Visual Function Endpoints in Clinical Trials

Clinical View

Eberhart Zrenner
Center for Ophthalmology
Institute for Ophthalamic Research
University of Tübingen
Germany

Content

Aim: Endpoints that assess Safety, Benefit, Reliability, and are feasible

- Basics: Structure and Function
- Function Testing: Psychophysics in Ophthalmology
- Function Testing Electrophysiology in Ophthalmology
- Retinal Imaging
- Assessing Activities of Daily Living
- Patient Reported Outcomes (PRO) of Visual Function
- Examples from Ongoing Studies

Financial Disclosure

The author performs or performed advisory tasks during the 5 most recent years for Acucela, Allergan, Bayer, Boehringer Ingelheim, Merck, Neurotech, Pfizer, Retina Implant AG, Servier and QLT; he is shareholder of Retina Implant AG and inventor on patents concerning electronic subretinal implants.
**Retinal Structure and Function**

Rod Photoreceptors
- High sensitivity
- Low spatial resolution
- No colour discrimination

Cone Photoreceptors
- Low sensitivity
- High spatial resolution
- Colour discrimination

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**The Phototransduction process: many things can go wrong**

Rhodopsin

[Image: Courtesy of W. Baehr]

**The Short, Middle and Long Wavelengths Sensitive Cones**

[Cone Mosaic in the Fovea]

[Image: Courtesy of T. Sharpe]

[Image: Courtesy of H. Waessle]

From: J. Dowling: The Retina. 1987

(courtesy of Paul R. Martin, 1998)

"Brightness Channel"

"Darkness Channel"

Information Processing in the Retina

~ 120 million photoreceptors

[Image: "the natural computer"

↓↓

~ 1 million ganglion cell fibres sending pulses to the brain

[Image: "ON"

"Brightness Channel"

"OFF"

"The natural computer"

[Image: Courtesy of Paul R. Martin, 1998]
Visual Acuity, Refraction, Anterior segment Examination

Reading speed, Pupil, Eye movement intracocular pressure

Colour vision

Cones

VEP

Functional Diagnostics
Best Corrected Visual Acuity (BCVA)

- Snellen chart
- ETDRS chart (Standard)
- Freiburg Visual acuity Test (FRACT) with Landolt C-ring
- Computer-Screen test

IOVS (2006) 47:1236-1240
Functional diagnostics

Color vision testing
- Colour vision: arrangement test
- Lanthony Panel D-15 test
- Roth 28-hue Test
- Farnsworth-Munsell 24 or 100 Test
- Anomaloscopy

WEB based evaluation tool: [http://www.torokinfo/colorvision/dir_for_use.htm](http://www.torokinfo/colorvision/dir_for_use.htm) (Dr. Bela Török)

Contrast Vision
- Pelli-Robson Chart
- Mesoptometer
  - With and without glare
- Hamilton Veale Test

Visual Field testing
- Static perimetry 30°
- Kinetic perimetry 90°
- Microperimetry
  - Central Vision
  - Eye Movement Compensated
Functional diagnostics:

- **Dark Adaptation**
  - Adaptometer (Roland Consult)

- **Pupillography**
  - Relative Afferent Pupillary Defect (RAPD)
  - Pupillography

**Summary 1**

**Psychophysics**

<table>
<thead>
<tr>
<th>Table 1.1: Functional 'markers' of the various circuits and cell populations of the visual system assessed by psychophysical and behavioral methods. (Adapted from: Wilkins DR, Principles of Ocular Pharmacology, 1990.)</th>
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</thead>
<tbody>
<tr>
<td><strong>Psychophysics</strong></td>
</tr>
<tr>
<td>Visual Acuity</td>
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<tr>
<td>Color Vision</td>
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**Surrogate Endpoints**

- A surrogat endpoint, according to the FDA, is a biomarker that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit." The best surrogate endpoint is a biomarker that changes along with clinical endpoints.
Clinical Electrophysiology of the Visual System

Electroretinogram (ERG)

Visually evoked potentials (VEP)

Multifocal ERG (mfERG)

Pattern ERG (PERG)

Electrooculogram (EOG)

Inner Retina

Electroretinogram: sites of action

DNL

Fibre Electrode

Jet Electrode

Multifocal ERG (mfERG)

5. Cone flicker Responses

ISCEV Standard Ganzfeld ERG

1. Isolated rod responses

2. Rod and cone Max. Responses

3. Inner Retina OPs

4. Isolated Cone Responses

5. Cone flicker Responses


For further information see: www.iscev.org
Example: Effects of Zatebradine, an \( I_{\text{Na}} \) channel blocker, 2.5 mg/kg, on flicker ERG.


Assessing the RPE / Photoreceptor complex:

ERG amplitude recovery after bleaching

If retinoid cycle is affected, time to reach threshold during dark adaptation may be useful after a bleach of 400 cd/m² (30 s).

Assessing the RPE / Photoreceptor complex:

Retinal visual cycle: all-cis-retinal is photoisomerized to all-trans-retinal and reconstituted to 11-cis-retinal. Formation of RPE lipofuscin is almost completely dependent on normal visual cycle function.
Multifocal ERG (mfERG) allows to electrically map retinal sensitivity.

Visually evoked cortical Potentials (VEP)

Retinal imaging

- Color photographs – posterior pole and periphery
- Fundus autofluorescence imaging (FAF)
- Fluorescence Angiography (FA)
- Optical coherence tomography (OCT)
Patient Reported Outcomes (PRO)

- A PRO is a measurement of any aspect of a patient’s health status that is reported and or scored directly by the patient, free of interpretation by a physician, researcher or other person. It is an account of how the patient functions or feels relative to a health condition or therapy.

- Good measurements should have unidimensionality, hierarchical order, and equal interval spacing.

Patient Reported Outcomes (PRO)

A PRO would measure any of the following:
- Symptoms
- Symptom impact and functioning
- Disability or handicap
- Adverse events
- Treatment tolerability
- Treatment satisfaction
- Health-related quality of life

PRO: Available instruments

- Activities of Daily Living Scale (ADLS)
- Reading, orientation/mobility, finding objects, social participation, financial handling
- Daily Living Tasks Dependent on Vision (DVT)
- Impact of Vision Impairment (IVI)
- Muscular Disease Quality of Life Questionnaire
- NEI-VFQ 25 (most common, well-equipped)
- Vision Factor Index (VF-14)
- Visual Function Index (VF-14)

Low-Luminance Questionnaire (LLQ)
- Miedziak’s instrument
- Vision-specific sickness impact profile (SSIP)
- Turano’s instrument
- VISION-Related Quality of Life Questionnaire
- Retinopathy-Dependent QOL
Ongoing Clinical trials in legally blind patients

Upcoming Clinical trials in legally blind patients

Relevant studies

Subretinal electronic implants

Safety and Efficacy of Subretinal Implants for Partial Restoration of Vision in Blind Patients (Zrenner)

- **Primary Outcome Measures:**
  - Activities of daily living and mobility significantly improve with implant-ON shown via activities of daily living tasks, recognition tasks, mobility, or a combination thereof.

- **Secondary Outcome Measures:**
  - Visual acuity/light perception and/or object recognition measured with TACT/BaLM/BaGA/VFQ-25.
  - Patient long term safety and stability of implant function.


Functional diagnostics in subretinal electronic Implants

- BaLM (basic light and movement test)
- BaGA (recognition of stripe patterns)

Functional diagnostics in subretinal electronic implants

- Tasks of daily living (more naturalistic scenes)

Gene therapy dramatically improves rod light sensitivity

U. Penn US study

Cideciyan et al., PNAS 2008;105:15112

Summary

- Monitoring of visual function for safety and efficacy in very low and ultra-low vision patients is difficult
- The tools are there, but have to be selected depending on the cellular target structure
  - Psychophysics
  - Electrophysiology as surrogate marker
  - Retinal imaging as surrogate marker
  - Assessment of Activities of Daily Living (ADL)
  - Patient Reported Outcomes (PRO) of visual function
- Some of the ongoing studies have developed novel tests in order to monitor ultra-low vision changes which, however, are not yet validated

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