



## Intermittent Exotropia Evidence-based Treatment & Designing Clinical Trials

Susan Cotter, OD, MS, FAAO, FCOVD  
Professor

© Susan Cotter 2016

### Financial Disclosures

No financial interest  
in materials or methods discussed herein

Grant Support NIH/NEI: EY011751

### IXT: What Do We Know?

### Intermittent Exotropia (IXT)

- Most common form of childhood-onset XT
- Normal alignment & sensory fusion sometimes

### IXT: Clinical Characteristics

- Intermittent fusion
- Good stereoacuity at near (generally)
- Amblyopia rare
- When tropic:
  - Diplopia
  - Suppression
  - ARC

### IXT: Most Common Signs & Symptoms

- ❖ Cosmesis
  - Blur
  - Asthenopia
  - Diplopia
  - Monocular eye closure in bright sunlight

### Clinical Tip: Cover Testing

- Test distance at far can make a difference
- Use remote test distance

DE XT	Mirror vs. 6m	3m vs. 6m
Increased angle 5-15Δ	55%	64%
Surgery (yes/no)	14%	32%
Surgical dose different	41%	32%

Samantha: IAXT (50%) 14Δ at 3m; CAXT 25Δ at 50ft

Kushner & Morton. Ann Ophthalmol 1982;14:86-9.

### What We Don't Know

### Natural History

- 75% progress over 3 years (Von Noorden<sup>1</sup>)
- 81% no change over 6 years (Hiles<sup>2</sup>)
- Most improve over time (Rutstein<sup>3</sup>)
- Most remain stable (Chia<sup>4</sup> & Romanchuk<sup>5</sup>)
- Most deteriorate (Nusz<sup>6</sup>)

2002 re 1966<sup>1</sup>; 1968<sup>2</sup>; 2003<sup>3</sup>; 2005<sup>4</sup>; 2006<sup>5</sup>; 2005<sup>6</sup>

### Treatment Effectiveness for IXT??

- Monitor; watchful waiting
- Refractive correction
- Patching
- Over-minus lens correction
- Prism
- Vision therapy
- Surgery

### Levels of Evidence

A pyramid diagram with seven horizontal layers. From top to bottom, the layers are labeled: Systematic Reviews, Randomized Controlled Trials, Cohort Studies, Case-Control Studies, Case Series, Case Reports, and Editorials, Expert Opinion. To the left of the pyramid is a small empty rectangular box.

### Interventions for Intermittent Exotropia (Review)

Hani SR, Gnanraj L.

THE COCHRANE COLLABORATION®

Available literature consists mainly of retrospective case reviews, which are difficult to reliably interpret and analyze. The 1 RCT found unilateral surgery more effective than bilateral surgery for basic IXT. However, across all studies, measures of severity and thus criteria for intervention are poorly validated, and there appear to be no reliable natural history data. There is therefore a pressing need for improved measures of severity, a better understanding of natural history and carefully planned RCTs of treatment to improve the evidence base for the management of this condition.

### Randomized Clinical Trial (RCT)

- Randomization?
  - Minimizes bias
  - Increases probability that confounding factors are equally distributed between treatment groups
  - Masking

### Randomized Clinical Trial (RCT)

- Clearly defined inclusion & exclusion criteria
- Clear protocol with defined follow-up schedule
- Appropriate sample size
  - Reduces chance of concluding there is no effect when in fact there is an effect (type II error)
- Standardized outcome assessment


### Outcome Measure for IXT?

- Time (%) of alignment or Control

### Ways of Assessing IXT Control

- Patient and parental report
- Cover testing
  - Proportion of time XT is manifest
  - Speed of recovery
- PEDIG IXT control scale

### PEDIG IXT Control Score

Control Score	Description	
5	Constant XT during a 30-sec observation period (before dissociation)	Observed during 2 30-sec periods; distance, then near
4	XT >50% of time during a 30-sec observation period (before dissociation)	
3	XT <50% of time during a 30-sec observation period (before dissociation)	
2	No XT unless dissociated (10 sec): recovery in > 5 sec	Worst of 3 consecutive trials of covering 1 eye for 10 sec at both D & N
1	No XT unless dissociated (10 sec): recovery in 1-5 sec	
0	Pure phoria: < 1 sec recovery after 10-sec dissociation	

Mohney BG, Holmes JM. An office-based scale for assessing control in intermittent exotropia. *Invest Ophthalmol Vis Sci* 2006;47(6):147-150.

### Control as Function of Magnitude?

Hatt et al. *Ophthalmology* 2008;115:371-6

## Intraday Variability: IXT

- Serial Cover Testing: 3 - 4 times in 1 day ( $\geq 2$  hrs apart)

8:00 -10:30 | 10:31-13:00 | 13:01-15:30 | 15:31-18:00

- Control - using IXT control scale (0 to 5)  
Variable - change in control  $\geq 2$  levels  
Stable - no change in control

Hatt et al. Ophthalmology 2008;115:371-6

## Summary: Intraday Study of IXT Control

- Control varied over 1 day in many patients
- Change occurs between spontaneous tropia and well-controlled phoria
- Worst control *not always* at end of day
- Control can vary even over 15-20 minutes  
 – MEPEDS example

Hatt et al. Ophthalmology 2008;115:371-6

## Is a Single Control Measure Sufficient?



- IXT control variable over a day and over an examination
- A triple control measure (mean of 3 during an exam) is closer to mean control over the day

Hatt et al. Am J Ophthalmol 2011; 152:872-876

## Treatments for IXT

- Monitor; watchful waiting
- Refractive correction
- Patching
- Over-minus lens correction
- Prism
- Vision therapy
- Surgery

## Clinical Tip: Refractive Correction Important for IXT

- Increased sensitivity to uncorrected ametropia?
- Provide equally clear retinal images
  - Promote accommodative accuracy
  - Discourage suppression
  - Promote improved sensory fusion
- Correct myopia, astigmatism, anisometropia
- Special cases: moderate/high hyperopia

## PEDIG RCT's for IXT

- Patching
- Over-minus lens correction
- Surgery



### Overminus Lens Therapy for IXT

- Rx more minus (or less plus) than distance refraction
- Mechanism?
  - Magnitude reduced by stimulating A/C
  - A/C triggers reflex fusional vergence
  - May allow clear distance vision, facilitating fusion
    - Stimulation of accommodation by:
      - Excessive convergence required for fusion (convergence accommodation)?
      - Reliance on excessive AC to overcome XT?

### Overminus Lens Therapy for IXT

#### Cotter's Clinical Impressions

### Overminus Lens Therapy

- Patient profile
  - Age?
  - Accommodative function?
  - AC/A ratio?
- Prescribing: How much overminus?
  - Decrease in IXT magnitude?
  - Decrease in IXT frequency?
  - If results in eso at near?

### Overminus Lens Therapy

- Length of treatment?
- Parental education – very important
- Myopia progression: no evidence of
  - Only retrospective chart reviews

*Group	Initial RE	Change After 5 Y	Change After 10 Y
Control (62)	0.00 ± 1.40	-1.40 ± 2.00	-2.41 ± 2.20
6-mo Tx (74)	0.00 ± 1.50	-1.52 ± 1.80	-2.34 ± 2.40
5-yr Tx (34)	-0.10 ± 1.50	-1.54 ± 1.90	-2.36 ± 2.10

\*Kushner BJ. Arch Ophthalmol 1999; 117:638-642  
Rutstein RP et al. OVS 1989; 66:487-491

### Intermittent Exotropia Study 3 (IXT3)

A Pilot Randomized Clinical Trial of Overminus Spectacle Therapy for Intermittent Exotropia



### Study Objectives

Assess initial short-term response to overminus lenses

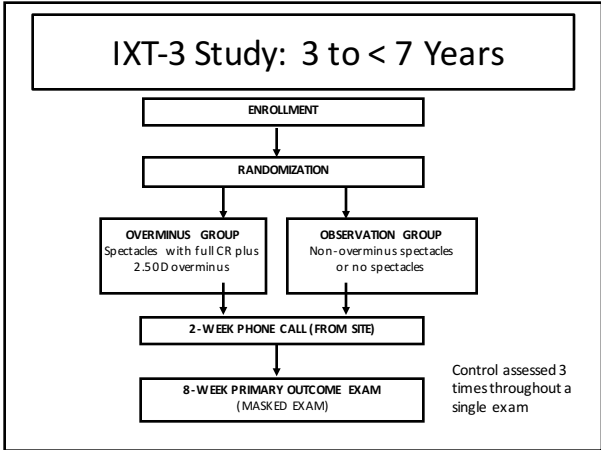
Treatment groups compared on:

- Study group mean distance IXT control scores (primary outcome)\*
- Proportion with improvement  $\geq 1$  point in distance control score\*
- Adverse symptoms, near VA, & compliance

\*Distance control score = mean of 3 tests at the visit

### Major Eligibility Criteria

- Age: 3 to <7 years
- IXT
  - Distance control score  $\geq 2$  (mean of 3)
  - Near control score  $\neq 5$  (mean of 3)
  - $\geq 15\Delta$  exo at distance by PACT
  - Near not exceed distance deviation by  $>10 \Delta$  (PACT)
- SE between +1.00 D and -6.00 D OD & OS



### Baseline XT Control At Distance & Near

### Results?

### Mean Distance Control at 8 Weeks

### 8-week Change in Distance Control

Worse

N/A                      N/A

Better

### Distance Control Treatment Response ( $\geq 1$ point improvement) at 8-week

37

### IXT3 Conclusions

- In this pilot RCT, overminus spectacles improved distance control at 8 weeks in children 3 to <7 years old with IXT
- Larger & longer RCT needed to assess effectiveness of overminus lenses on *and off* treatment

### Intermittent Exotropia Study 5 (IXT-5)

RCT of Overminus Spectacle Therapy for Intermittent Exotropia



Enrollment Will Be Open Soon! 3 to <10 years

### IXT-2: A Randomized Trial Comparing Part-time Patching with Observation for Children with Intermittent Exotropia

Susan A. Cotter,<sup>1</sup> Danielle L. Chandler,<sup>2</sup> Brian G. Mohny,<sup>3</sup> and Jonathan M. Holmes<sup>3</sup> on behalf of the Pediatric Eye Disease Investigator Group (PEDIG)

<sup>1</sup>SCCO at Marshall B. Ketchum University

<sup>2</sup>Jaeb Center for Health Research

<sup>3</sup>Dept of Ophthalmology, Mayo Clinic

*Ophthalmology* 2014;121(12):2299-310

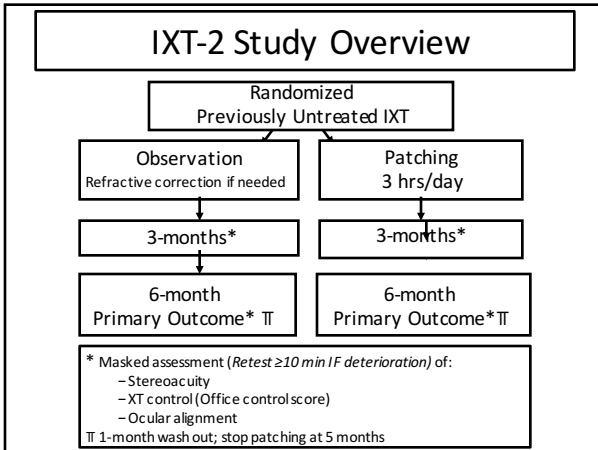


### Study Objective

- Effectiveness of prescribed part-time patching for reducing risk of deterioration of IXT over 6 months among children aged:
  - 3 to <11 years
  - 12 to 35 months

### Major Eligibility Criteria

- Age: 3 to <11 years; 12 months to 35 months
- Previously untreated IXT (any type)
  - IXT or CXT at distance; & IXT or XP at near
  - $\geq 10\Delta$  at distance
  - $\geq 15\Delta$  at distance +/- near
- Near stereoacuity of 400" (only older cohort)
- No amblyopia or amblyopia tx in last year
- Investigator / child / parent willing forgo all other IXT treatment until deterioration criteria met



### Primary Outcome Deterioration by 6 Months

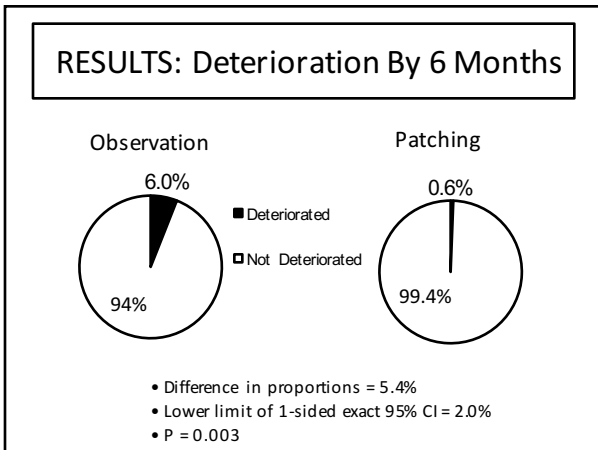
- Constant XT  $\geq 10\Delta$  at Dist & Near\*  
 -by SPCT & throughout exam
- Near stereopsis: drop  $\geq 2$  octaves from baseline\*

Preschool Randot Stereoacuity	
Baseline Stereo arc sec	Stereo at FU visit to meet deterioration*
40	200 or worse
60	400 or worse
100	400 or worse
200	800 or worse
400	Nil

\*Confirmed by retest

- ### Also Considered Deterioration
- If non-protocol tx started without meeting formal deterioration criteria
  - Allowed exceptions:
    - Debilitating diplopia
    - Overwhelming social concern (parent/child)
    - Failure to keep up with stereo age-norms

### Results?



### Deterioration By 6 Months

Deterioration by 6 Months	Observation (N=165)	Patching (N=159)
Number (%) Deteriorated	10 (6.0%)	1 (0.6%)
• Formal deterioration criteria met	7 (4.2%)	1 (0.6%)
Constant XT $\geq 10\Delta$ D&N	1 (0.6%) **	0
Stereo worsened $\geq 2$ octaves	6 (3.6%)	1 (0.6%)
Both criteria	0	0
• Started treatment against protocol	3 (1.8%)	0

\*\*Had 40 sec RDS on Randot Preschool; protocol-required UCT not performed

- Difference in proportions = 5.4%
- Lower limit of 1-sided exact 95% CI = 2.0%; P = 0.003



### Post-Hoc Alternative Definition of Deterioration By 6 Months

Deterioration by 6 Months	Observation (N=165)	Patching (N=159)
Stereo worsened $\geq$ 2 octaves	6 (3.6%)	1 (0.6%)

- Difference = 3.0%
- Lower limit of 1-sided exact 95% CI = 0.2%; P = 0.04

12 to 35-Month-Old Kids?

### Deterioration By 6 Months 12 to 35-Month-Old Children

Deterioration by 6 Months	Observation (N=87)	Patching (N=90)
TOTAL Number (%) Deteriorated	4 (4.6%)	2 (2.2%)
• Formal deterioration criteria met	2 (2.3%)	2 (2.2%)
Constant XT $\geq$ 10 $\Delta$ D&N		
• Started treatment against protocol	2 (2.3%)	0

- Difference in proportions = 2.4%
- 1-sided exact 95% CI = -3.8% to +9.4%; P = 0.27

*Ophthalmology* 2015 Aug;122(8):1718-1725

### Conclusions: Part-time Patching for IXT

- Deterioration over 6 months uncommon in both treatment groups
- PT patching showed small effect for decreasing deterioration over 6 months in 3 to <11 years
  - Both management approaches reasonable for children 3 - 10 years with IXT
- No difference in effect for 12 to 35 months
  - Insufficient evidence to recommend part-time patching for treatment of IXT in children 12-35 months

### Best Treatment for IXT

- Monitor; watchful waiting
- Refractive Correction
- Patching
- Over-minus lens correction
- Prism
- Vision therapy
- Surgery



### Thank You

