Weaning From Atropine—Possible Bias Despite Randomization

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There is increasing evidence that atropine, 0.05%, as a daily topical eye drop is effective in slowing progression of childhood myopia.[1,2] Evidence of effectiveness for lower doses (eg, 0.01%) remains mixed,[3] and practitioners often currently prescribe 0.05%. On stopping such higher doses, there appears to be a greater rebound effect than with lower doses, and a subsequent increase in the rate of myopic progression.[4] Therefore, practitioners, patients, and families often face the question of whether it is better to wean atropine treatment rather than stop treatment abruptly.

In this issue of *JAMA Ophthalmology*, Zhang and colleagues[5] report results from a randomized clinical trial (RCT) to address this question of whether to wean a patient from atropine drops or whether to stop the atropine drops abruptly. Participants assigned to weaning, referred to as the taper group, received 0.05% for 6 months, 0.025% for 6 months, and no treatment for 24 months. Those who were assigned to stopping abruptly, referred to as the stop group, received 0.05% for 12 months followed by 24 months of no treatment. The study's primary finding was that the taper group had a mean myopic progression that was 0.24 diopters less than that in the stop group (a 30% reduction) over 3 years despite receiving 6 months of lower-dose treatment.

Although randomization reduces many forms of potential bias, often leading to robust evidence that can be applied to practice, there are features of RCT conduct and analysis that may still inadvertently introduce bias. One potential postrandomization cause of bias is loss to follow-up, particularly if loss to follow-up is nonrandom and differs between treatment groups.

Zhang et al[5] report that dropout rates over 3 years were similar between the taper and stop groups, but the proportions were reported as 29.5% in the taper group and 24.2% in the stop group. The difference (5.3%) was reported as not statistically significant ($P = .35$), but failure to find a statistically significant difference is not the same as evidence of no difference, especially when the comparison was not preplanned with appropriate statistical power. The 95% CIs are more informative than *P* values because they give the readers more information about a range of plausible differences consistent with the observed data. Additionally, even if dropout rates are similar, differential loss to follow-up can still occur if the reasons for

dropout differ by group. Unfortunately, the true reasons for participant dropout, and whether they are related to treatment assignment, are often unknowable.

Differential loss to follow-up by treatment group is also problematic if there are major imbalances in baseline factors between completers and noncompleters, particularly if those factors might influence outcomes. Although the authors report that characteristics were similar, the data in eTable 1 in Supplement 2 indicate differences.[5] Compared with completers in the stop group, completers in the taper group had greater mean myopia at enrollment into the stop vs taper phase of the RCT. Evaluating whether this difference is statistically different is not helpful because, again, absence of a statistically significant difference is not the same as evidence of no difference. Statistical adjustment for myopia at randomization in the primary analysis reduces the impact of the imbalance but does not totally eliminate the potential impact of high loss to follow-up. Having said that, the authors reported no imbalance in mean axial length at randomization, and their analysis of change in axial length also yielded a small but statistically significant benefit of tapering (0.11-mm mean difference, equivalent to a 25% reduction).

The authors should be commended on using multiple imputation to account for missing data in a sensitivity analysis. Multiple imputation may mitigate potential bias of loss to follow-up, but the method assumes that missing data are missing at random. If those with greater progression were more likely to drop out, then assessment of the mean outcome would be biased. In addition, if baseline factors related to outcome were not measured and incorporated into the model, then multiple imputation will still be inadequate to address bias. Tipping point analysis[6] and pattern-mixture models[7] are additional methods to evaluate the robustness of the missing-at-random assumption that could have been implemented. With a high proportion of missing outcome data (approximately 27%), the primary finding of a small treatment effect may be sensitive to the missing-at-random assumption and nullified by even a modest violation of that assumption. An example would be a scenario in which participants lost to follow-up in the taper group had slightly greater progression than those lost to follow-up in the stop group. In that scenario, had all data been observed, the primary study result may well have been nonsignificant.

The most desirable solution for future RCTs is to do everything possible to avoid loss to follow-up and thereby maintain advantages of the original random allocation of treatment assignment. This imperative may be easier said than done, particularly in RCTs where follow-up must span many years, such as for interventions in myopia progression. In the meantime, readers should be aware of the impact of loss to follow-up in RCTs and incorporate that knowledge into their interpretation of study results.

An additional potential problem with analysis of RCT data is selecting an outcome where the starting point is not at randomization, but sometime after randomization. The authors report the proportion of good response to treatment discontinuation as a secondary outcome, with a starting point 1 year after randomization. This method is problematic because in any RCT, 1 year after randomization, the treatment groups would very likely differ in known and unknown ways, in part due to loss to follow-up and differences in adherence to the study treatment, and most of the benefits of randomization would have been lost.

Addressing the pragmatic clinical question of whether to taper or stop atropine, 0.05%, eye drops in a child who is being treated for myopia progression, once the patient, family, and treating practitioner have decided to end treatment, the study by Zhang et al[5] likely provides

the most rigorous evidence to date (albeit with the caveats discussed). If 1 more year of treatment is acceptable, the current evidence suggests that tapering may result in small but statistically significant reductions in myopic progression and axial elongation over 3 years compared with continuing atropine, 0.05%, for 1 more year and then stopping abruptly. Perhaps a more common clinical scenario would be a different dichotomous choice between stopping abruptly right now or continuing at a reduced dose before stopping. In such a scenario, there appear to be 2 potential advantages to weaning: the lower myopic progression reported by Zhang and colleagues and an additional period of receiving a lower, but possibly effective, dose of atropine. Nevertheless, to broadly apply the findings by Zhang and colleagues,[5] it would be preferable to have additional RCTs with lower rates of loss to follow-up, additional RCTs in non-Asian populations (who likely have lower rates of myopic progression[8]), and long-term data on the durability of effect.

Article Information

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