Ophthalmic Findings in Adults

Peripheral and Central Nervous System Drugs Advisory Committee

January 7 & 8, 2009

Day 1

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Vigabatrin Ophthalmic Adverse Effects

- 1998 FDA Not Approvable action based on visual adverse effects
  Complex Partial Seizures (CPS)

FDA asked sponsor to:

- Characterize visual adverse effects
- Describe how to monitor and prevent

Vigabatrin Ophthalmic Adverse Effects

- ***Day 1***
  - ***Emphasis on adults***
  - ***Complex partial seizures indication***
  - ***NDA 20427***

- Day 2
  - Emphasis on infants and young children
  - Infantile spasms indication
  - NDA 22006

Ophthalmic Adverse Effects

- Location (visual acuity vs. peripheral vision)
- Severity
- Functional effects/visual disability
- Reversibility
- Stability
- Time to onset and speed of progression
- Dose and Time Effect
- Monitoring and Prevention

Data Sources

- Mostly cross-sectional studies and case series
- Susceptible to error and unintended bias
- Quality control a concern
- May support *qualitative* conclusions
- No well-designed, prospective, longitudinal studies
  - Many questions <u>impossible</u> to address accurately with available data

Visual Field Study 4020

- Open-label study of field defect in CPS assessed by perimetry at regular intervals
- 550 adults, 184 children
- 3 study arms:
  - *Previously treated* and remaining on VGB
  - *Previously treated* but stopped prior to entry
  - Not treated prior to or during study
    - Only 7 patients started vigabatrin during study

Visual Field Study 4020

- Large study, but data of limited use
- *Patients don't represent unbiased population*
  - Likely less severely affected
  - Patients not fitting expected pattern excluded
  - High dropout rate
- Poor quality vision testing

Bias for less severely affected

"Current vigabatrin patients have already undergone visual field assessment(s). Since the vigabatrin is withdrawn in most cases where a typical VFD is diagnosed, ***as a consequence nearly all patients remaining under vigabatrin have no VFD***."

Study 4020 steering committee, Sept 1999

Poor Quality Vision Testing

"As a general consideration, the experts stressed the difficulty to obtain perimetries of good quality: only 10% Goldmann and 50-60% suprathreshold and threshold perimetries are of good quality."

Study 4020 steering committee, Oct 1999

High Dropout Rate

- 2,583 patients screened
- 735 enrolled
- 524 with 1 or more evaluable fields
- Little data for each patient:
  - 2 fields: 140
  - 3 fields: 111
  - 4 fields: 81
  - 5 fields: 57

Table 33, 4020 Study Report

Potentially More Reliable Data

- Study R003
  - Prospective study aborted after only 25 patients
- 'Pooled Cohort' Study
  - Cross section of defined patients in vigabatrin studies ongoing when field defect found
- Detailed case series and case reports
  - Miller et al, 1999 Neurology
    - visual acuity and retinal abnormalities
  - Westall (children with CPS and IS)
  - Best and Acheson, 2005 Eye… and others

- **Location: Acuity vs. Field Defect**
- Severity
- Functional effects/disability
- Reversibility
- Stability
- Time to onset and speed of progression
- Dose and Time Effect
- Monitoring and Prevention

Field Defect

- No doubt vigabatrin can cause field defect

Visual Acuity/Central Retina

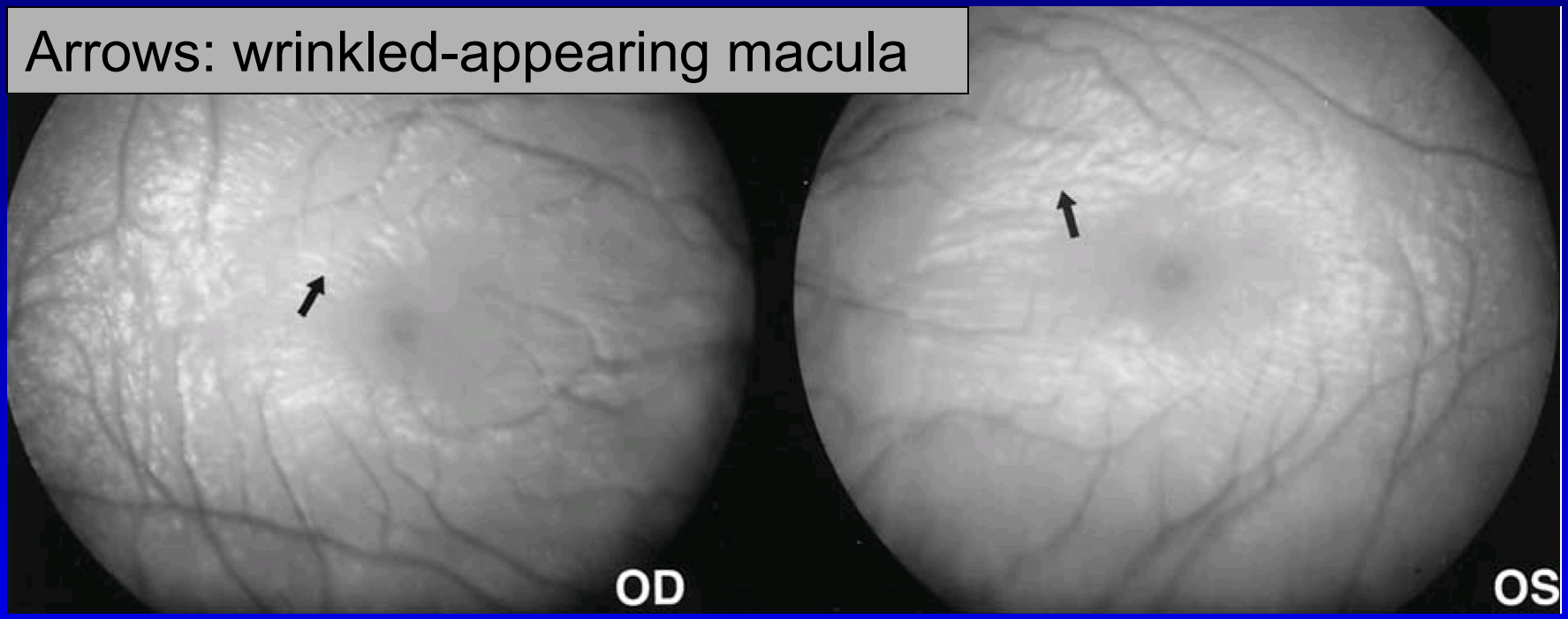
- Not well studied (severity, frequency)
- Published studies indicate damage can occur

Visual Acuity/Central Retina

Miller et al, 1999

- Case series of CPS patients in a sponsor safety study
  - 32 on vigabatrin, mean treatment ≈ 4 years
    - 12 with apparent reduced acuity, to 20/25-20/60
    - 19 with apparent reduced color vision
  - 10 matched controls
    - All normal acuity and normal color vision

Central Retina: Anatomic Damage



10 year old girl, CPS
4 years vigabatrin

Buncic et al., 2004 Ophthalmology (Case 1)

Similar wrinkling reported in adults
Krauss and Miller, 1998 Neurology (Cases 1,2,4)

Damage to Acuity

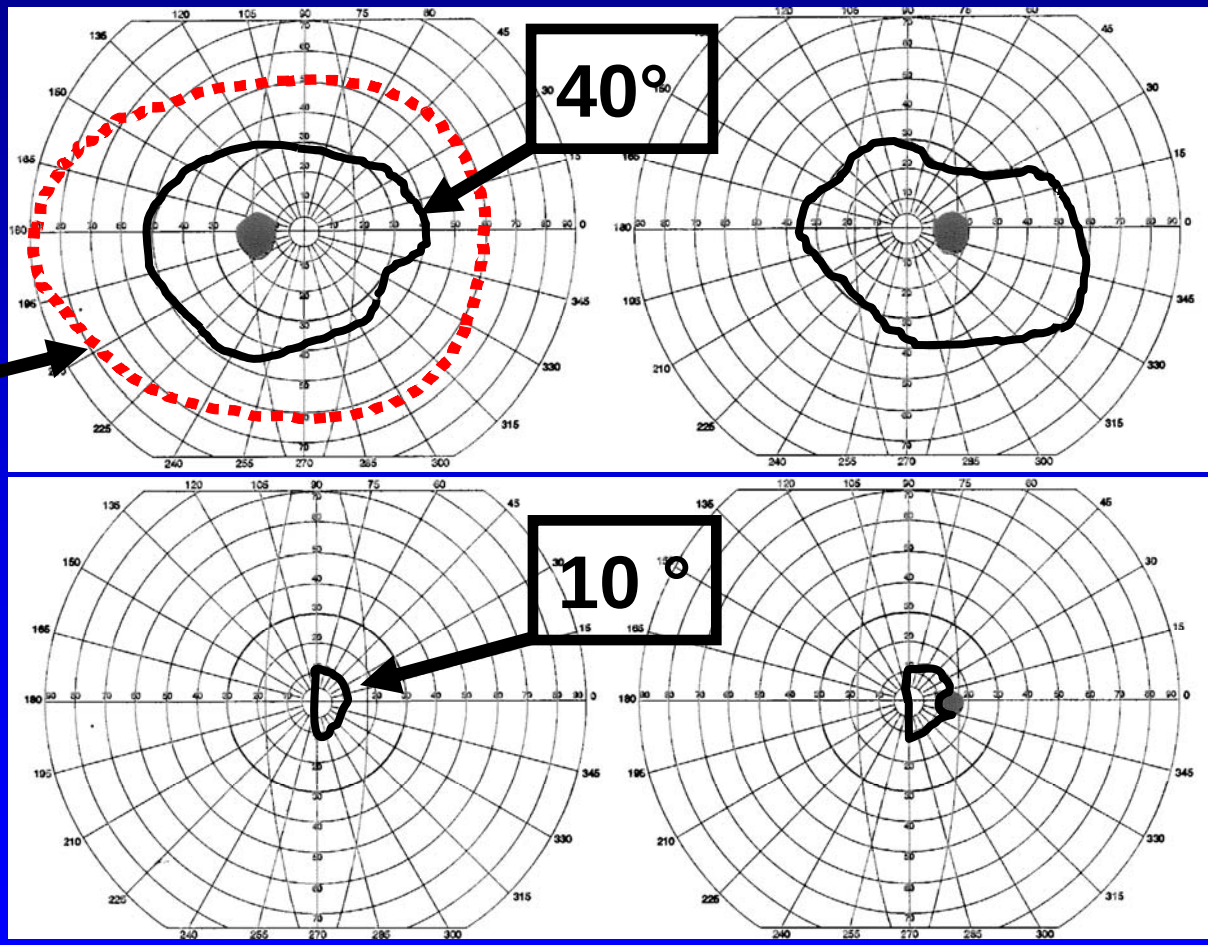
- Even ‘mild’ damage may impair function
- Progressive damage not excluded
- Concern for future additive damage
  - ‘loss of functional reserve’
  - macular degeneration, glaucoma, etc.

- Location
- **Severity**

  <u>Almost all data limited to field constriction</u>
- Functional effects/disability
- Reversibility
- Stability
- Time to onset and speed of progression
- Dose and Time Effect
- Monitoring and Prevention

Field Constriction

- Highly variable
- Mild to severe



With homonymous hemianopsia

Russell-Eggitt et al., Eye 2000

Prospective Trial Data

- Study R003
  - 25 subjects out of planned 200
  - Median cumulative dose 1,100 g
  - Median duration of treatment 500 days
  - 7 patients (28%) developed field defect
  - 6 of 7 before or shortly after 1 year
- 4 of 7 defects ***MILD*** (30-40°)
- 3 of 7 defects ***MODERATE*** (20-30°)

Pooled Cohort Study

- Cross section of patients in vigabatrin studies ongoing when field defect found

  Strengths

  - High proportion of defined cohort tested
  - 454 patients, 64 exposed less than 6 months
  - Unexposed control with low false-positives for field defect

Pooled Cohort Study

Weaknesses

- Field test at single time point
- Field test method not standardized
- Studies had different baseline characteristics
- *Conducted by previous sponsor and documented only in Periodic Safety Update Reports*

Pooled Cohort Study

Field Constriction		
Mild	22%	(N=20)
Moderate	31%	(N=29)
Severe	27%	(N=25)
‘Other cause’ (e.g. glaucoma)	20%	(N=18)

PSUR 5, 1998, page 26 of 33

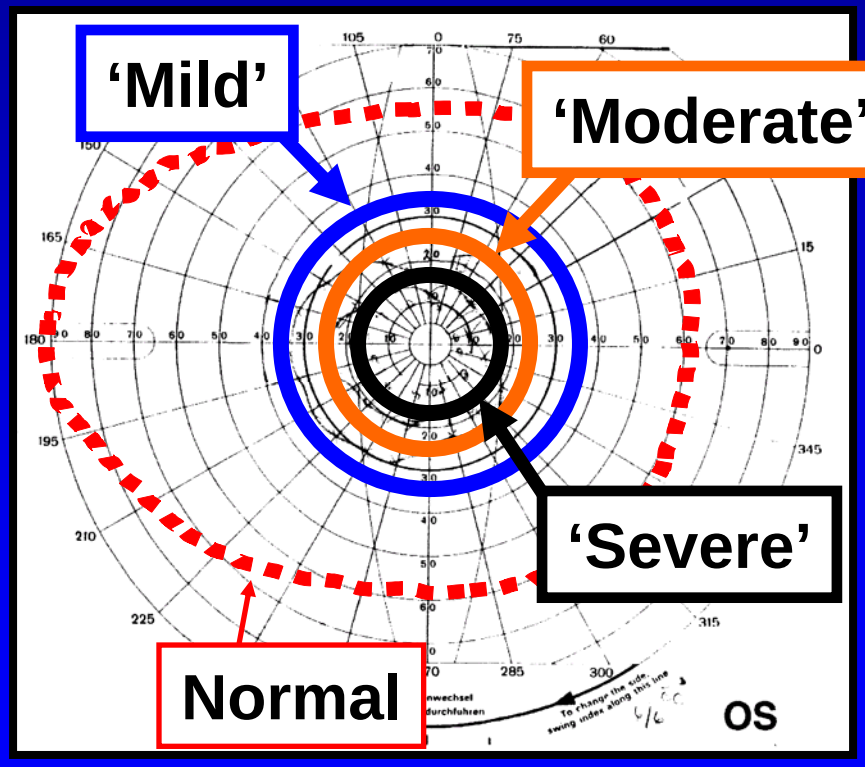
FDA Severity Conclusions

By 5 years,

Roughly 1/3 patients affected

<u>Roughly equal distribution</u>

Mild	30-40°
Moderate	20-30°
Severe	10-20°



- Location
- Severity
- **Functional effects/disability**
- Reversibility
- Stability
- Time to onset and speed of progression
- Dose and Time Effect
- Monitoring and Prevention

Functional Affects/Disability

- Reliable data not available for vigabatrin
- ‘Asymptomatic’ ≠ clinically insignificant
  - Insidious loss of any function often difficult for patients to appreciate
- Symptoms attributed by some patients to other causes
  - Clumsiness, drowsiness

Estimate of Disability from Visual Field Defect

- Field Severity
  - Mild — Inability to drive car
  - Moderate — Bump into objects, ‘clumsiness’
  - Severe — Difficulty with daily activities
- Most patients remain able to do household chores, shopping, necessary business

- Location
- Severity
- Functional effects/disability
- **Reversibility**
- **Stability**
- Time to onset and speed of progression
- Dose and Time Effect
- Monitoring and Prevention

Reversibility

- Visual damage essentially irreversible
- Rare reports of partial improvement

Stability

Two distinct questions:

Stability with continued vigabatrin use

Stability after stopping vigabatrin

Continued Use

- Most data is cross sectional
  - Fundamentally can't address if vision continues to decline if continue vigabatrin
- Lack of accurate, long term visual field testing required to address question

Continued Use

- Study 4020
  - 35% (12/33) progressed on vigabatrin
  - 13% (3/17) progressed who ***never took***
    - Likely false-positive/background noise

Qualitatively, progression with continued use

Continued Use

- Little evidence of field defects closer than ≈10 degrees of fixation…
- However, may be diagnostic bias
  - Vigabatrin ‘not supposed’ to cause central loss
  - *Vigabatrin patients with central loss reported*
    - Diagnosed with macular degeneration or glaucoma

Diagnostic Bias?

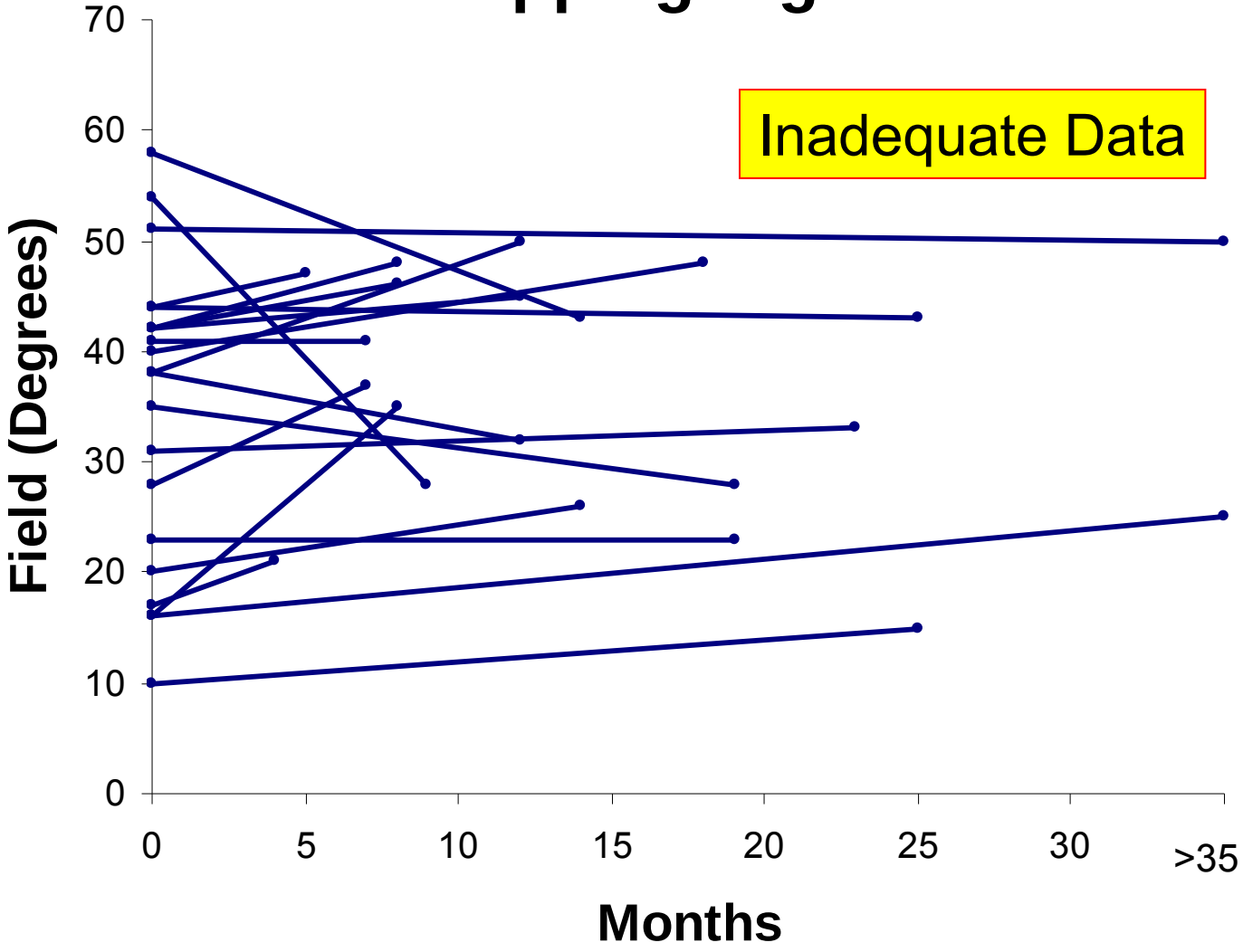
- A 60 year old many taking VGB 2 g/day for 5 years developed 'senile macular degeneration.' Other findings included abnormal color vision and bilateral visual field constriction.

Patient 199710611

Progressive Vision Loss After Stopping

- *Even slow progression after stopping vigabatrin would greatly increase risk*

Change in Visual Field After Stopping Vigabatrin?



Newman et al., 2002, Eye 16:567-571

Progressive Vision Loss After Stopping

- In *most* patients vision does not *rapidly* deteriorate after stopping VGB
- However, there are cases of apparent progression

- Location
- Severity
- Functional effects/disability
- Reversibility
- Stability
- **Time to onset and speed of progression**
- Dose and Time Effect
- Monitoring and Prevention

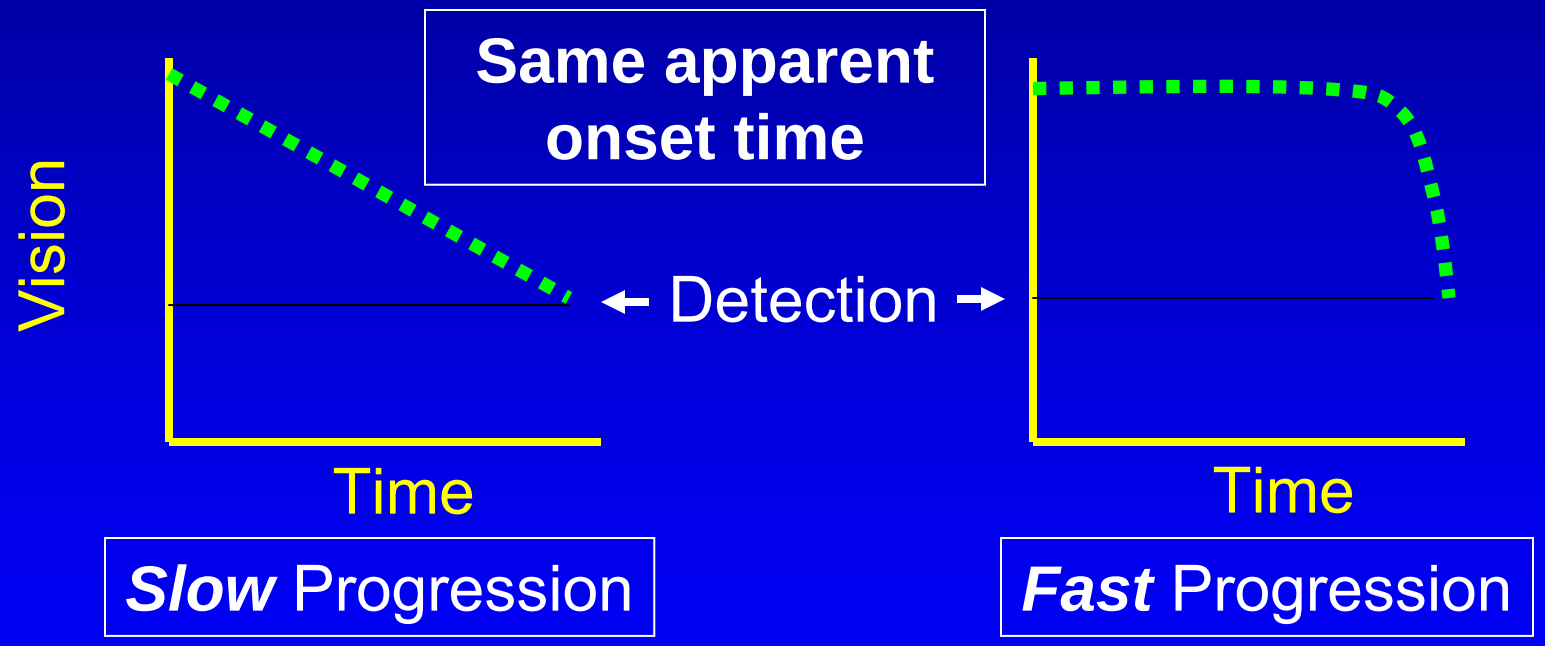
Timing of Ophthalmic Damage

- Available studies, by design, poorly address time to onset and speed of progression
- Most patients treated years before study entry
- Mainly cross-sectional data
- Prospective longitudinal data needed to answer

‘*Time to Onset*’

Versus

‘*Speed of Progression*’



Time to Onset

- Prospective study R003
  - 25 subjects
  - 7 patients (28%) developed field defect

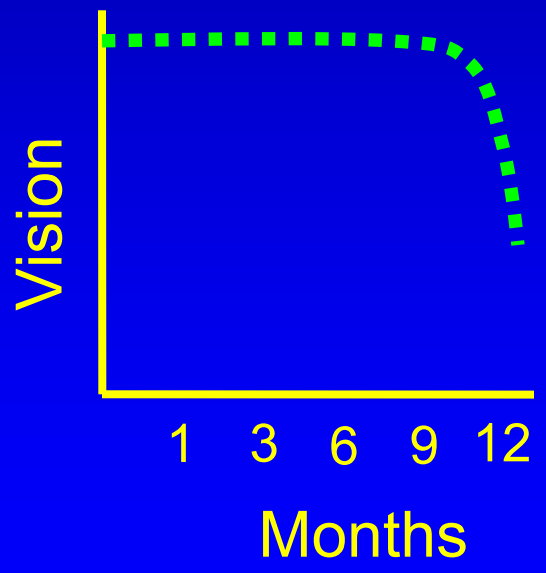
1 after ≈2 months treatment

5 before or shortly after 1 year

Speed of Progression

- *Study R003*
- ***Vision testing every 3 months***
- 3 of 7 defects not detected until '**moderate severity**'

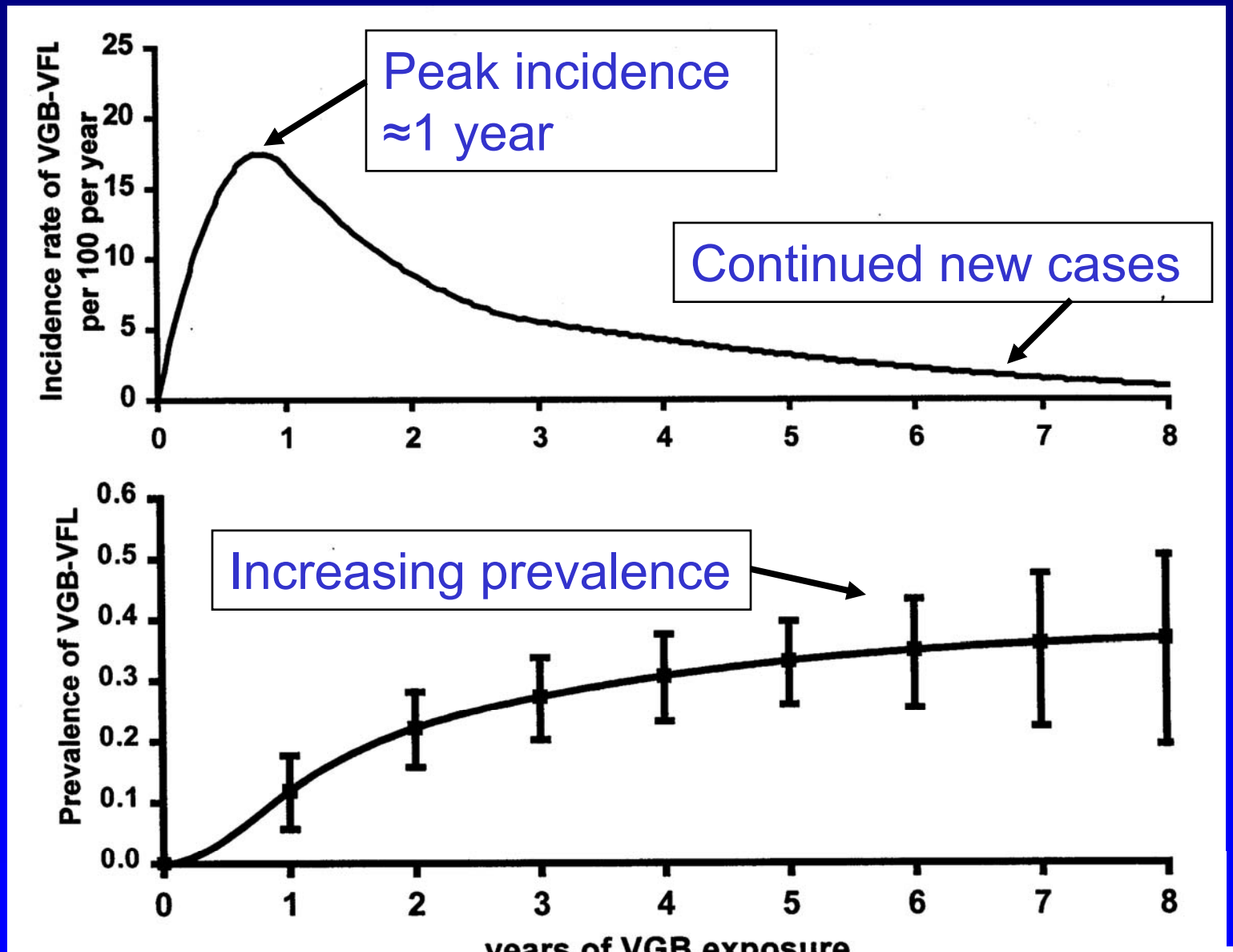
Element of '*Sudden*' Progression?



‘Pooled Cohort’ Study

- Cross section of patients in vigabatrin studies ongoing when field defect found
- Previous sponsor modeled incidence of field loss
  - by study design *ongoing*, not new defects detected

Incidence and Prevalence

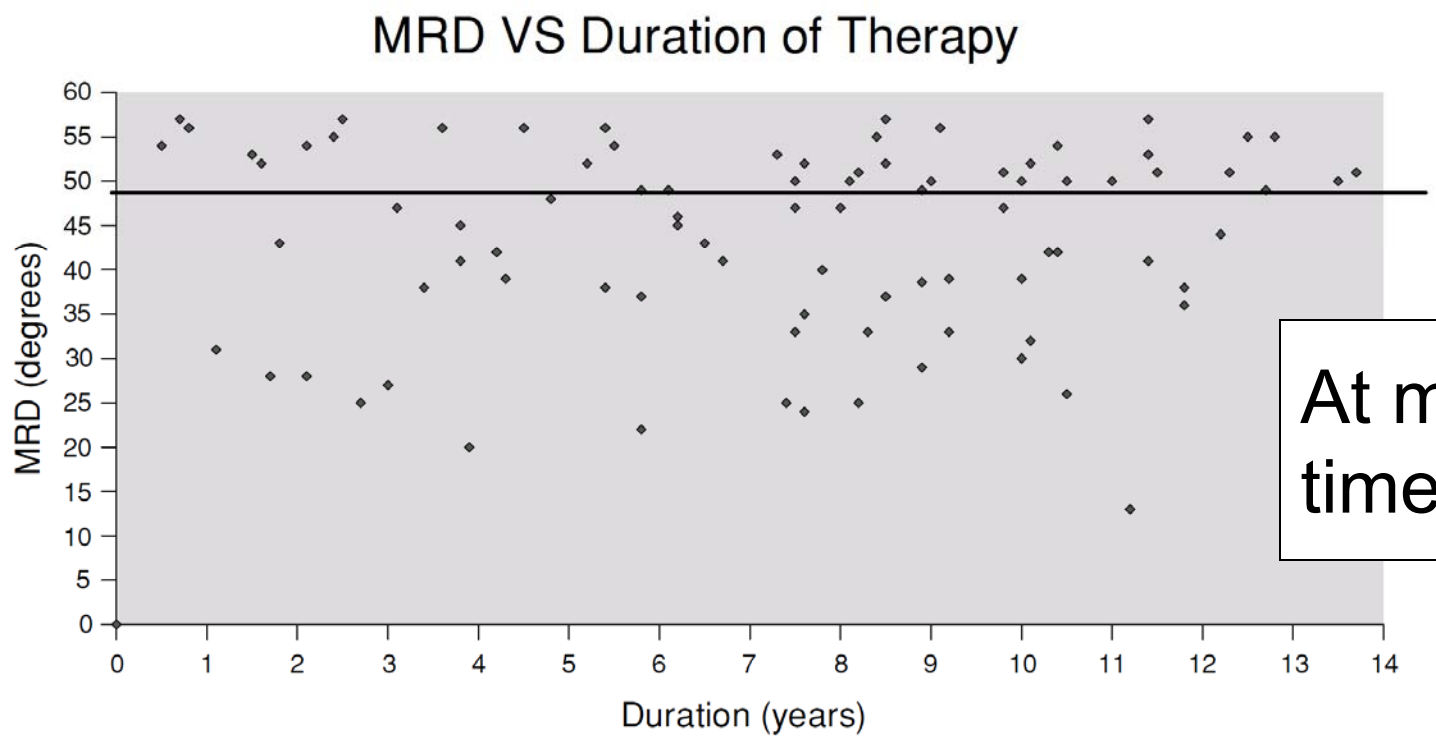


PSUR 7, pg 486

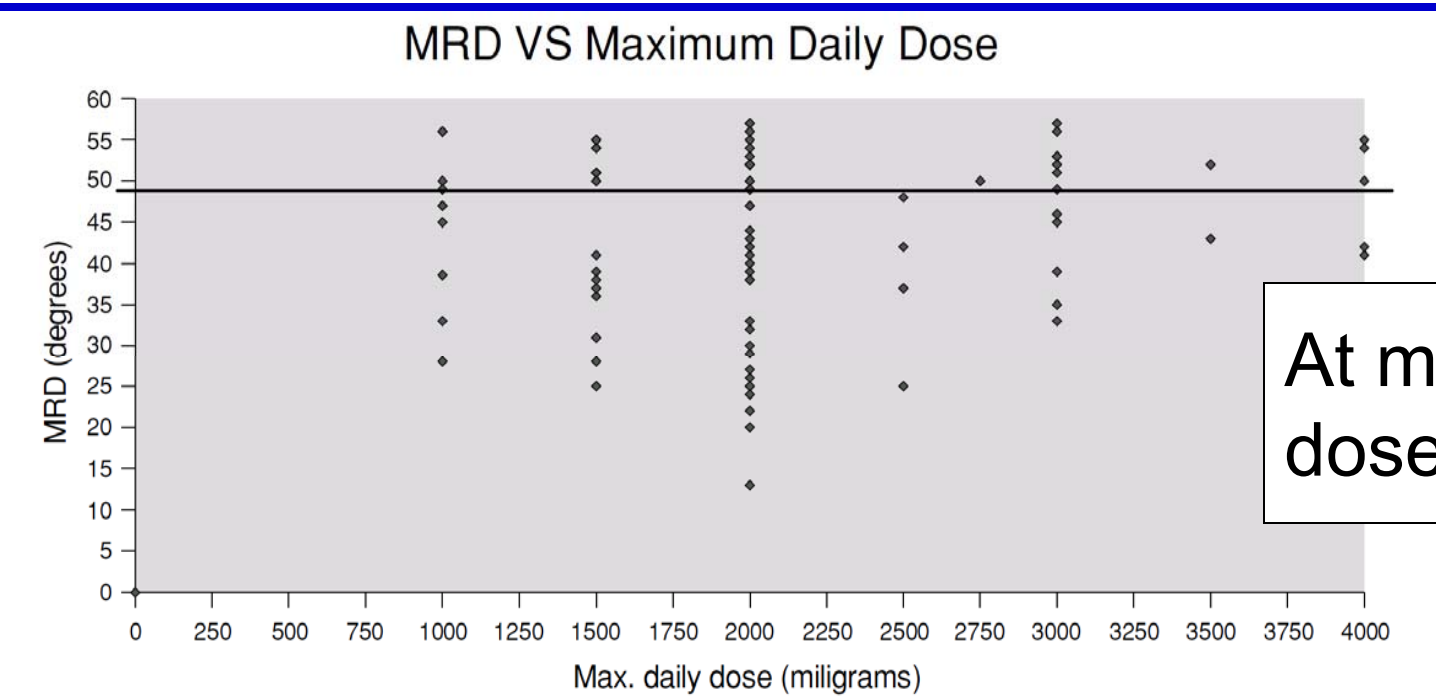
Conclusions: Time to Onset

- *Detected* at < 2 months in some patients
- Peak incidence at ≈1 year

- Location
- Severity
- Functional effects/disability
- Reversibility
- Stability
- Time to onset and speed of progression
- **Dose and Time Effect**
- Monitoring and Prevention



At most weak time Relationship



At most weak dose Relationship

Kinirons et al., Epilepsia, Vol. 47, No. 2, 2006

Conclusions: Exposure

Over range of doses with data available…

- High risk even with ‘short’ use
- High risk even with ‘lower’ dose

- Location
- Severity
- Functional effects/disability
- Reversibility
- Stability
- Time to onset and speed of progression
- Risk Factors
- **Monitoring and Prevention**

Monitoring and Prevention

- Adults and older children
  - Direct testing of field (perimetry) and acuity
- Young children and patients that can't perform subjective tests
  - Electroretinography most used
  - Little data about other methods

Monitoring and Prevention

Little evidence about testing to *prevent* damage

Preventing damage more difficult than *Detecting* damage

Visual Field Testing

"The results of perimetry can often be inconclusive and frequently require one or more confirmatory repeat examinations, even though the results of the subsequent tests can remain equivocal"

Wild, JM. Et al, Invest. Ophth. Visual Sci 2006

Perimetry

- Subjective
- Demands concentration and attention
- Particularly difficult for patients with any degree of cognitive impairment
- Epilepsy patients appear to perform test less well
  - Potentially 20% not monitorable by perimetry

Harding et al., Neurology 2000

Perimetry

- A learned skill
- First several tests often unreliable
- Field expected to ‘increase’ over several tests as patient skill increases
  - High risk of inaccurate baseline
  - Confounds early diagnosis

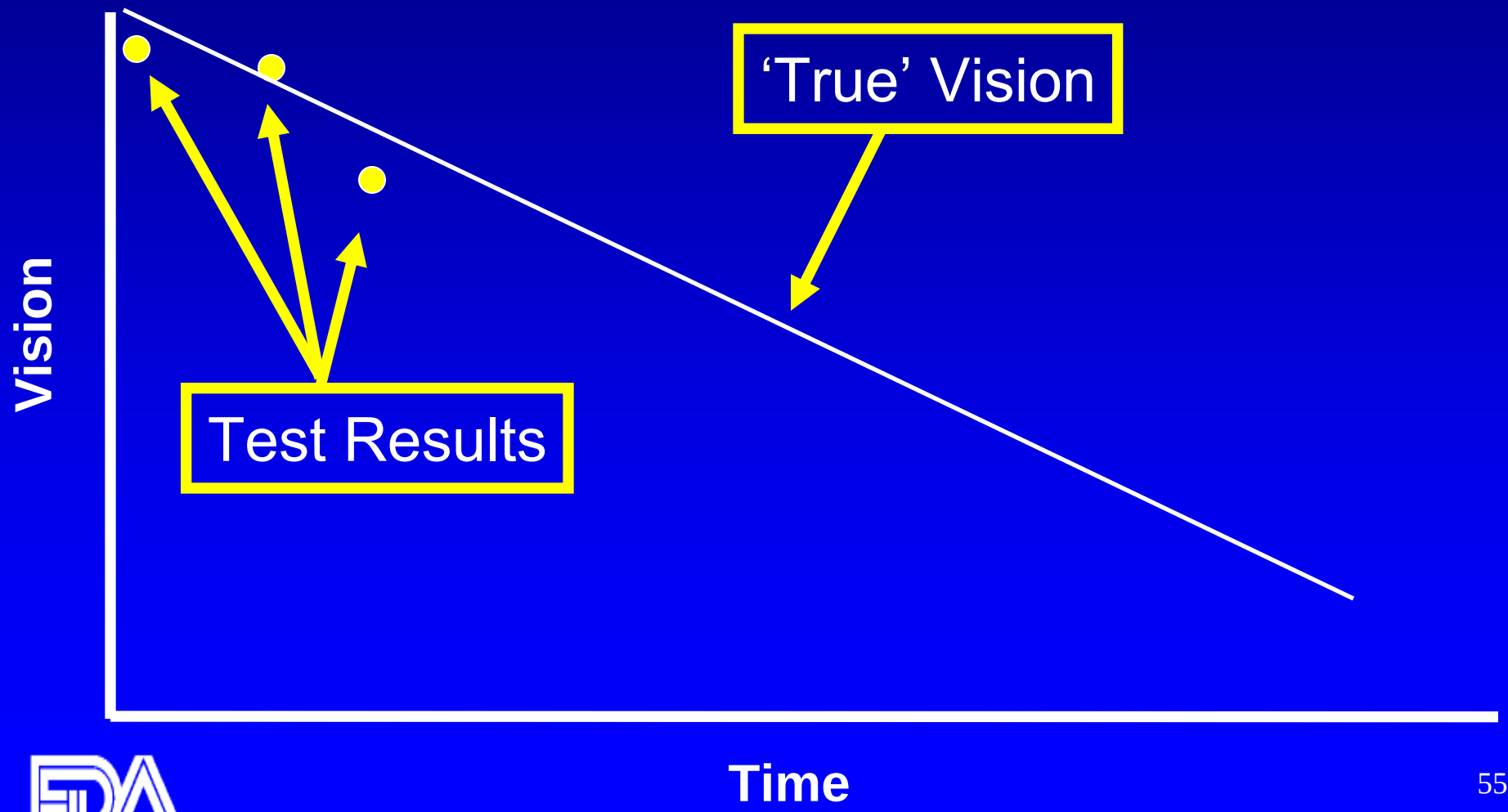
Perimetry

- Critical variables for prevention
  - Time course of damage

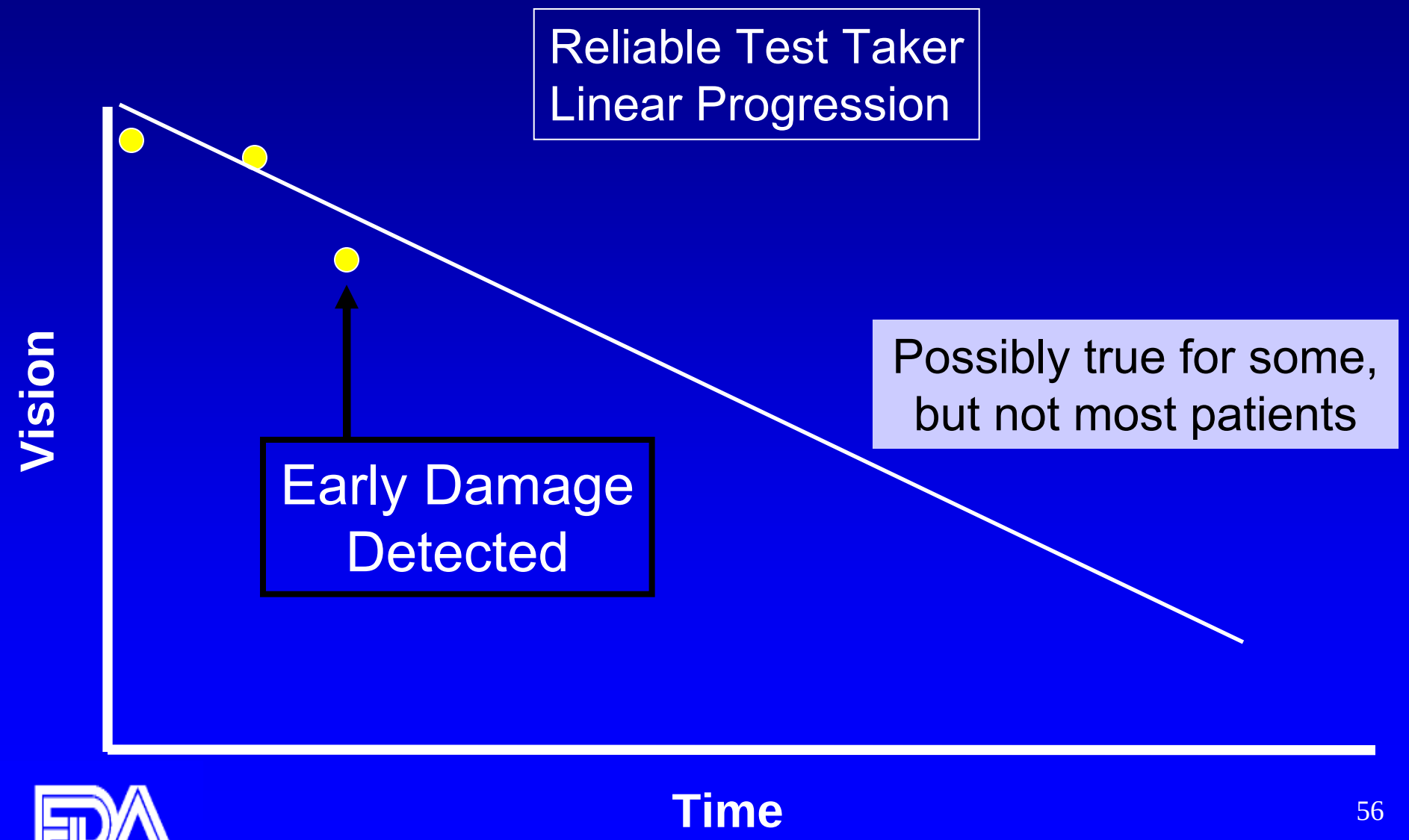
    '*Prevention* window'

  - Test sensitivity, specificity, etc.
  - Test frequency

Perimetry: Possible Results

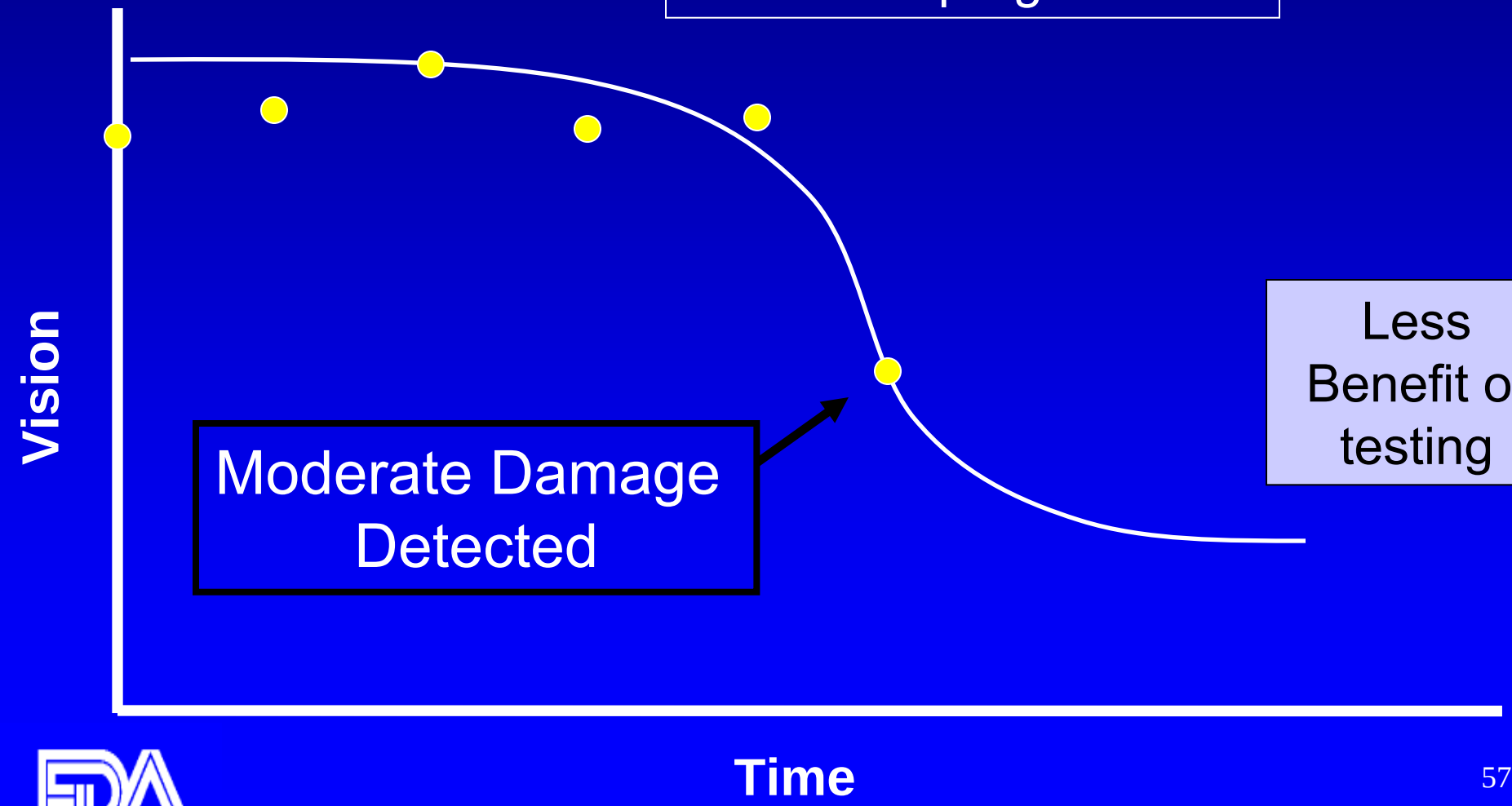


Perimetry: Possible Results



Perimetry: Possible Results

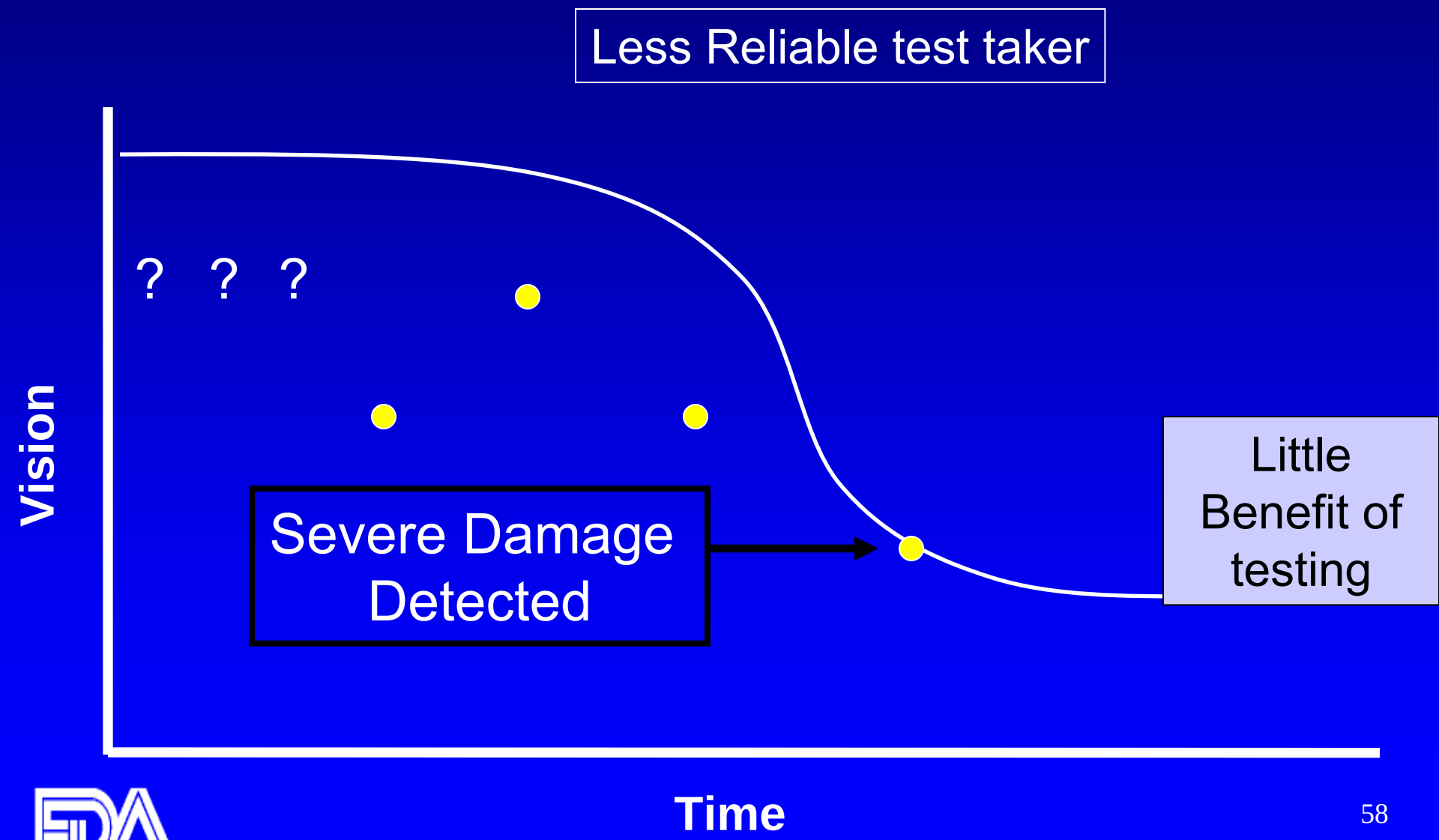
Reliable test taker
Non-linear progression



Moderate Damage Detected

Less Benefit of testing

Perimetry: Possible Results



Monitoring and Prevention

- Patients that can't perform perimetry:

Electroretinography (ERG), 30 Hz flicker

- Sponsor: "the most sensitive and specific index of retinal injury underlying peripheral VFD"

ERG Sensitivity Appears Poor

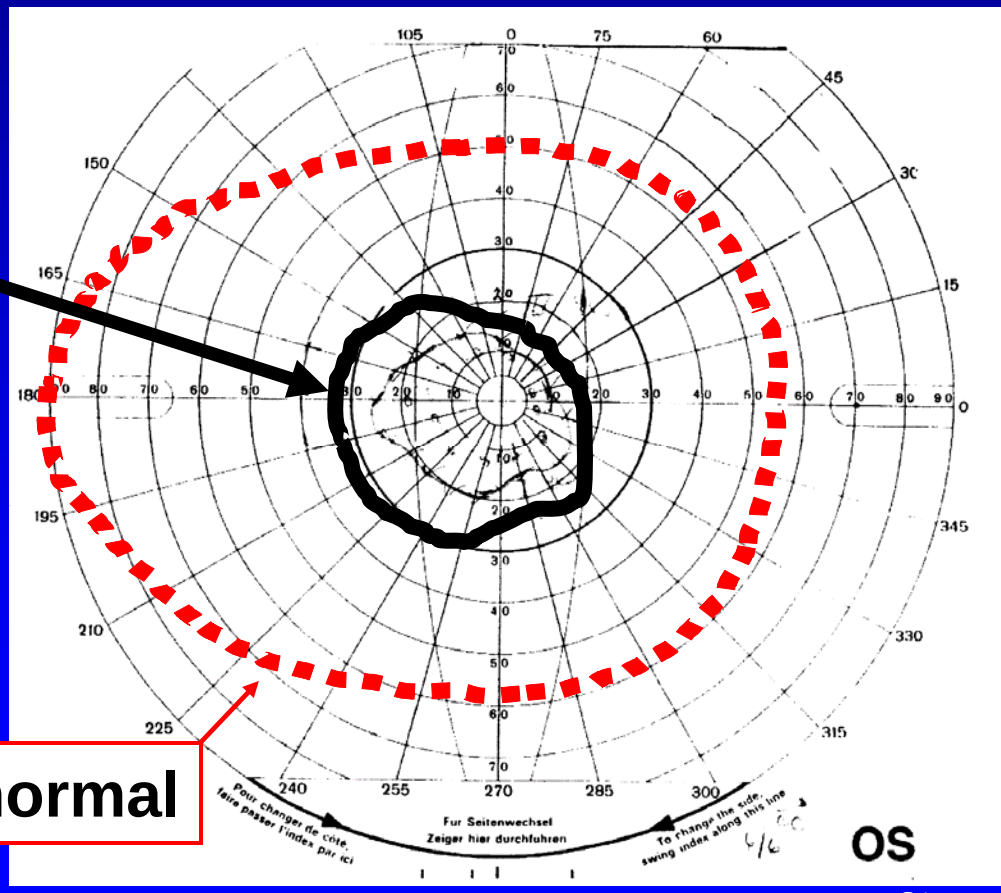
- Study R003
  - 0 of 4 patients with mild damage detected by ERG
  - 1 of 3 patients with moderate damage detected

ERG Sensitivity Appears Poor

- 10 year old girl, CPS
- 4 years vigabatrin

Severe field constriction

NORMAL 30 Hz ERG



Case 1, Toronto Group (Buncic et al., 2004)

Summary and Conclusions
Vigabatrin Visual Damage in CPS

Summary and Conclusions Adults with CPS

- Vigabatrin causes visual field constriction
  - Onset and progression variable, unpredictable
  - 1/3rd or more affected after several years
    - about equal proportion mild, moderate, severe

Summary and Conclusions Adults with CPS

- Damage to central vision probably occurs
  - little data on severity and frequency
- Progressive damage after stopping drug
  - Inadequately studied
  - Potential large clinical consequence

Summary and Conclusions Adults with CPS

- Visual disability occurs, but largely unstudied
- Even in patients that fail to spontaneously recognize vision loss, disability can be present

Summary and Conclusions

- Peak incidence of visual damage at ≈ 1 year
- Onset at a few weeks or months not rare
- Weak time and dose dependence
  - No safe exposure time or dose known

Summary and Conclusions

- Safety monitoring
  - FDA unaware of way to reliably prevent damage
  - FDA unable to propose sound monitoring plan