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The ROYAL COLLEGE of OPHTHALMOLOGISTS

COMMENT

Cochrane corner: Atropine: an ancient remedy for a twenty-first century problem?

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This Cochrane corner commentary will consider the findings of a recently published Cochrane Review by Walline et al. on 'Interventions to slow progression of myopia in children' [1]. This is an update to a previous version of the review published by the same team in 2011. The review, which included 41 randomised controlled trials recruiting 6772 children with myopia, investigated the comparative efficacy of 15 different optical and pharmacological interventions to slow the progression of myopia. The authors reported moderate-certainty evidence that antimuscarinic eye drops reduced the progression of myopia and attenuated axial elongation. Atropine showed the largest effect size, with an estimated 1.00 dioptre (D) reduction in myopia from baseline at 12 months compared with placebo. In terms of adverse effects, children receiving antimuscarinic eye drops were more likely to experience accommodative difficulties, photophobia and allergic reactions than participants receiving placebo. In one of the largest trials [2], 17% of children in the atropine group failed to complete the study compared to 5% in the placebo group. Studies investigating optical interventions such as multifocal spectacles or specialised contact lenses, showed that these had only a small benefit in slowing myopia (typically ≤ 0.20 D).

Myopia is an important public health problem, affecting ~30% of the population globally. With current trends, the condition is predicted to affect 50% of the population by 2050 [3]. Marked ethnic differences in age-specific prevalence exist, with myopia already reaching 'epidemic' proportions in parts of East and South East Asia. For example, in urban areas of countries in these regions, up to 90% of children are myopic by the time they complete their high school education [4]. Whilst a low degree of myopia is often regarded as a minor inconvenience, high myopia (≤−6.00 D) is a major risk factor for a number of potentially blinding ocular pathologies, such as retinal detachment, myopic macular degeneration and glaucoma. Given the rapid increase in myopia prevalence and the associated risk of developing visually debilitating pathological myopia, there is a pressing need to develop and evaluate interventions to prevent myopia or slow its progression. Over the past 10 years, the number of published articles on 'myopia control' has increased exponentially (Fig. 1).

In such a rapidly moving field, it is particularly important that high quality systematic reviews are available to synthesise the accumulation of often conflicting research evidence to inform current practice. Given the large number of competing interventions for myopia control, there are considerable advantages in conducting a review that presents information on comparative effectiveness. A network meta-analysis (NMA) provides an analytical method for such a review. A NMA offers an advantage over a conventional pairwise meta-analysis in that it provides both direct comparisons of individual trials as well as indirect comparisons that were not directly evaluated in the included trials. A non-Cochrane NMA was published in 2016 [5] comparing 16 separate interventions for myopia control in children. This review similarly concluded that the most effective interventions were pharmacological and specifically treatment with antimuscarinics such as atropine and pirenzepine.

Atropine, whose name derives from Atropos, one of the three Fates in Greek mythology, who was said to determine a person's moment of death, is an extremely potent poison that has been widely used in medicine since ancient times [6]. In the recent Cochrane update, evidence for the efficacy of atropine came from the findings of three RCTs that investigated the effect of higher doses of atropine (0.5% and 1.0%) versus placebo [2, 7, 8]. Although demonstrating the effectiveness of these agents, based on their effect on

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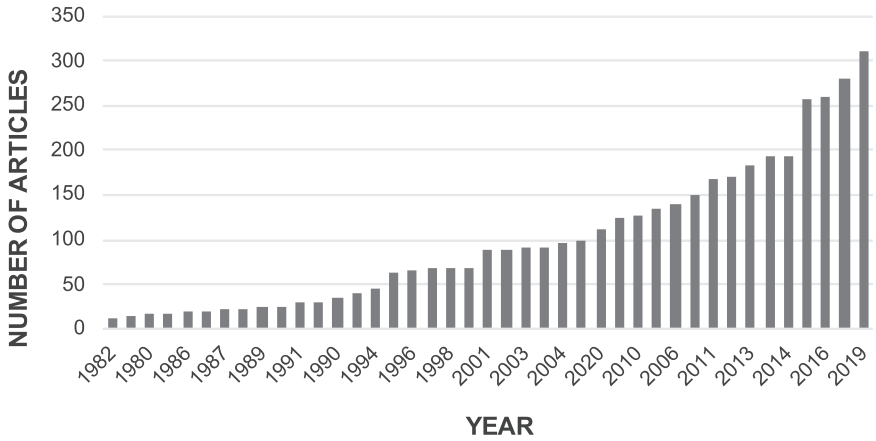

Fig. 1 The cumulative number of publications relating to myopia control published annually from 1982 to 2019. The graph shows the number of articles retrieved from a PubMed search query using the term 'myopia control' from January 1982 to December 2019.

spherical equivalent (SE) refractive error and axial length (AL), there are a number of problems associated with the use of these higher concentrations of atropine including risk of side effects and a pronounced myopic 'rebound' following cessation of treatment. A follow-up to the 'Atropine for the Treatment of Childhood Myopia (ATOM)' study [2], that provided the strongest evidence for the effectiveness of 1% atropine, investigated the use of three lower doses of atropine (0.5%, 0.1% and 0.01%) [9]. Whilst the ATOM 2 study was limited in not having a placebo group, it demonstrated that atropine 0.01% was the most effective of the three treatment arms in slowing myopia progression with fewer side effects.

An Ophthalmic Technology Assessment by the American Academy of Ophthalmology published in 2017 [10], concluded that 'Level I' evidence supports the use of atropine to prevent myopic progression". The review suggested that it may be preferable to use the lower 0.01% concentration due to the reduced likelihood of rebound and lower incidence of adverse effects. However, a number of clinical uncertainties were recognised, including the optimal time to initiate and discontinue therapy and whether the evidence arising almost exclusively from trials conducted in East and South East Asia are generalisable to other ethnic groups.

Further evidence of the efficacy of lower doses of atropine comes from the recently published 'Low-concentration Atropine for Myopia Progression (LAMP)' study [11, 12], which investigated the effect of a range of low dose atropine concentrations (0.01%, 0.025% and 0.05%) compared with placebo. All doses reduced myopia progression in a concentration-dependent manner, with 0.05% atropine being the most effective in controlling both SE myopic progression and AL elongation over a 1-year period. All concentrations were well tolerated, with only a small reduction in amplitude of accommodation and pupil dilation with symptoms of photophobia reported in only 7.8% of participants using the 0.05% dose.

The limited data on populations outside Asia may in part explain why atropine therapy is less widely prescribed in these regions. This is compounded by the lack of availability of a licensed low-dose atropine preparation in many countries. There are a number of ongoing placebo-controlled trials of 0.01% atropine currently underway in the UK, Ireland and Western Australia [13–15]. These studies will provide valuable information on the efficacy and tolerability of low dose atropine in predominantly White populations.

As new evidence emerges on interventions for myopia control, it is important that high quality systematic reviews are available to clinicians that encompass these new data. Cochrane Eyes and Vision have recently registered a NMA on interventions for myopia control in children. As well as including new evidence on pharmacological interventions (including combination therapy with other interventions [16–18]), this review will also incorporate newly published trials on novel optical interventions and include a brief economic commentary. For example, a dual-focus soft contact lens that integrates a central zone providing the distance correction with peripheral zones of myopic defocus, which has been shown to slow changes in SE refraction and AL in a trial in children aged 8–12 years [19].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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