5 year Clinical Trial on Atropine for the treatment of Myopia (ATOM2)

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(This presentation describes an off-label use of Atropine eyedrops as a form of myopia control)
1% Atropine eyedrops have been around for many years, and are approved for use in babies and young children for the treatment of amblyopia (lazy eye), but previous studies have suggested that it may also slow down the progression of myopia in older children.

- **ATOM1**: placebo-controlled double-masked RCT, 1999 to 2004
- 400 children, 6-12 years, -1 to -6D, (mean: -3.5D)
- Treatment group: 1% atropine o.n. in one eye, other eye untreated
- Control group: Vehicle eyedrops in one eye, and other eye untreated
- 3 year study: 2 years of treatment, 1 observational wash-out year
Atropine for the Treatment of Childhood Myopia: Effect on Myopia Progression after Cessation of Atropine

- First 2 years: 77% reduction in mean progression of myopia, strong correlation with axial length
- Usual side-effects: pupil dilation, glare, loss of accommodation
- Year 3: significant rebound of myopia progression upon cessation of atropine 1% eyedrops
Study Aim: to compare safety and efficacy of 3 lower doses of atropine
- double-masked RCT, 2006 to 2012
- 400 children, 6-12 years, ≥-2D,
- Randomized: 0.5% (n=161)
  0.1% (n=155)
  0.01% (n=84)
- Slightly older children (9.7 yrs vs 9.2 yrs), higher myopia (-4.7D vs -3.5D) vs ATOM1
- Bilateral eye treatment
- 5 year study:
  Treatment phase 1: 2 years of treatment
  Treatment phase 2: Year 3: wash-out year
  Treatment phase 3: Year 4,5: continuing progressors restarted on treatment with one dosage


Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: Changes after stopping Atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol 2014;157:451-457

Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2

Myopia Control with Atropine 0.01% Eyedrops

E-pub (accepted July 2015), Ophthalmology
**ATOM2**

**Refractive Change**

**Ophthalmology**
2012;119:347–354

**Dose-related response, but clinically small differences**

**Mean Spherical Equivalent:**
- Before study started: -4.7D
- 0.5% atropine: -4.6D (1.9)
- 0.1% atropine: -4.8D (1.4)
- 0.01% atropine: -4.9D (1.5) (p=0.20)

**Consolidating ATOM 1 and 2, it appears that 0.01% atropine is clinically similar to 0.1%, 0.5% and 1.0% in efficacy, as compared to placebo**
Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)

Mean Photopic Pupil Size:
- Baseline: 3.9 mm
- 0.01% Atropine: 5.1 mm
- 0.1% Atropine: 6.7 mm
- 0.5% Atropine: 7.5 mm

Mean Mesopic Pupil Size:
- Baseline: 4.7 mm
- 0.01% Atropine: 5.5 mm
- 0.1% Atropine: 6.9 mm
- 0.5% Atropine: 7.8 mm

(P<0.001)
**ATOM1+2 Safety Data**

- No serious adverse events during entire study – no cataract, glaucoma, retinal disease, no systemic side-effects

- Very minor side-effects: glare – 1%, no loss of near vision


• Atropine treatment stopped at 24 months
• One year washout period: 365 children (89%)
• Pupil size, accommodation all returned to normal
ATOM1+2: Phase 2: washout stage (year 3)

- Atropine treatment stopped at 24 months
- One year washout period: 365 children (89%)
- Pupil size, accommodation all returned to normal

- Clear rebound phenomenon, but dose-related
- 0.01% atropine had minimal rebound
**ATOM2:**  Phase 3: all those still progressing (5 years) restarted on Atropine 0.01% after Washout

- **Phase 1** (2 years) (n=400)
  - Received atropine 0.01% for 24 months (n=84)
- **Phase 2** (1 year) (n=365)
  - Stopped atropine treatment
  - Washout period for 12 months (n=71)
  - Stopped atropine treatment
  - Washout period for 12 months (n=139)
  - Stopped atropine treatment
  - Washout period for 12 months (n=138)
- **Phase 3** (2 years) (n=345)
  - Continued myopia progressors (> -0.5D) all restarted on atropine 0.01% for 24 months (n=192)
  - Analysis after 24 months of atropine 0.01% (n=17) (24%)
  - Analysis after 24 months of atropine 0.01% (n=82) (59%)
  - Analysis after 24 months of atropine 0.01% (n=93) (68%)

- Received atropine 0.1% for 24 months (n=155)
- Received atropine 0.5% for 24 months (n=161)

Randomized (n=400)
ATOM2: Proportion that progressed >0.5D at washout (between 24-36 months)

- The percentage of children who continued to have progressive myopia after the washout period related to the original concentration of atropine used in Phase 1:
  - 0.5% atropine group: 68% progressed
  - 0.1% atropine group: 59% progressed
  - 0.01% atropine group: 24% progressed

- Children requiring retreatment were:
  - younger
  - had less myopia at baseline
  - greater increase in myopia at Phase 1
ATOM1 (3 year) and ATOM2 (5 year) data

Myopia slowed by in a dose-related response, but the effects were fairly similar despite the different dose concentrations.

Greater rebound with the higher atropine concentrations:
- 24% (A0.01), 59% (A0.1) and 68% (A0.5) had progressed > 0.5D in washout and were restarted on A 0.01%

Change in SE (-1.38D) signif less in A0.01 at 5 yr

Same -1.4D increase in placebo group at 2.5 yr
So what have we learnt from the ATOM trials?
(in the last 14 years!)

- **Atropine eyedrops** *reduce myopia progression and axial elongation* in children in a *dose-related* manner, but a *rebound phenomenon* occurs with the higher doses of atropine.

- **Atropine eyedrops are safe**, with no serious adverse events, but in the higher doses, the side-effects of pupil dilatation, loss of accommodation and near vision limits practical use.

- **Atropine 0.01% has the best therapeutic index**, with clinically insignificant amounts of pupil dilatation, near vision and accommodation loss, and yet is as effective as the higher doses.

- **Atropine 0.01% appears to retard myopia progression by 50%, and retreatment after a period of treatment cessation still appears to be equally effective.**

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7. Chia A, Chua WH, Li W, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping Atropine 0.01%, 0.1% and 0.5% (ATOM2). Submitted AJO 2013.
8. Chia A, Lu QS, Tan D. Myopic control in children re-started on Atropine 0.01% after a 12 month washout period (ATOM2). Being prepared for submission.
What is the Impact?

- We can now prevent myopia progression, safely, and effectively, in children

- Atropine 0.01% eyedrops once a day, appears to be able to reduce myopia progression by about 50%, through the retardation of axial elongation, with minimal symptoms, and with minimal rebound upon cessation

- Further clinical trials on low-dose atropine in Japan, and UK are planned.
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1959-1999