–28] The severity of parental myopia, however, could be important. One study found that the presence of one or two highly myopic parents ($\geqslant$5.00D) led to an increased risk of high myopia (the odds ratios of developing mild to moderate myopia of 1.25–4.75D were 2.5–3.7, and for myopia higher than this, $>$5.5).[29] Despite this, around 40–43% of those with high myopia have been found to be without myopic parents.[29,30] (High myopia is defined as $\geqslant$5.00D[29] and $\geqslant$6.00D[30].)

Progression of myopia

An understanding of myopic progression could help clinicians predict who is likely to progress to high myopia. Despite an association between earlier myopia onset and higher final myopia, this does not hold in all cases. Even in later onset myopia, progression to high severities has also been observed. For example, developing myopia at age 15 years has been observed to lead to final degrees of 1.50–6.00D.[31] But is there any evidence surrounding a level of myopia progression that could be 'abnormal', or suggest that intervention would be appropriate?

As shown in Fig. 1, progression of myopia has been observed to be faster in younger children than older children.[32,33] The graph displays the average progression of myopia in D/year for the age groups studied. Unfortunately the studies combined the upper and lower age ranges and the graph does lose detail at these points. However, it is interesting to note that the studies found similar progression rates for each age category, even when performed in different geographical locations. Saw's study[33] studied children in Singapore, a country with higher incidences of myopia,[34] and Hyman's study[32] displays data from COMET in North America, a country with lower myopia prevalence.[2]

But what level of myopic progression could be considered great enough to consider treatment? Firstly, there are some limitations to this graph which must be considered. The results are average progression rates at each age and the graph is merely to display the patterns found by the studies visually. No further statistical analysis can be gained from this. Furthermore, the children were not followed from myopia onset at 7 years until the age of 10 years. Saw's study followed the same children for 13–40 months[33] and the COMET data is from the first year of the study.[32] Each child would have had a different age of myopia onset. Genetic high myopia may have earlier age of onset,[21] and in view of its aetiology, may display faster progression than the common, later developing myopia. In this case, children studied from a young age could have had faster progression due to an earlier onset, progressive 'type' of myopia. The data included in Fig. 1 are average progression from a selection of children, some of whom will progress to high degrees of myopia and others who will not. It therefore does not display 'normal' myopic progression. Despite this, these were the only studies found that displayed this information. The graph could therefore give a very general comparison of whether a child's annual myopic progression could be relatively

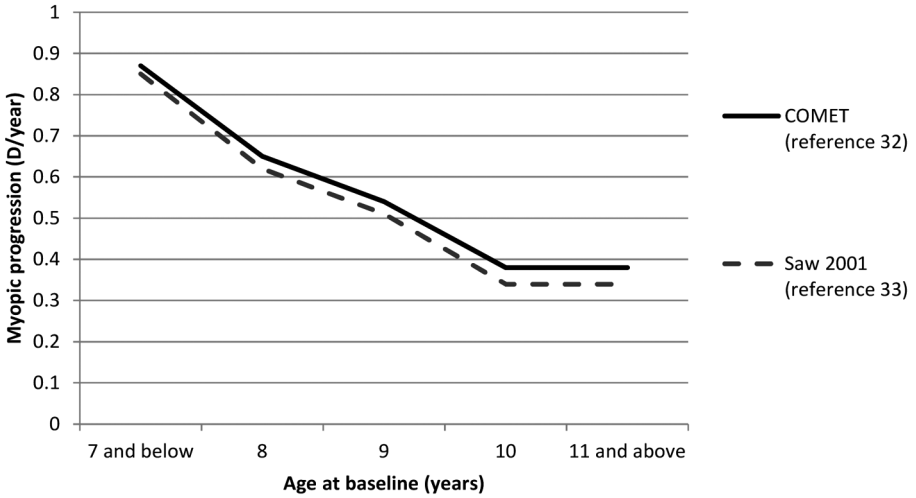

Fig. 1. The change in myopic progression with age,[32,33] with the assumption that the pattern between time points is linear. COMET (2005): '7 and below' includes children 6–7 years old. '11 and above' includes just 11-year-olds.[32] Saw (2001): Category '7 and below' includes children 7 years and below, and '11 and above refers' to 11- and 12-year-olds.[33]

high or low; however, its weaknesses must be considered. Currently, further research is needed in order to define reliably normal and abnormal myopic progression.

An insight into the long-term progression of high myopia specifically comes from a study that followed for 40 years (reviewed every decade) those with myopia $\geqslant$6.00D at 14 years old.[35] The progression of myopia was an average of −2.09D/10 years (from 16 to 26 years) and −1.00D/10 years (from age 26 onwards). While the mean change is small (approximately 0.2–0.1D/year), there was considerable variation between participants, with a range of progression of 0 to−8.00D/10 years (from 16 to 26 years old) and 0 to −14.00D for the entire period (14–54 years old). This study also noted that the stable, non-progressing eyes were the least myopic part of the distribution. These cases could just be at a 'high severity' end of common myopia, rather than a type of 'pathological' myopia that continually progresses. Either way, it has been observed in this study that progression of already high myopia is not a problem just observed in children and may continue well into adulthood.

Near work and accommodation: A factor that could affect myopic progression?

Near work and accommodation have long been implicated in the development of myopia; we all know the stereotype of highly educated people wearing glasses. Myopia is shown to occur more frequently with increased education and IQ,[36,37] with the assumption that this leads to more reading and accommodation. Higher incidences of myopia are also seen in professions with profound near work involvement, such as microscopy.[38] But could increased reading activity lead to faster myopic progression and/or final higher degrees of myopia?

An early theory was that myopia was caused by accommodation. If accommodation happens frequently, then theoretically compensatory growth of the eye could relieve the accommodative demand. However, there is ample evidence against accommodation as the main factor in myopia development.[39–42] This evidence comes from a selection of animal studies and lens-induced myopia where compensatory myopic growth is created by placing negative lenses over the eye.[43] The lenses both create hypermetropic defocus and stimulate accommodation. However, lens-induced myopia still develops in animals when accommodation is artificially prevented by lesions of the Edinger-Westphal nucleus or ciliary nerve sections.[39,40] Furthermore, animal studies have demonstrated that separate areas of the retina can be induced with different refractive errors, dependent on the stimulus given to different parts of the visual field.[41,42] Therefore, in order for accommodation to mediate eye growth, it would need to focus independently on individual retinal areas. There would also need to be efferent projections from the retina; and there is no evidence to support either of these possiblities.[41] Therefore it is the blur stimulus, the hypermetropic defocus created by negative lenses, that seems to be the stimulus for myopic development rather than exertion of accommodation. In view of this, the role of accommodative lag (an accommodative condition that creates hypermetropic defocus) and its relationship with myopia has recently been considered.

When looking at a near object or through minus lenses, most individuals accommodate slightly less than needed to focus the object.[44] This is termed accommodative lag (accommodative stimulus minus accommodative response). But could accommodative lag lead to increased myopic progression? In two well-designed, randomised, masked studies of progressive addition lenses (PALs),[44,45] the fastest mean progression of all children occurred in those with higher accommodative lag. The first study,[44] part of COMET, defined high accommodative lag as $\geqslant$0.43D. Children wearing SVLs with high lag progressed by -1.60 ± 0.08D/3 years and those with lag lower than this progressed by -1.36 ± 0.08D/3 years. The second study[45] defined high accommodative lag as $\geqslant$1.8D, and those with high

lag progressed by −1.48D/18 months and those with lower lag progressed by −0.99D/18 months.[45] It was also noted that even faster progression occurred in large accommodative lag, if combined with closer reading distance (<31.2 cm; −1.68D/3 years) and esophoria (−1.72D/3 years).[44] The presence of an esophoria could be significant; esophoria often occurs with excess accommodation (in uncorrected hypermetropia), but it can also be observed with deficient accommodation.[46,47] Exertion of accommodation increases the esophoria; therefore relaxation of accommodation occurs to maintain binocular vision. Accommodative lag and relaxation of accommodation both lead to greater levels of hypermetropic defocus. The findings from these studies are supported by another study that reported deficient accommodation in progressing myopia but not stable myopia.[48] However despite this, conflicting evidence comes from two well-designed studies which found no relationship between accommodative lag and myopic progression.[49,50] In all studies, accommodative response to a near target was measured by autorefractor. This current conflict of evidence could suggest that a measure of accommodative lag may not be distinct enough to clinically distinguish between progressive and non-progressive myopia.

Treatment to prevent the progression of myopia

Progressive addition lenses

Bifocals and PALs have been prescribed for myopia for over 50 years, as an alternative to SVLs that are otherwise prescribed.[7] If there were a causal relationship between myopia, near work and accommodation, then theoretically a reduced-power near section would reduce myopic progression through alleviating accommodation and accommodative lag during near work.[51] In view of the hypothesis that this treatment works by reducing retinal blur, it could be argued that PALs are more suitable than bifocals, because they allow clear vision over a range of distances. This treatment does slow myopic progression, but treatment effects (difference in progression between the treatment group and SVL group) are small. For example, this treatment has been found to slow myopic progression by 0.19D/3 years,[52] 0.57D/2 years,[53] 0.25D/2.5 years[51] and 0.21D/18 months.[54]

Despite this small reduction in progression, some subsets of myopic children have shown better responses to this treatment.[44] The small effects obtained from the above studies may have resulted from failure to stratify these subsets, leading to lower average differences. Recent studies have suggested that the response to PALs is influenced by accommodative lag.[44,45,55–57] In the two large, well-designed trials COMET[44,55] and COMET2,[56] children were randomly assigned to either SVLs or PALs (+2.00D addition for 3 years). Children with high accommodative lags (⩾0.43D by autorefractor) had a treatment effect of 0.33 ± 0.11D/3 years, with progression slowed to -1.27 ± 0.08D/3 years. Those with lower accommodative lags had a treatment effect of 0.07 ± 0.11D/3 years, with progression of -1.28 ± 0.08D/3 years.[44] Furthermore, these effects increased if high accommodative lag was present in combination with less myopia at study entry (<2.25D, 0.48D/3 years), shorter reading distance (<31.2 cm, 0.44D/3 years) and esophoria (⩾2^{Δ}; 0.64D/3 years) ($p < 0.05$ in all). Consequently, COMET2 studied only children with near esophoria (⩾2^{Δ}) and accommodative lag (⩾0.50D). Accommodative lags of ⩾1.50D and 0.50–1.49D received a treatment effect of 0.41D/3 years and 0.24D/3 years respectively. Overall the treatment effect was 0.28D/3 years (with a cut-off of ⩾1.00D of accommodative lag). This was statistically significant but still a clinically negligible result. However, another randomised trial found somewhat improved effects. Bifocals (1.50D addition) with or without base-in prismatic lenses (6^{Δ}) were introduced to children with ⩾0.50D of myopic progression in the previous year.[57] They produced treatment effects of 0.59D/2 years and 0.85D/2 years, respectively ($p < 0.01$). The reasoning for base-in prisms was that in orthophoric and exophoric children, a near addition induces an exophoric shift, creating positive fusional vergence; which has been proposed to reduce the near addition effect.[57] This study found the prismatic bifocals statistically significant even in those with low accommodative lag (≤1.00D), whereas the standard bifocals were only significant in children with high accommodative lag (>1.00D).

Pharmaceutical approaches

Atropine

Atropine is a non-selective muscarinic cholinergic antagonist,[12] often instilled as eye drops. Unfortunately atropine is a strong cycloplegic, leading to photophobia, mydriasis and loss of accommodation; requiring expensive photo-chromic bifocal lenses.[58]

Atropine 1%, instilled daily (often for 1–2 years), has been found to reduce myopic progression by 0.79–1.25D/year;[59–62] atropine 0.5% daily resulted in a reduction of 1.02D/year[63] and 0.92D/18 months.[54] This is considerably better than PALs, with atropine slowing progression to minimal rates; in some studies 'reversal' of myopia was found (+0.03–0.30D/year).[59,60,62,64] However, questions remain as to whether a reduced level of myopia is maintained after treatment and whether the treatment is worth all the time, stress and side effects.

As discussed earlier, high myopia sometimes has different aetiology, for example genetic mutations of connective tissue, which can relate to scleral wall expansion.[17,65] Most studies reviewed were not specific to high myopia, therefore it could be questioned whether atropine is effective in myopia of different aetiology. Only two of the studies specifically assessed high-degree myopia: Fan[59] (1% atropine, initial myopia 3.00–9.75D) and Chou[66] (0.5% atropine, initial myopia 6.25–12.00D). However, the results are difficult to interpret due to methodological issues. For example, Chou's study had unequal duration of treatment (2.1–4 years), and the control group was not comparable, as it was taken from a 6–20 month follow-up before atropine commencement. Given that progression could be inversely proportional to age,[31,32] to determine the effects of treatment the groups would need to be the same age. Therefore the com-

parison of a period 6–20 months before treatment with progression in the following 2.1–4 years of treatment may result in a falsely high efficacy of atropine. Chou's study noted one participant ($n = 20$) and Fan[59] recorded three children ($n = 23$) who progressed more than −1.00D throughout the period of atropine treatment, which could demonstrate a subtype of myopia resistant to treatment. However, the researchers did not specify how long atropine was used for (unequal treatment durations), nor the level of myopia, age, compliance or progression before treatment. Without this information it is not possible to tell whether −1.00D of progression was relatively high or low (it could be an improvement from a previously higher rate) or whether the particiants just did not comply. However, despite the weaknesses, both studies demonstrated that atropine was effective in most high degrees of myopia (>6.00D).

Little is known about myopic progression following cessation of atropine, as few of the reviewed studies assessed progression following treatment. One of these few reported progression of a mere −0.06D/year at 1–3 years post-treatment.[62] However, the reliability of this is questionable, as a conflicting phenomenon was demonstrated during the study. The method involved atropine treatment uniocularly for 1 year and for the fellow eye the following year, for up to 4 years. After atropine treatment swapped to the fellow eye (leaving the previously treated eye without treatment), the previously treated eyes displayed accelerated progression rates of 0.81–0.99D/year, much higher than the minimal −0.06D/year that was later reported as post-treatment progression. The reasons for this disparity are unclear. Possibly the most reliable study into post-treatment progression was by Tong,[67] who followed the subjects from a large ($n = 346$), randomised, parallel-group, placebo-controlled trial by Chua.[60] The participants were followed for 1 year after a 2-year course of daily 1% uniocular atropine. The mean refractive progression after cessation of atropine was 3 times the rate of the placebo-treated eyes. At study completion the atropine-treated eyes were still 0.93D less myopic than the placebo-treated eyes; however, the atropine-treated eyes were still progressing and had not reached a plateau. Therefore, if the study were to follow the children for longer, the atropine-treated eyes could have continued to progress to the level of the placebo eyes, rendering the prior 2 years of treatment ineffective.

Pirenzepine

Pirenzepine comes in the form of an ophthalmic gel and, like atropine, is a muscarinic antagonist. However, it is less selective in binding to the M_1 muscarinic receptor, causing less mydriasis and cycloplegia.[68] Thus bifocals and photo-chromic spectacles are not necessary, potentially leading to better compliance.

Only three studies were found that had investigated pirenzepine for myopia in humans, but although few in number, they were large, multicentre, randomised, double-masked, placebo-controlled trials. Pirenzepine 2% twice daily reduced myopic progression by 0.27 to 0.41D/year,[69–71] and 2% once daily, by 0.14D/year.[69] Although not as effective as atropine, the reduced cycloplegia could make pirenzepine a more attractive option. However, again there is no literature regarding myopia progression after treatment.

Safety of pharmaceuticals

The safety of long-term pharmaceuticals is another consideration. Atropine was well tolerated in most studies, with no serious adverse events.[59–61,63,72] The amplitude of accommodation and blurred near vision returned to normal after 1 year of treatment.[67] Pirenzepine was also well tolerated, with uncommon side-effects of headaches, common cold, 'flu, papillae/follicles and body rash;[67–71,73] only one serious adverse event, possibly due to medication, was reported (abdominal colic, 0.4% of 236 children).[69] Despite this, the majority of studies lasted for short periods of time and potential long-term side effects of atropine, such as ultraviolet damage from prolonged cycloplegia or premature presbyopia,[67] may not have manifested during this time. No literature was found that addressed these issues.

Discussion

High myopia is more likely to develop if there is a family history of high myopia,[29] an earlier age of onset (congenital to 6–7years old),[19,21,25,29] or alongside a syndrome.[18,19] However, not all cases of high myopia are due to genetics, syndromes or pathology,[17] and not all will have family history of myopia.[29,30] As it stands there is no evidence surrounding what could be 'normal' or 'abnormal' myopic progression. Some myopia may appear 'unstable' or 'anomalous', continually progressing even into late adulthood, whereas other cases may show stabilisation at low to moderate degrees of myopia,[35] and it is currently difficult to predict either. In this case, consideration of family history, the initial severity of myopia and a close observation of the individual's myopic progression may all help deduce whether high myopia or increasing severity of myopia is a real possibility.

Current evidence suggests that following atropine treatment, myopic progression is accelerated. Could this effect may be reduced if the patient is weaned from treatment, or if treatment is continued until an expected age of myopia cessation? Is this the same for pirenzepine? Further research is needed, although as it stands there is no evidence that these treatments are worth the endeavour in the long term. Furthermore, no literature was found addressing the long-term side effects of atropine or pirenzepine. Yet for some, pharmaceutical treatment is the only effective option available at present. Therefore its use (if at all) should perhaps be reserved for patients with early-onset, progressive myopia, in which case the choice appears to be to attempt to reduce myopic progression or face potentially disabling consequences of severe myopia. Treatment should be related to the individual and to the aetiology. For example, introduction of these treatments may not be appropriate in the case of syndromic myopia, where these pharmaceuticals could be an addition to a child's already complex series of health concerns.

Furthermore in syndromic myopia especially, reducing the severity of myopia may be futile. It has been noted that sudden retinal detachment in the first 20 years of life is common in Stickler syndrome.[19] The retinal detachment associated with this syndrome is also observed with degeneration of the retina and vitreous,[74] and may not necessarily be secondary to myopia but to the syndrome itself. Whether the long-term benefits of reduced myopia are worth the stress and risks of daily drug instillation is a decision that will rest ultimately with the clinician and the patient or their parents. Further research into the mechanism of myopia development is needed to find more effective pharmaceutical management.

What of PALs and bifocals? PALs have been found to be more effective in children with higher accommodative lag than lower lag,[44] and more so if combined with esophoria.[44] When introduced specifically for progressive myopia, there is evidence to suggest that this treatment may be more effective, and even effective in low accommodative lag if base-in prisms are also used.[57] However, the treatment effects are still clinically negligible.[44,56,57] Despite this, it may not be time just yet to dismiss PALs and bifocals. Further research is required into the mechanisms of this treatment, when and whom to target, and whether ultimately treatment with PALs or bifocals, with or without base-in prisms, leads to lower grades of myopia at its stabilisation. Without this information, clinicians are unable to create succinct evidence-based guidelines surrounding this treatment.

So, are we doing enough for the patient with myopia? With the information available at present, it can be argued that we are. Currently there is no long-term, reliable evidence for any of the treatments and it is not known how much reduction in myopia is obtained, whether the effects last and whether such reductions in myopia reduce the risk of pathological complications. However, there is evidence to justify and support a decision to use these treatments in individual circumstances. The search for more successful treatments to reduce myopic progression is ongoing, and it will be interesting to see the results of future trials.

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