Study of visual field defects in patients with epilepsy receiving Vigabatrin

Pedro Antonio Gonzalez

.

Submitted for the Degree of M.D.

University of Glasgow

Electrodiagnostic Imaging Unit

Tennent Institute of Ophthalmology

Glasgow

June 2007

Abstract

Vigabatrin, a GABA (γ-aminobutyric acid) agonist is a drug widely prescribed in Europe and Asia between 1989 and 1997 for drug resistant, partial epilepsy and has been associated with visual field defects. Uncertainity in the effect of Vigabatrin on vision resulted in decreased prescriptions. However, there has been poor reproducibility in previous studies due to many factors, especially poor sensitivity and specificity of tests for Vigabatrin associated visual dysfunction. The wide field multifocal electroretinogram (WF-mfERG) can objectively measure discrete areas of retinal function up to 90 degrees. The results of 204 patients with epilepsy divided into four groups are presented. A subgroup of 89 patients had repeat investigations. The patients were divided into four groups.

Group 1.The Vigabatrin group comprised patients who had been taking Vigabatrin for at least 1 year (56 patients).

Group 2. Forty nine patients who had previously taken Vigabatrin for at least 1 year but had stopped taking this treatment for at least 2 years comprised the ex-Vigabatrin group.

Group 3.The GABA group had 46 patients who used other anti-epileptic drugs (AED) with GABA action other than Vigabatrin.

Group 4. Fifty three patients who had never used an AED with GABA action including Vigabatrin made up the non-GABA group.

Surprisingly, the percentage of patients with visual field defects were high in all groups investigated (Vigabatrin group 59%, ex-Vigabatrin group 46%, GABA group 30.2% and non-GABA group 21.2%). However, abnormal bilateral WF-mfERG responses were only found in the Vigabatrin group

(48%) and the ex-Vigabatrin group (22%). The study suggests that there are probably different causes of visual field abnormalities in patients with epilepsy not related to Vigabatrin.

We propose that the most sensitive and specific tests that can be used to detect visual dysfunction associated with Vigabatrin is the WF-mfERG

List of Contents

Chapter 5 Vigabatrin and electrophysiology

Chapter 6 Clinical findings of Vigabatrin

Chapter 7 Retinal toxicity and visual field defects

Chapter 8 Multifocal Electroretinogram

Chapter 9 Materials and Methods

Chapter 10 Results

Chapter 11 Final Discussion

Chapter 12 The Future

List of Publications and presentations

'Progression of neuro-retinal toxicity in patients on Vigabatrin; objective assessment using the wide field multifocal electroretinogram'
Gonzalez P, Parks S, Kelly K, Brodie M
Epilepsia Volume 45, supplement 7, 2004, 188:B.07

'The effect of pupil size on the multifocal electroretinogram'
Gonzalez P, Parks S, Dolan F, Keating D
Documenta Ophthalmologica 109: 67-72, 2004

"Is peripheral retinal dysfunction a reason for stopping Vigabatrin?"
Gonzalez P, Keating D, Brodie MJ, Parks S.
The Association for Research in Vision and Ophthalmology May 2004.

'Progression of neuro-retinal toxicity in patients on Vigabatrin; objective assessment'
Gonzalez P, Keating D, Brodie MJ, Parks S.
International Society of Clinical Electrophysiology in Vision, Puerto Rico 2004 – Dcocumenta Ophthalmologica

'Neuro-retinal toxicity with Vigabatrin: What is the story'
Gonzalez P, Keating D, Brodie MJ, Parks S.
American Journal of Ophthalmology 221(Suppl): 215-216, 2005

'Progression of neuro-retinal toxicity in patients on Vigabatrin; objective assessment'
Gonzalez P, Keating D, Brodie MJ, Parks S.
International Society of Clinical Electrophysiology in Vision, Puerto Rico 2004

'The assessment of neuro-retinal toxicity in patients with epilepsy on Vigabatrin'
Gonzalez P, McCall A, McQuiston A, Keating D, Kelly K* Brodie MJ* Parks S.
International Society of Clinical Electrophysiology in Vision, Glasgow 2005

'The Influence of Latitude on Vigabatrin Induced Neuroretinal Toxicity'
Gonzalez P
British Society for Electrophysiology, Glasgow 2005

'Progression of neuro-retinal toxicity in patients on vigabtrin'
Gonzalez P, Kelly K, Parks S, Brodie MJ
Scottish Epilepsy Research Conference Dundee 2005

'The monitoring of retinal toxicity with the wide field multifocal electroretinogram'
Gonzalez P, Kelly K, Parks S, Brodie MJ
Scottish Epilepsy Nurse Meeting 2005

'My experience in Research as a Clinician'
West of Scotland Post-graduate Meeting, Glasgow 2006

'Neuro-retinal toxicity with Vigabatrin: Where we are now'

Gonzalez P, Keating D, Brodie MJ, Parks S.
368 – B287
SERI-ARVO meeting on Research in Vision and Ophthalmology, Singapore 2005

'The effect of pupil size on the multifocal electroretinogram'
Gonzalez P, Parks S, Dolan F, Keating D
4246 – B707
The Association for Research in Vision and Ophthalmology, Ft. Lauderdale, 2004

'Is peripheral retinal dysfunction a reason for stopping Vigabatrin?'
Gonzalez P, Parks S, Keating D, Brodie M
4552-B910
The Association for Research in Vision and Ophthalmology, Ft. Lauderdale, 2005

'Assessing retinal toxicity of Vigabatrin and other GAGA-ergic drugs in patients with epilepsy'
1658-B521
Gonzalez P, Parks S, Keating D, Brodie M
The Association for Research in Vision and Ophthalmology, Ft. Lauderdale, 2006

'Acumulated load of Vigabatrin in the development of retinal toxicity'
Gonzalez P, Parks S, Keating D, Brodie M
1251-B210
American Academy of Ophthalmology, Las Vegas 2006

List of Figures

List of Tables

Dedication

To Elsie, Rita, Arthur, Shelisa and Gillian

My long suffering family for putting up with me

Quotation

"Judge of a man by his questions rather than by his answers"

Voltaire

French author, humanist, rationalist, & satirist (1694 – 1778)

Chapter 1

Summary

Epilepsy is a common disabling neurological condition in the world.

Epileptic seizures are symptoms experienced or demonstrated in someone who has episodes of abnormally increased electrical activity in the brain. In the brain regulatory inhibitory mechanisms normally prevent this excess activity. Such mechanisms include dampening of synaptic conduction by neurotransmitters such as γ-aminobutyric acid (GABA). Vigabatrin enhances GABA inhibitory action by irreversibly binding to a degradatory enzyme (GABA-transaminase) increasing GABA levels in the brain (as well as other parts of the body, such as the retina) thereby decreasing the occurrence and spread of seizures in some patients.

Epilepsy will not be fully controlled in 25-30% of cases. For everyone, the search for additional effective and well tolerated anti-epileptic drugs is an important one.

Vigabatrin was found to be in an excellent drug in patients with drug-resistant partial seizures and in infantile spasms and was widely prescribed. Since 1997, seven years following its licence being issued, there have been many reports of visual field defects occurring in some patients on Vigabatrin resulting in dramatic decrease in prescribing.

A literature review has also shown discrepancy on the aetiology, prevalence and contributing factors in patients with visual field defects. As will be explained Vigabatrin has complex actions on the retina that are reversible and irreversible, both with acute and chronic effects. Hence separating the chronic permanent changes which is predominantly represented by visual field defects from acute reversible changes is difficult.

The clinical picture is further complicated by the difficulty in separating the actions of Vigabatrin from those of increased GABA levels since Vigabatrin increases GABA levels and it is difficult to separate the actions of these two compounds.

Other unknown factors may prove to be important. A recent study by Izumi has indicated that high light levels may be significant.(1)

There are other problems: people with epilepsy have poor attention and concentration which may make subjective testing difficult.

The results of visual field testing and even changes in objective tests such as electroretinograms (ERG) and multifocal ERG (mfERG) reflect the multiple physiological/pathological processes occurring at the same time making it difficult to draw reliable conclusions form the data gathered.

The ERG is a mass electrical response of the retina to light stimulation. The method of recording the electrical response is by stimulating the eye with a bright light source such as a flash produced by a Ganzfeld bowl. The intense flash of light elicits a biphasic waveform recordable at the cornea (a-wave and b-wave). Measurement of the amplitude and latency of the a-wave and b-wave using light flashes of different intensities in dark adapted and light adapted eyes provides information global retinal function. The international Society for Clinical Electrophysiology of Vision (ISCEV) sets standards for stimuli and recording responses. Responses are normally divided into rod, maximal, oscillatory potential, cone and flicker responses. Previous studies using the ERG to examine the retina in patients taking Vigabatrin have shown multiple abnormalities including decreased oscillatory potential amplitude, reduced cone b wave amplitude and decreased flicker amplitudes indicating global retinal dysfunction associated with Vigabatrin use. Unfortunately authors have disagreed on the significance of the ERG parameters in the development of visual field defects.

Vigabatrin is as an effective AED but may be unsafe. Therefore we need to clarify the causes and possible prevention of the visual field defects.

The National Institute on Drug Abuse is interested in evaluating the safety and efficacy of Vigabatrin for the treatment of cocaine and methamphetamine dependence. Studies with Vigabtrin have been fast tracked by the U. S. Food and Drug Administration (FDA). There are currently no medications approved by the FDA for the treatment of cocaine and/or methamphetamine dependence which have substantial negative public health impacts. We need to find an effective way ofpreventing the development of visual field defects.

Vigabatrin may predominantly affect the peripheral retina. Multifocal ERG (mfERG) is an objective technique in which simultaneous recording of a collection of focal electrical impulses from the retina corresponds to localized areas of retinal function. Hence the mfERG can differentiate central retinal function from peripheral retinal function. Commercial mfERG systems can map discrete areas of retinal function but the field of view is limited to central 30 to 50 degrees. A custom built system by the electro-diagnostic

Imaging Unit in Glasgow assesses up to 90 degrees field of view, the wide field mfERG (WF-mfERG).

The mfERG evokes electrophysioloical responses using a stimulus consisting of multiple scaled hexagonal elements which are independently switched between low or high luminance (black or white). The luminance of each run is controlled by mathematical series called m-sequences an array of '0's and '1's. The m-sequences enable each element to independently stimulate a focal area of the retina and each area of retinal function can be calculated from the global electric response generated from the cornea. Responses gives a 'map' of retinal function and each response consist of multiple waveforms, N1 first negative deflection, P1 first positive deflection and N2 second negative deflection. The amplitude and latency of individual responses or the average of groups of responses are measured.

The first report in the literature of the WF-mfERG by Parks and Keating showed an increase in implicit time in peripheral retinal responses. It was thought that a WF-mfERG parameter might be able to separate those with visual field defects from those without in patients who had taken Vigabatrin. (2)

A larger study by APrks and Keating investigated 32 patients on Vigabatrin compared to 34 patients with epilepsy who had never taken Vigabatrin. (3) 59% of the Vigabatrin group had visual field defects and none of the controls. The most consistent overall predictor of bilateral visual field defects was the difference between central and peripheral latency, abnormal if greater than 2 milliseconds. Using this parameter all patients with visual field defects showed abnormalities (100% sensitivity) and only 2 out of 13 patients without a field defect showed retinal abnormalities (86% specificity).

This thesis concentrates on attaining knowledge of the effect of Vigabatrin on the retina allowing early detection of toxic effects.

Chapter 2

Epilepsy

2.1 Introduction

Epilepsy should not be understood as a single disorder, but rather as a group of syndromes with vastly divergent symptoms but all involving episodic abnormal electrical in the brain that produces seizures of different types and severity. A careful history and appropriate investigations are essential for diagnosis. Epilepsy is usually controlled, but not cured, with medication, although surgery may be considered in difficult cases. Not all epilepsy syndromes are lifelong – some forms are confined to particular stages of childhood. This section outlines the different types of epilepsy and the management of epilepsy including investigations and pharmacotherapy.

2.2 Definition of epilepsy and seizures

Epilepsy is a chronic, recurrent physical condition caused by a sudden, unprovoked, brief change in how the brain works. It is thought to occur when nerve cells in the brain discharges electrical impulses at a rate higher than normal. This “electrical storm” is abnormal and leads to seizures.

Seizures are sudden, uncontrolled waves of electrical activity in the brain which may cause involuntary movement, minor physical signs, abnormal feelings or loss of consciousness or a combination.(4) The type of symptoms and seizures depend on where the abnormalities take place in the brain, what its cause is, and such factors as the patient's age and general state of health. Seizures can be caused by head injuries, brain tumors, lead poisoning, maldevelopment of the brain, genetic and infectious illnesses, and fevers. In more than half of the patients with seizures, no cause can yet be found.

2.3 Epidemiology

Around 50 million people in the world have epilepsy. It is a common serious neurological condition with an annual incidence in developed countries of 50-70 cases per 100 000 population.(5) In developing countries, the figure is higher due to more primitive obstetric services and greater likelihood of cerebral infection and head trauma. The prevalence of epilepsy is around 1% worldwide. The incidence varies greatly with age, with higher rates in early childhood, lower levels in early adult life and a second peak in those aged over 65 years.(6)

2.4 Classification of Epilepsy

1. Idiopathic and generalised. There is no seizure warning or underlying brain lesion and it is often associated with a family history.

2. Symptomatic and localisation-related. This type of epilepsy is associated with aura, a specific site of onset and an identifiable cause.

These two types can be differentiated by history and appropriate investigations such as electroencephalography (EEG) (see section 2.6.1) and brain imaging (see section 2.6.2). It is important to differentiate between the two types as they normally respond to different pharmacotherapy. Investigations are useful if positive but may be negative and the diagnosis of epilepsy is often a clinical one.

Common	Occasional

Sleep deprivation	Dehydration
Alcohol withdrawal	Barbituate withdrawal
Television flicker	Benzodiazepine withdrawal
Epileptogenic drugs	Hyperventilation
Systemic infection	Flashing lights
Head trauma	Diet and missed meals
Recreational drugs	Stress
Menstruation	Intense exercise

Table 2.3.1 Factors lowering seizure threshold

2.5 Classification of seizures

According to the classification established by the International League against Epilepsy, seizures can be divided into two groups: partial seizures which arise from one small region of the brain and generalized seizures which arise from multiple brain areas simultaneously.

Partial seizures originate in a focal region of the cortex and are divided into those that impair consciousness (complex partial) and those that do not (simple partial). Both types of partial seizures can spread rapidly to other cortical areas through neuronal networks, resulting in secondary generalized tonic-clonic seizures.

The following is an accepted classification of epileptic seizures by Brodie and Scachter.(7)

<u>Partial Seizures</u>
Simple - preservation of awareness.
Complex - impairment of consciousness.
Secondary generalised

<u>Generalized Seizures</u>
Absence - a brief loss of awareness

Myoclonic - sudden and brief contractions of a single group of muscles or of the entire body

Tonic - stiffening of muscles of the body, generally those in the back, legs, and arms

Tonic-Clonic – tonic phase; usually involves the entire body, characterized by muscle rigidity which causes the person to fall to the ground and may appear to cry out as air is expelled from their body, clonic phase; violent rhythmic muscle contractions causing the limbs to jerk

Atonic - the loss of muscle tone, causing the person to fall to the ground

Vigabatrin has been found to be effective in patients with pharmaco-resistant partial seizures(8). Exact figures are difficult to obtain but in the Epilepsy Unit at the Western Infirmary in Glasgow approximately 6% of patients with epilepsy have been prescribed Vigabatrin at some time.

Infantile spasms are a specific type of seizure seen mainly in West's Syndrome, an epilepsy syndrome of infancy and early childhood. The onset of infantile spasms in West's syndrome is predominantly in the first year of life, typically between 3-6 months. These seizures typically clinically present as a sudden bending forward and stiffening of the body, arms and legs and may be associated with arching of the torso. Spasms tend to begin soon after arousal from sleep. Individual spasms typically last for 1 to 5 seconds and occur in clusters, ranging from 2 to 100 spasms at a time. Infants may have dozens of clusters and several hundred spasms per day and are incapacitated. Infantile spasms usually stop by age 5, but are often replaced by other seizure types. West's Syndrome is characterized by infantile spasms, hypsarrhythmia (abnormal, chaotic brain wave patterns) and mental retardation. Other neurological disorders, such as cerebral palsy, may be seen in 30-50% of those with infantile spasms. Tuberous sclerosis is a rare, multi-system genetic disease that causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin.

Vigabatrin is the drug of choice in patients with infantile spasms especially those with tuberous sclerosis.(9)

2.6 Diagnostic Techniques

2.6.1 Electroencephalography (EEG)

Electroencephalography (EEG) is the neurophysiological measurement of electrical activity in the brain obtained by recording from electrodes placed on the scalp or, in special cases, subdurally or in the cerebral cortex. These resulting traces represent a summation of post-synaptic potentials from a large number of neurons and represent voltage differences between different parts of the brain and not actual electrical currents.

EEG is useful as a tool for monitoring a patient's epilepsy. It can be also used as a diagnostic tool in certain clinical situations such as to distinguish epileptic seizures from other types of attacks, for example psychogenic non-epileptic seizures, syncope, sub-cortical movement disorders and also to categorize seizures for the purposes of treatment.

Consequently EEG can help with the classification of epilepsy and support the classification of partial or generalized seizures. However a standard EEG can be insensitive(4). Activation techniques, including hyperventilation, sleep deprivation and photic stimulation can be helpful in uncovering abnormalities.

A positive EEG is therfore helpful in confirming a diagnosis of epilepsy but a negative test does not rule it out.

2.6.2 Brain imaging

Brain imaging gives information on the structure of the brain.

Computed Tomography (CT) scanning uses a series of x-rays of the head taken from many different directions and uses software that performs numerical integral calculations on the measured x-ray series to estimate the attenuation of an x-ray beam in a small volume of the brain. Cross sectional images of the brain are produced. A brighter area on the image represents denser tissue.

Magnetic Resonance Imaging (MRI) uses a main magnetic field and radio-frequency waves to produce high quality two- or three-dimensional images of brain structures without the use of ionizing radiation (X-rays) or radioactive tracers. During an MRI scan, a large cylindrical magnet creates a magnetic field around the head of the patient. Radiofrequency

impulses are transmitted to achieve spatial localization. When the magnetic field is imposed, each point in space has a unique radio frequency at which the signal is received and transmitted. Sensors read the frequencies and a computer uses the information to construct an image. The detection mechanisms are so precise that a change in structure over time can be detected. Images of both surface and subsurface structures can be recreated with a high degree of anatomical detail. MRI scans can produce cross sectional images in any direction i.e. transverse, sagittal and coronal.

Neuro-imaging is essential in the appropriate evaluation of most patients with epilepsy, particularly for those presenting with partial seizures. CT and MRI both allow the identification of structural lesions. However, because of its superior ability to differentiate between different soft tissue structures in the brain,(10), MRI has higher sensitivity and specificity.

Pathological findings vary with age for example stroke and tumours are more common in the elderly. Among children, MRI images are particularly useful in identifying congenital abnormalities such as cortical migration disorder.

2.7 Management of epilepsy

The aim of epilepsy management is to prevent seizures without drug related side effects.

Most patients experiencing more than one well-documented or witnessed seizure require treatment. Exceptions include patients with widely separated seizures or provoked seizures for which avoidance activity may be sufficient prophylaxis (e.g. concomitant illness, photosensitive epilepsy) and patients unlikely or unwilling to take medication (e.g. alcohol abusers and drug addicts).

Management mainly consists of pharmacological treatment although vagus nerve stimulation and epilepsy surgery are useful treatments in selected patients.

A single drug is normally introduced at low doses with increments over a number of weeks depending on the urgency and the type of anti-epileptic drug. This is to establish an effective and tolerable regimen.(4) This helps to avoid concentration-dependent side-effects, in particular central nervous system toxicity, the presence of which is likely to discourage the patient from persevering with long term therapy. An additional benefit of

this cautious approach is that it allows tolerance to develop to sedation or cognitive impairment. Such a policy usually allows detection of potentially serious idiosyncratic reactions such as rash, hepato-toxicity and blood dyscrasias. However there are exceptions: it took 8 years from the licensing of the drug Vigabatrin until the first reports of adverse effects on vision (see section 4.1).(11)

A single anti-epileptic drug, rather than a combination of antiepileptic drugs, enhances compliance and provides a wide therapeutic window while producing complete seizure control in more than 70% of patients.(12) Measuring the serum blood concentration when steady state has been reached confirms appropriate compliance and provides a useful baseline for further dosing if seizure control is not complete.

Before prescribing a combination of AED therapy due to a lack of efficacy, the clinician considers possible reasons (listed below) for the lack of response of a patient's seizures to treatment. Possible reasons are listed below.

Some reasons for failure of a single AED:

<u>Wrong diagnosis</u>
Other medical causes e.g. syncope and cardiac arrhythmia
Pseudo-seizures
Underlying brain neoplasm such as meningioma

<u>Wrong drug</u>
Inappropriate for seizure type
Kinetic/dynamic interactions

<u>Wrong dose</u>
Too low
Side-effects preventing dose increase

<u>Wrong patient</u>
Poor compliance with medication
Inappropriate lifestyle (e.g. alcohol abuse)

If treatment with a first line anti-epileptic drug as mono-therapy proves ineffective, achieving complete seizure control with additional mono-therapy trials is unlikely.(12) Some patients show useful improvement in seizure frequency or severity with a combination of AED.

2.8 Conclusion

Epilepsy is a common, debilitating condition. Careful history and appropriate investigations are essential so that appropriate treatment can be given. The goal of treating people with epilepsy is the maintenance of a normal lifestyle by complete seizure control without side effects. Vigabatrin has been shown to be very effective in West's syndrome and drug resistant partial seizures. Increasing the inhibitory neurotransmitters in the brain like GABA is one of the ways to stop seizures and GABA is discussed in chapter 3. Vigabatrin may also reduce seizures by other actions and these mechanisms will be discussed in Chapter 4.

Chapter 3

GABA (γ-aminobutyric acid)

3.1 Introduction

GABA was identified in the brain in 1950(13) and was first proposed to be an inhibitory neurotransmitter in 1958.(14) GABA has been shown to be the principal inhibitory neurotransmitter in the cerebral cortex and is present in up to 40% of all synapses(15) which maintain the inhibitory tone that counterbalances neuronal excitation.(16) When this balance is disturbed, seizures may ensue.

A number of pathological conditions are associated with GABA-ergic dysfunction including epilepsy, tardive dyskinesia and Huntington's chorea.(17) GABA has also been implicated in chronic drug use, producing long-lasting down-regulation in neurons associated with the brain reward circuitry and reducing dopamine (another neurotransmitter thought to be involved in addiction) levels; hence Vigabatrin has been used with some success in cocaine addiction.(18)

GABA is also a major inhibitory neurotransmitter in the retina and is present on multiple retinal cell types.(19) GABA has also been proposed to be directly toxic to neurons in one study but these results could not be duplicated.(20)

Vigabatrin causes a higher rise of GABA levels in the retina than in other parts of the nervous system (cortex 160% of control, retina 221% of control)(21). Neuro-retinal toxicity has been proposed to stem from the higher percentage increase in retinal GABA levels(22). However, it is interesting to note that even at the highest dose of Vigabatrin in one study, actual retinal GABA concentrations reached only 50% of basal brain levels. The highest levels of GABA achieved are in the brain because the brain has the highest initial concentrations of GABA. It is possible that retinal ganglion cells are relatively sensitive to the effects of Vigabatrin when compared to the brain.

3.2 GABA synthesis

Neither GABA, nor its precursor glutamic acid, enters the brain from the blood in significant quantities. The carbon chains of both neurotransmitters are derived from glucose via glycolysis and the entry of pyruvate into the Kreb's cycle.(23) GABA is formed within GABA-ergic neuron axon terminals by carboxylation of α-ketoglutarate to glutamic acid which is then decarboxylated by glutamic acid decarboxylase (GAD) to GABA (see figure 3.2.1).

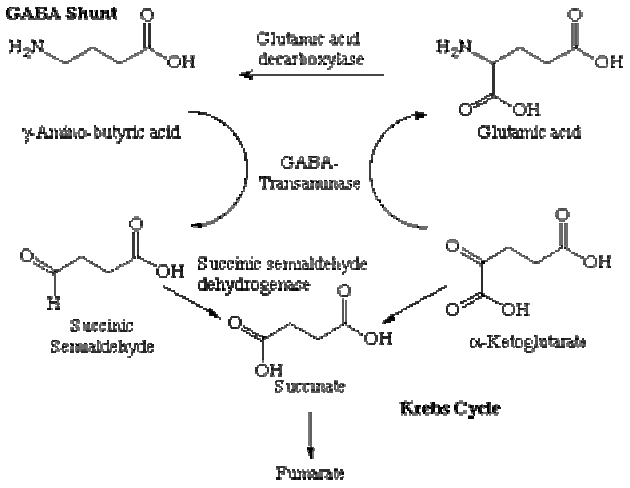


Figure 3.2.1 Synthesis of GABA via glycolysis and Kreb's cycle

(modified from www.neurosci.pharm.utoledo.edu/MBC3320/GABA.htm)

GABA transaminase (GABA-transaminase) is a pyridoxal dependent homodimer protein(made up of two identical, smaller molecules) known to be inhibited along with other similar transaminases by pyridoxal phosphate scavengers such as hydroxyalanine, hydrazines and in high doses by aminooxyacetic acid.(24) Other more selective blockers of GABA-transaminase include γ-acetylenic-GABA and ethanolamine-0-sulphate. Vigabatrin is poorly selective when compared with these.(25)

3.3 GABA release

There are two types of pre-synaptic GABA release, vesicular and non-vesicular. Vesicular release is calcium dependent, is sensitive to tetanus toxoid and is triggered by high potassium concentrations. Non-vesicular release occurs as a consequence of reversal of a GABA transporter in the cell membrane, is calcium independent and results in sodium influx. This type of release is thought to contribute to the ambient level of GABA in the synapses.

3.4 GABA receptors

The effect of GABA is mediated by receptors in the cell membrane and results in a reduction of neuronal excitability by the generation of an inhibitory post synaptic potential(IPSP), a negative voltage across the cell membrane resistant to further stimulation. Three types of GABA receptors have been identified to date and will be discussed below

3.4.1 $GABA_A$ receptors

$GABA_A$ receptors are ligand-gated ion channels that hyperpolarize the neuron by increasing inward chloride conductance and thus have a rapid inhibitory effect(26) influencing the early portion of the GABA mediated IPSP. The $GABA_A$ receptor complex is a protein complex made up of five units that contains binding sites for GABA, barbiturates, benzodiazepines, picrotoxin and neurosteroids.(27)

3.4.2 $GABA_B$ receptors

$GABA_B$ receptors are G protein coupled receptors that hyperpolarize the neuron by increasing potassium conductance or decreasing calcium entry in the cell membrane thereby inhibiting the pre-synaptic release of other transmitters,(28) thus having a slow inhibitory effect. $GABA_B$ receptors are present on both excitatory and inhibitory axon terminals. Activation is associated with a decrease in neurotransmitter release and thus $GABA_B$ agonist drugs can be either antiepileptic(29) or proepileptic.(30)

The role of $GABA_A$ and $GABA_B$ receptors in the generation of GABA mediated IPSP can be demonstrated. Bicuculline methiodide, a $GABA_A$ inhibitor inhibits the early portion of the IPSP whereas CGP-35348, a $GABA_B$ inhibitor, blocks the slow inhibitory effect seen in the later portion of the IPSP. Both drugs given together block the entire IPSP.(31)

3.4.3 $GABA_C$ receptors

$GABA_C$ receptors are integrated into the cell membrane and are ligand gated. These receptors stabilise membrane potential by increasing chloride conductance which permits chloride entry into cells mediating fast and sustained responses.

Thus $GABA_A$ and $GABA_B$ receptors mediate inhibitory responses while $GABA_C$ receptors mediate excitatory responses.

Although recent studies indicate a wide distribution of $GABA_C$ receptors in many parts of the central nervous system,(32) these receptors are most prominently expressed in the vertebrate retina.(33), play a role in retinal signal processing(33) and play an important role in shaping signal transmission from bipolar cells to ganglion cells in the retina.(34) As $GABA_C$ receptors are concentrated in the retina, in the cone system it is one hypothesis that they may play a role in the side effects seen with Vigabatrin such as visual field defects though this has not been proven (see section 3.6).

The characteristics of the GABA receptors are summarized in Table 3.4.1.

	$GABA_A$ Receptor	**$GABA_B$ Receptor**	**$GABA_C$ Receptor**
Category	Ligand-gated channel	G-protein coupled receptor	Ligand-gated channel

Subunits	Ά,β,γ,δ,ε	GBR1, GBR2 (2 N-terminal variants)	1,2,3
Agonists	Muscimol, THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol)	Baclofen	
Antagonists	Bicuculline, Picrotoxin	Phaclofen, CGP-35348	TPMPA (1,2,5,6-Tetrahydropyridin-4-yl) methylphosphinic acid), Picrotoxin
Desensitization	Yes	No	No
Modulator	Benzodiazepines Barbiturates Neurosteroid		Zinc

Table 3.4.1 Characteristics of GABA receptors.

3.5 Epilepsy and the role of GABA

Experimental and clinical studies have provided evidence which indicates that GABA has an important role in the mechanism and treatment of epilepsy.

1. Abnormalities of GABA-ergic function have been observed in genetic and acquired animal models of epilepsy.(32, 33)
2. Reductions of GABA mediated inhibition have been reported in human epileptic brain tissue.(35)
3. GABA agonists suppress seizures and GABA antagonists produce seizures.(36)
4. Benzodiazepines and barbiturates work by enhancing GABA-mediated inhibition.(37)
5. Drugs that increase synaptic GABA are potent anticonvulsants.(36)

3.6. GABA: its role in the retina and the development of retinal toxicity

When administered systemically, Vigabatrin has been shown to cross the blood-retinal barrier and can be detected throughout the retina by immunocytochemical techniques.(38)

The retina is approximately 0.5 mm thick and lines the back of the eye. The optic nerve contains the ganglion cell axons running to the brain and, additionally, incoming blood vessels that open into the retina to vascularize the retinal layers and neurons. A radial section of a portion of the retina reveals that the ganglion cells (the output neurons of the retina) lie innermost in the retina closest to the lens and front of the eye, and the photosensors (the rods and cones) lie outermost in the retina against the pigment epithelium and choroid. All vertebrate retinas are composed of three layers of nerve cell bodies and two layers of synapses. The outer nuclear layer contains cell bodies of the rods and cones, the inner nuclear layer contains cell bodies of the bipolar, horizontal and amacrine cells and the ganglion cell layer contains cell bodies of ganglion cells and displaced amacrine cells.

A simple wiring diagram of the retina emphasizes only the sensory photoreceptors and the ganglion cells with a few interneurons connecting the two cell types such as seen in the figure below.

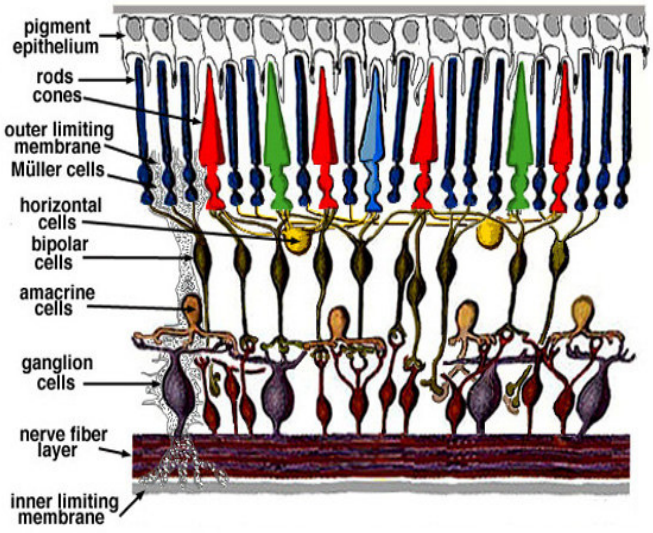


Figure 3.6.1 Diagram of retina

There are two main theories of retinal toxicity associated with Vigabatrin use: a direct action and an indirect action that may be due to increased GABA levels.

Vigabatrin increases GABA concentrations in the retina more than in other tissues, such as in the brain. GABA-transaminase is the enzyme which degrades GABA. GABA-transaminase is 22% of the level in rat cortex , while it is 260% of the level control in the retina of rats with Vigabatrin use in one study(21). Hence GABA levels are increased to a greater degree in the retina as compared the brain by an unknown mechanism.

Sills and Brodie have surmised that since there is such a large percentage increase in GABA levels in the retina as opposed to the brain that GABA is implicated in the Vigabatrin associated retinal toxicity debate.

There are other points to note. Importantly Sills has shown that even at the highest dose of Vigabatrin, actual retinal GABA concentrations reached only 50% of basal brain levels(22). So the higher percentage increase in the retina GABA levels still do not elevate GABA levels in the rat retina to higher levels than rat brain GABA levels.

Vigabatrin concentrations were also increased and found to be five times higher in the retina than any other brain region.(21) It is difficult to separate the action of these two

compounds to determine if one, both or neither are responsible for Vigabatrin associated visual defects. In animal models it is difficult to control for GABA because GABA is broken down before therapeutic or toxic levels are achieved in the brain and retina. In acute toxicology studies in isolated retina slices where GABA and Vigabatrin can be applied directly to the retina, Izumi has shown light and Vigabatrin were found to be significant in causing retinal photoreceptor damage rather than GABA(1).

GABA is found in bipolar, horizontal, amacrine and ganglion cells and has a role in the modulation of phototransduction from the retinal photoreceptor cells to the ganglion cells.(19) Multiple subtypes of GABA-ergic retinal cells have been identified. These include 1 type of rod bipolar cell, 8 to 11 types of cone bipolar cells and 10 to 20 amacrine cells.(39)

Figure 3.6.2 shows a schematic diagram depicting the main GABA-ergic pathways in the outer retinas of vertebrates.(40)

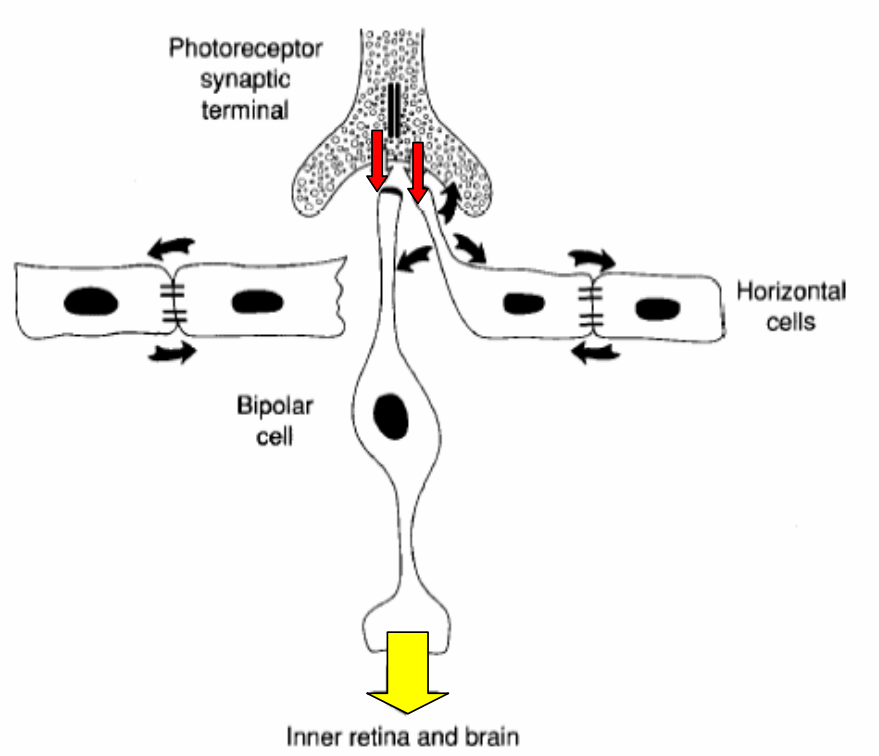


Figure 3.6.1 The main GABA-ergic pathways in the outer retina.
(modified from webvision.med.utah.edu)

The main GABA-ergic elements are the horizontal cells which form a synctium by gap junctions (indicated by =). Horizontal cells and bipolar cells receive glutamatergic inputs from photoreceptors (red arrows). Horizontal GABA-ergic cell outputs indicated by solid arrows are directed onto photoreceptors (negative feedback) bipolar cells and horizontal cells themselves. After initial processing, the bipolar cells transmit to the inner retina and and to the brain (yellow arrow).

Amacrine and horizontal cells contain a homogenous population of GABA receptors. Bipolar cells exhibit both $GABA_A$ and $GABA_C$ receptors with a much higher proportion of $GABA_A$ on cone bipolar cells than on rod bipolar cells.(41) One of the tests used to monitor Vigabatrin effect on the retina is the ERG (explained in detail in chapter 8). One parameter that has been reported to be affected is the cone ERG b wave (a measure of Muller cell function with mainly cone system interaction that will be discussed more fully later in the thesis). Kapusta-Bruneau reports on appropriate activation the $GABA_A$ receptors decrease cone ERG b wave amplitude, whereas $GABA_C$ receptors increase cone ERG b wave amplitude(42) in isolated rat retinas. Coupland and Miller have reported cone ERG b wave reduction in people on Vigabatrin with visual field defects. Therefore investigators have presumed the $GABA_C$ receptors in the cone system have been selectively affected and it has been inferred that this may be due to this difference in distribution of GABA receptors.(43;44)

3.7 Conclusion

GABA has been shown to be a major, frequently inhibitory neurotransmitter in the brain and retina. The manipulation of GABA synthesis, storage and breakdown and its interaction with 3 GABA receptors has had success in the management of epilepsy. The effects of increasing GABA concentrations in the retina are unknown. It is one theory that retinal toxicity is due to increased levels of GABA in the retina though Sils has shown in one study actual retinal GABA concentrations reached only 50% of basal brain levels(22) although the percentage rise was higher in the retina.(21). suggesting there may be other mechanisms such as a direct effect of Vigabatrin.

Chapter 4

Vigabatrin

4.1 Introduction

Vigabatrin was the first 'designer' antiepileptic drug developed. It was manufactured to increase GABA levels in the nervous system and thus decrease seizures. Vigabatrin was licensed in the UK in 1989. It is a useful treatment for refractory partial seizures and is the drug of choice for infantile spasms. There has been recent interest in its use for amphetamine and cocaine addcition. However in 1997, Eke and co-workers reported three cases of bilateral concentric visual field constriction with Vigabatrin.(11) More than 100 research papers have since confirmed the link between Vigabatrin treatment and visual dysfunction. A variable prevalence (0.14% to 80%) of bilateral visual field defects (VFD) has been reported but most studies agree about 50% of patients on Vigabatrin develop visual field defects. (100;122;123) Patients may be asymptomatic but visual dysfunction may be progressive and irreversible and have important clinical implications such as driving.

4.2 Origin and design

Vigabatrin was specifically designed to enhance GABA function in the CNS(45) and was synthesized as a substrate for GABA aminotransaminase (GABA-transaminase) in 1977 by Jung et al at the Merrell laboratories in France (now Sanofi-Aventis, 2004).(46)

4.3 Chemistry (pharmacology)

Vigabatrin (4-amino-hex-5-enoic acid, γ-vinyl GABA, Sabril®) is an ethyl analogue of GABA (4-aminobutyric acid). The structure of Vigabatrin is shown in Figure 4.3.1 and compared with GABA.

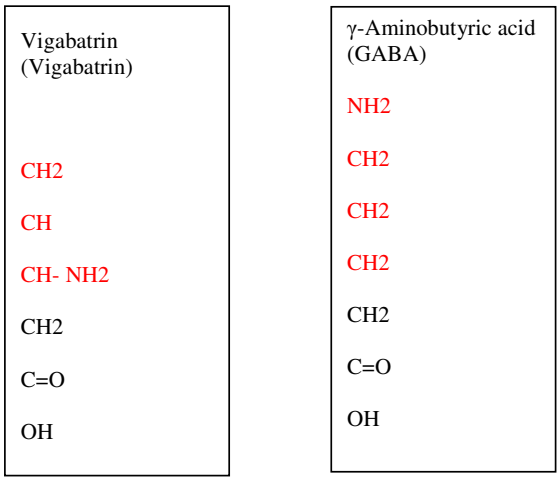


Figure 4.3.1 Comparison of the chemical structure of Vigabatrin and GABA

The only difference between the two molecules is that there is a vinyl function on the carbon bearing the amine group. Like GABA, it is a water soluble, polar molecule. The compound is a white to off-white crystalline solid with a melting point of 171-177 °C. The molecular weight is 129.16g/mol.

Vigabatrin exists as a racemic mixture and exhibits no optical activity (a racemate is a mixture of equal amounts of left- and right-handed stereoisomers of chiral (an object that is non-superimposable on its mirror image) molecules. The two isomers rotate plane-polarised light in opposite directions. Therefore a racemic mixture does not rotate plane-polarised light). The pharmacological activity and toxic effects of Vigabatrin have been shown to be associated with the (+) enantiomer (one of the mirror image forms of the molecule). The (-) enantiomer appears to be entirely inactive.(47)

4.4 Mechanism of action

Vigabatrin belongs to a class of enzyme activators that are called K_{cat}, suicide substrates or mechanism based inhibitors. Vigabatrin is converted in vivo to its active form by GABA-transaminase, the enzyme that catalyzes the conversion of GABA to succinic semialdehyde. Vigabatrin irreversibly inhibits GABA-transaminase(48) by replacing GABA as a substrate for GABA-transaminase. Enzymatic activation produces an intermediate which binds covalently to the active site, thereby consuming both enzyme and inhibitor in an irreversible reaction. GABA levels increase in the brain which inhibits electrical activity thus decreasing seizures.

The pharmacological action of Vigabatrin is related to the kinetics of GABA-transaminase so a concentration effect cannot be demonstrated. For this reason the drug can be administered once a day despite its short elimination half life.

A single parenteral dose of Vigabatrin (1500mg/kg) reduces mouse brain GABA-transaminase activity to around 20% of control levels and consequently produces a 4-fold increase in whole brain GABA concentrations. This effect persists for over 24 hours, with GABA-transaminase activity and GABA concentrations only returning to normal upon the synthesis of new enzyme protein over a period of 4-5 days.(17)

More recent experimental studies suggest that in addition to an effect on GABA-transaminase, Vigabatrin also may block GABA uptake. This was shown using primary cultures of rat cortical astrocytes by Leach.(49) It has been suggested that Vigabatrin may induce tonic inhibition via GABA transporter reversal without increasing vesicular GABA release by Wu(50). However the concentration of Vigabatrin required to block GABA uptake (IC_{50} ~250µM) suggests that it may only occur at the highest therapeutic doses thus questioning its clinical relevance.

Hanaya has shown GABA increased by inhibition of GABA-transaminase with Vigabatrin inhibits abnormal excitation of hippocampal CA3 neurons of the spontaneously epileptic rat (SER) via $GABA_A$ receptors.(51)

It is important to note that alteration of GABA may not be the only antiepileptic mechanism of the drug. Vigabatrin also decreases glutamate in the hippocampus and aspartate in the hippocampus, cortex and cerebellum by Halonen(52) which are excitatory neurotransmitters.

4.5 Efficacy

4.5.1 In vitro cultures

At the cellular level Vigabatrin inhibits GABA-transaminase with an IC_{50} of 89µM in neurons and 132µM in glial cells (IC_{50} is the concentration of an inhibitor that is required for 50% inhibition of its target). (53)

4.5.2 In vivo

Animal models for seizures and epilepsy have played a fundamental role in our understanding of the physiological and behavioral changes associated with human epilepsy. In vivo animal models have been categorized into models of seizures and those of epilepsy.
The following animal models have been tested with Vigabtrin:

Vigabatrin is devoid of activity in the maximal electroshock model (generalized tonic-clonic model).(54)

In the pentylenetetrazol test Vigabatrin has variable anticonvulsant effects observed when Vigabatrin is high and pentylenetetrazol is moderate to low (generalized absence/myoclonic model).(55)

Vigabatrin has efficacy only at high concentrations in audiogenic seizures in the DBA/2 mouse and those induced by the inverse benzodiazepine agonist DMCM.(56)

Vigabatrin is effective in blocking seizures induced by the systemic administration of bicuculline and picrotoxin (antagonists of $GABA_A$ receptors).(57)

Vigabatrin has variable anticonvulsant activity in the kindling model (partial seizures).(58)

4.6 Pharmacokinetics

4.6.1 Absorption

At therapeutic doses in man Vigabatrin produces dose-related increases in CSF concentrations of free and total GABA, homocarnosine (the GABA-histidine dipeptide) and beta-alanine. These biochemical changes are consistent with an inhibition of GABA-transaminase activity in brain.

Racemate

In all pharmacokinetic studies absorption was rapid with the peak concentration reached in the first 2 hr after dosing between 0.5 and 3g (59-61). The lag time (time delay between drug administration and first observed concentration above the lower limit of quantification (LOQ))was calculated to be between 2 and 30 min in one study(59) and 10 to 16 min in another with the absorption half-life in the latter study ranging from 13 to 36 minutes (61). The mean terminal half life was between 5 and 7 hr. (62)

Approximately 60 – 80% of the drug was recovered unchanged in the 0 to 24 hr urine indicating a bioavailability of at least 60 -80 %.

Enatiomers

In 6 healthy volunteers Vigabatrin single dose kinetics were determined for both enantiomers. (60) Peak plasma concentrations were reached for both at between 0.5 and 2 hr after a 1,500 mg oral dose. In each subject the (-) and (+) enantiomer peak concentrations were reached at the same time. The ratio of peak concentrations of (-) and (+) was 1.85. The plasma concentrations of the two enantiomers did not differ after 24 hours.

The mean terminal half life ($t_{½}$), which is a measure of the time taken for a drug to leave the systemic circulation, for the (-) enantiomer was 485 minutes and 447 minutes for the (+) enantiomer.(60)

Area under the curve (AUC) estimates bioavailability (fraction of administered dose that reaches systemic circulation) for non intravenous doses. AUC was 39.2 µmol $min.ml^{-1}$ for (-) enantiomer and 30.1µmol $min.ml^{-1}$ for (+) enantiomer. One explanation for the discrepancy is that (+) enantiomer is used by GABA-transaminase as a substrate while the (-) enantiomer is inactive.

Ultimately these absorption characteristics are unimportant as the anti-epileptic effects of Vigabatrin outlast the drug by several days.

4.6.2 Distribution

Vigabatrin is not protein bound.(63) It is a highly water soluble compound (33mg/ml) and has a wide distribution in the body with an apparent volume of distribution of 0.8 l/kg. (total body water is 0.6 l/kg) A comparison with the extrapolated or initial volume of distribution with the steady state volume indicates that between 50-75% of the drug is outside the central blood compartment at steady state.

In man, CSF Vigabatrin levels have been analysed showing that the concentration of Vigabatrin in the CSF was 10% of that in the blood indicating blood brain barrier penetration. (64)

Thus, with systemic availability upon oral administration, blood-brain barrier penetration and biochemical activity in the CNS, the prerequisites for potential uses of Vigabatrin in neurological disorders were demonstrated in clinical pharmacological studies.

4.6.3 Accumulation

It was initially thought that accumulation of Vigabatrin is unlikely. Accumulation did not occur in the CSF and plasma in patients treated with Vigabatrin on a chronic daily basis.(65) Surprisingly, one study in rats showed Vigabatrin concentrations in the retina were 18.5-fold higher than those in the brain.(21) The reasons for this large disparity is unknown but may suggest a different mechanism of Vigabatrin transport into the eye and may be linked with its toxic action on the retina.

4.6.4 Metabolism

The majority of Vigabatrin is excreted as the unchanged drug. There have been no metabolites identified in humans (60).

4.6.5 Excretion

Vigabatrin is eliminated primarily via the kidneys with about 65% of the administered dose found unchanged in the urine within 24 hours.

In healthy volunteers the elimination half-life is 5-8 hr and the total clearance is about 1.7-1.9 ml/min/kg with renal clearance accounting for 70% of the total clearance. Elimination is not influenced by the dose (0.5 to 3g) or by duration of treatment. (60)

4.7 Pharmacodynamics

Vigabatrin is a 50/50 mixture of (+) and (-) enantiomers. The pharmacological activity and the toxic effects of Vigabatrin are associated only with (+) enantiomer.(59) The (-) enantiomer appears to be entirely inactive. In most biologically active compounds, the inactive enantiomer is considered to be an impurity that can influence the pharmacokinetics and action of the active enantiomer as well as contribute to the compound's toxicity.(60) However for enzyme inhibitors such as Vigabatrin, the pharmacokinetics of the drug itself are less important than for other drugs because GABA-transaminase has a longer half life than Vigabatrin.(46) The pharmacological effects are determined by the half-life of the enzyme rather by the drug or the (+) enantiomer.

4.8 Clinical use in epilepsy

4.8.1 Short term add on

At first, the efficacy of Vigabatrin was evaluated in two single blind pilot studies in Europe by Schechter and Gram.(66;67). Gram demonstrated a 50% reduction in median seizure frequency from placebo to active treatment period lasting 12 weeks.(67) Gram findings were correlated by Schechter in his study where 60% of the patients achieved complete seizure control, the active period being 4 weeks.(66) In the United States, a larger single-blind, placebo-controlled multi-centre study in 89 patients produced similar results by Browne.(68)

Several short-term, double blind, placebo-controlled crossover studies with Vigabatrin as add-on therapy have been reported.(69-72) Vigabatrin has been administered in doses ranging from 2 to 4g for between 7 and 12 weeks. Most patients had drug resistant complex partial seizures with or without secondary generalisation. In one of these studies Mumford demonstrated Vigabatrin produced a greater than 50% decrease in seizure frequency in 46% of the total of 98 patients having only partial seizures.(73) In another study, Ring showed Vigabatrin responders were randomized into a double-blind placebo-controlled phase. The patients on Vigabatrin maintained a 55% reduction of seizure frequency, whereas those on placebo experienced a 19% increase in seizure activity.(74) A multi-centre dose response trial in the United States of America compared treatment with 1g, 3g or 6g of Vigabatrin to placebo and found a statistically significant decrease in seizures for those treated with 3g or 6g in patients with partial seizures.(75)

4.8.2 Long term add on

There have been several open-label follow up studies of Vigabatrin responders.(76-79) The antiepileptic efficacy and the good clinical tolerability are generally maintained during treatment for up to 6 years. The treatment-related withdrawal rate in these studies is approximately 20% with the majority of patients treated for over 12 weeks discontinuing Vigabatrin mostly because of insufficient efficacy rather than side effects(80) before it was discovered that visual field defects were associated with Vigabatrin.

4.8.3 Monotherapy

In an open-label monotherapy study comparing initial Vigabatrin monotherapy with carbamazepine (CBZ) monotherapy Kalviainen has shown 60% of patients in both groups have been treated successfully.(81)

4.8.4 Studies in children

Chiron followed the use of Vigabatrin in patients up to 24 months old with drug resistant infantile spasms.(82) During a mean follow up period of 3.2 months, 68% of the patients experienced a greater than 50% reduction in their seizure frequency and 43% became totally seizure–free.

4.9 Spectrum of activity in epilepsy

4.9.1 Efficacy in relation to seizure type

According to analysis of published clinical experience in 487 patients, Vigabatrin is more effective against partial seizures than against generalized epileptic syndromes.(83) In children and mentally retarded patients there has been a trend towards greater response in partial epilepsies (45;84;85). Vigabatrin is a drug of choice in the treatment of intractable infantile spasms.(82)

Patients with mixed seizure types, EEG abnormalities, intellectual impairment and severe and frequent seizures are relatively resistant to Vigabatrin (83;86) but this is typical of all major AED. Vigabatrin decreases absence seizures and myoclonic epilepsy.(83;86;87) Exacerbation of seizures have also been reported in some patients with partial epilepsy(85-87) and have been reported with all GABA-ergic drugs.

4.9.2 Efficacy by dose

The usual daily dosage of Vigabatrin used in clinical trials has been 2g to 4g for adults.

In one of the early pilot dose-ranging studies a dose of 1g/day given over 2 weeks had some effect in reducing seizure frequency, whereas the effect was more marked during a 2g/day period.(66) In another pilot study the reduction in median seizure frequency was similar for both the 1g and 2g/day periods.(67) Some of these patients showed a further reduction in seizure frequency when the dose was increased to 3g/day. Both these pilot studies indicate a dose-linked efficacy that was reinforced by other studies.(69;70;73)

However, doses beyond 4 g/day usually give no extra benefit.(75) These findings suggest that there is an optimally effective dosage or even a ceiling to effective dosage for an individual patient. Starting doses of 2g/day are recommended.(73) The starting dose is then titrated on an individual patient-by-patient basis to gain the best response.

4.10 Toxicity

4.10.1 Long term toxicity – pathological examination

Long term toxicity studies involve the chronic administration of the candidate compound to experimental animals for periods of up to one year. Thereafter the animals are subjected to intensive pathological examination.

Vigabatrin has been the subject of several long term toxicity investigations comprising two studies in Sprague Dawley (albino) rats and one study in Lister-Hooded rats(88;89) and four studies in beagle dogs.(88;90-92)

In a rat model, Neal showed the spinal cord and brain show greater tolerance to the toxic action of Vigabatrin compared to the retina.(93)

The two rat studies performed by Gibson and Butler employed Vigabatrin doses of 30 – 300 mg/kg per day and were conducted for three and twelve months respectively. The rat toxicity studies revealed significant intra-myelinic oedema (vacuolisation) in the cerebellum, optic tracts, hippocampus and thalamus in albino rats.(88;89)

The studies of Vigabatrin toxicity in the dog revealed significant intra-myelinic oedema in the fornix columns, optic tracts, thalamus, hippocampus and hypothalamus. (88;90-92) However, the distribution is limited to the brain and is reversible upon discontinuation of therapy as shown by Butler.(47)

Butler concludes that in treated humans there has been no documentation of intra-myelinic oedema.(47;89) Cohen agrees that intra-myelinic oedema does not appear to be extrapolated to man.(94)

There has been one post-mortem pathological report on a human treated with long term Vigabatrin as reported by Ravindran. The main findings of the visual system were peripheral retinal atrophy with loss of ganglion cells and loss of nerve fibres in the optic nerves, chiasm, and tracts. In this individual it would seem that there was injury within the ganglion cells in the retina.(95) However clinically, optic neuropathies result in loss of visual acuity, defective colour vision and abnormal visual evoked responses. Central visual acuity, colour vision and visual evoked response have been reported as unaffected in patients on Vigabatrin in several studies. It seems that in most patients the ganglion cell layer is not the primary area of pathology but may represent secondary changes.

Buncic has described in one clinical study a proposed 'characteristic' type of optic atrophy affecting predominantly the nasal part of the disc.(96) This pattern of nerve loss does not correlate with most reported visual field defects in patients on Vigabatrin which are predominantly nasal (100;122;123) (which would occur with predominantly temporal optic disc atrophy).

Another study using optical coherence tomography suggested there was a reduction in the retinal nerve fibre layer in patients with Vigabatrin associated visual field loss. It is difficult to make reliable measurements of retinal nerve fiber layer thickness in the same patient(97) and the study compared the retinal nerve fiber layer in patients without epilepsy making the conclusions suspect. However the study shows that vigabatrin does have a long term effect on the retina. Other studies have showed retinal degeneration was found to be dependent on light exposure.(88)

Two studies, one the post mortem results as reported by Ravindran, the other using the wide field multifocal electroretinogram as reported by McDonagh have suggested that Vigabatrin selectively affects the peripheral retina.(3;95) Jensen disputes this hypothesis and suggests that Vigabatrin associated retinal toxicity is diffuse, inducing subtle central visual dysfunction and more severe peripheral visual defects where cell density is lowest. However the study was done using the ERG which gives a global retinal response and so difficult to differentiate between peripheral anad central defects.(98)

Wilson, Arndt and Wong suggest that the visual field constriction seems to be permanent.(99-101) This hypothesis is supported by the degree of atrophy seen on pathological examination of nervous tissue of dogs given Vigabatrin. (95) Krakow refutes that visual field loss is reversible claiming in his patients visual field defects improved on discontinuing Vigabatrin.(102)

There have been reports of visual field constriction associated with other GABA-ergic drugs progabide and tiagabine.(103;104) These reports have largely been discounted by Kalviainen.(105)

4.10.2 Short term toxicity

The possibility of light levels being an important factor was raised by Butler in one study in which disorganization of the outer nuclear layer occurred in retinas of Sprague-Dawley

(albino) rats but not Lister-Hooded (pigmented) rats.(89) Gibson corraborated in another study where no retinal lesions were identifiedafter administering Vigabatrin orally for 1 year to Sprague-Dawley rats. This study hypothesized that light has a critical role in Vigabatrin retinotoxicity.(88)

A recent study aimed to identify factors contributing to acute Vigabatrin neuro-retinal toxicity. Sprague-Dawley (albino) rats were used for in vivo and ex vivo experiments in light and dark environments by Izumi. Retinas incubated with Vigabatrin under light had degeneration of photoreceptor outer segments, loss of photoreceptors and structural disruption of outer limiting membrane and damage to Muller cells in all areas of the outer retina (i.e. not only in the periphery) which seemed to be time and dose dependent. Retinas incubated with no light with Vigabatrin and retinas incubated in the light or dark with GABA showed no change. This is a surprising result suggesting that photo-toxicity may be the main underlying pathological mechanism for Vigabatrin associated visual field defects and is unrelated to GABA.(1)

Vigabatrin is not recommended in pregnancy because it is known to be teratogenic. Two cases of visual field defects developing in children with intrauterine dosing has been published by Sorri(106) suggesting that Vigabatrin has crossed the placental barrier. It is possible the field abnormalities reported occurred intrauterine or the changes occurred postpartum when the infants were exposed to light. Harding disputes this in which he reported 5 children of 3 mothers with no effect of intrauterine vigabatrin exposure. (153)

4.10.3 Aetiology – toxicity studies

Several possible mechanisms of Vigabatrin toxicity have been proposed by Comaish and Izumi. These have included increased physiological effect of GABA, non specific actions e.g. increased α-aminoadipic acid, inhibition of mitochondrial ornithine aminotransferase, GABA shunt and glutamate excitotoxicity-metabolic dysfunction that may cause ischaemia and accumulation of undesirable metabolites, apoptosis, effect on glucose metabolism, effect on oxidative damage(107) and recently photo-toxicity.(1)

It is possible that Vigabatrin causes a decrease in cerebral and/or ocular circulation as the primary mechanism of pathology. Spanaki has described in one study a 13% decrease in global cerebral blood flow combined with an 8% decrease in cerebral metabolic rate for

glucose as a result of Vigabatrin therapy.(108) Raised GABA levels may have an important role to play in exacerbating ischaemia. Edvinsson has shown GABA has a role in the regulation of vascular tone. Specific GABA receptors have been demonstrated both in vivo and in vitro as being functionally viable in eliciting a vasodilatory response in the presence of GABA.(109) In contrast Kelly has demonstrated in another study that systemic administration of GABA-ergic agonists in the rat model results in a reduction in cerebral glucose metabolism and a decrease in cerebral blood flow(110) probably due to increased CSF GABA levels.

Retinal blood flow and pulsatile ocular blood flow are reduced in epileptic patients as compared to healthy volunteers as shown by Hilton and Hosking. (111;112) The reduction in pulsatile ocular blood flow was further exacerbated in Vigabatrin treated epilepsy patients compared with those treated with conventional AED(112). Previously reported optic nerve pallor(11;113;114) and narrowing of retinal arterioles(115) may be indicative of a primary ischaemic mechanism. This effect may be GABA-mediated, due to pre-existing ischaemia, due to reduced metabolic demands(112) or due to photo-toxicity.

There have been a number of studies investigating the effect of systemic drugs or vasoactive stimuli that have showed parallel changes in the brain and the eye(116;117).

Physiologically a reduction in retinal and/or choroidal blood flow will have a direct effect on the health and functioning of the neural retina. In Vigabatrin patients, more pronounced toxic retinal effects and therefore a greater haemodynamic compromise may be expected.

Vigabatrin effects on vision remain an enigma. It is likely that several cells and regions are affected. Genetically determined variations in local tissue, drug deactivations or clearance, most probably in the retina, are likely to play a role in determining who develops visual dysfunction.

4.11 Adverse effects

Vigabatrin is generally well tolerated in patients with epilepsy. Adverse events are mainly CNS related and probably a secondary consequence of increased GABA levels caused by Vigabatrin. The safety of Vigabatrin was evaluated in 2081 epileptic patients treated in clinical trials. The relationship of adverse events to Vigabatrin therapy was not clearly established as patients were taking other antiepileptic drugs concomitantly. The most

frequently reported adverse events were somnolence (12.5%), fatigue (9.2%), and weight gain (5%).(80)

Adverse events reported with a frequency of less than 1% include: anxiety, emotional lability, behavioral disturbances including psychosis, irritability, tremor, abnormal gait, speech disorder, increased appetite, dyspepsia and constipation.(80)

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with Vigabatrin treatment.

Laboratory data indicate that Vigabatrin treatment does not lead to renal or hepatic toxicity. Chronic treatment with Vigabatrin may be associated with a slight decrease in haemoglobin, which rarely attains clinical significance.(80)

4.12 Drug interactions

Vigabatrin is neither protein bound nor metabolized and does not influence the cytochrome P450-dependent enzymes.(118) Vigabatrin has limited ability to produce significant drug interactions. Administration of Vigabatrin causes a 20% decrease in plasma phenytoin concentrations but usually this interaction has been of limited practical significance. (118) There are no other known interactions with most concurrently used AED.

4.13 Vigabatrin and Visual Field Defects

4.13.1 Introduction

Eke et al described 3 cases of severe visual field constriction in patients on Vigabatrin.(11) A number of studies have since linked visual dysfunction, often visual field defects with Vigabatrin use. The prevalence remains poorly defined with reports of visual field defects ranging from 0.3%(119) to 75% of patients treated with Vigabatrin.(120-122) Most reports claim at least 50% of patients have visual field defects. (101;123;124) It is not clear why some patients develop visually disabling field constriction while in some subjects the visual field defects are mild and asymptomatic or undetectable; in one study 0.2% (1 out of 713) patients using Vigabatrin had a symptomatic visual field defects. (101;123;124) It is also unclear whether stopping the drug is the best way to manage patients with visual field

defects as there have been reports of sudden death associated with discontinuing Vigabatrin.(125)

The most commonly described visual field defects is bilateral constriction present in both eyes, involving the nasal retina more than the temporal.(126) However, other descriptions such as generalised constriction have been described. (127) Some authors theorise there is not peripheral field constriction but a reduced sensitivity overall in the total visual field noticed more in the periphery because there are fewer cells in the periphery.(35)

Many patients on Vigabatrin are asymptomatic. One of the possible reasons is there is a relative preservation of temporal fields in both eyes. The predominant area of field loss in most patients seem to be the nasal field where the visual fields of the two eyes overlap so the actual visual loss can be compensated for and allow patients to maintain good mobility. Also, patients unconsciously develop coping mechanisms to deal with peripheral field loss, such as turning their heads.

4.13.2 Monitoring

There are many difficulties in monitoring patients with epilepsy on Vigabatrin for visual field defects.

Perimetry is a subjective technique requiring considerable attention and cooperation from patients. Patients with epilepsy can have delayed reactions or fluctuating attention due to seizure activity and drug treatment.(128) Therefore visual fields may not be reproducible. Lawden has shown in one study in patients with epilepsy 35% (11 out of 31) of patients were unable to complete visual field testing.(114)

It is even debatable whether the best method to use is kinetic or static perimetry. Kinetic Goldmann perimetry allows examination to the extreme periphery of the visual field and measures the “true” visual field. Graniewski-Wijnands has found that manual kinetic perimetry was not the appropriate method of examination of the visual field in this patient group due to the length of time the test takes. Brain damage or lack of alertness secondary to Vigabatrin caused a delay in reaction time leading to a more concentric visual field constriction than detected with Humphrey Field Analyzer with Esterman strategy.(129) Also Newman showed 10% of patients could not perform kinetic fields because of cognitive problems (130) and it is very operator dependent and not as quantitative as static

Humphrey perimetry. Computerised static perimetry measures generalised sensitivity loss but has the advantage of improved repeatability and is non operator dependent. In this particular patient group with poor attention, computerised static perimetry with repeatability indices seems to be the preferred method and was the method used in this study.

In addition, in this study we could compare Humphrey perimetry (120° field of view) with wide field multifocal electroretinograms (WF mfERG), field of view 90°.

A review of the literature shows that different methods of visual field examination were described and there were even different ways of calculating visual loss using the same method. It is difficult to compare these studies.

Another confounding factor is the use of other anti-epileptic drugs that may be responsible for bilateral field defects. Hayashi in one study found a greater field constriction in patients on Vigabatrin and valproate (VPA) than Vigabatrin and carbamezepine (CBZ). It was previously thought that VPA is likely to increase the inhibitory action of GABA in the retina(131) and this explains the additive toxicity when Vigabatrin is combined with VPA as compared with CBZ. However, the electroretinography results were the same for both groups and hence can not be attributed to retinal toxicity alone as described by Arndt(132).

4.13.3 Humphrey perimetry

Prevalence of visual field defects using static Humphrey perimetry in patients with epilepsy on Vigabatrin have varied from 33%(133) to 68%(134) but most studies show about 50% of patients have field defects.

An over estimation of nasal visual field loss can be due to the test program used. The normal visual field extends 90 degrees temporally and 60 degrees nasally. A concentric loss of 20 degrees will show a field of 70 degrees temporally and 40 degrees nasally i.e. an apparent nasal predominant loss as described by Hardus.(135)

4.13.4 Goldmann perimetry

The prevalence of visual field defects using kinetic perimetry in patients with epilepsy on Vigabatrin have varied from 20% (130) to 92%.(136) One study by Besch has found no difference between nasal and temporal fields.(137)

Ultimately both static and kinetic perimetry are designed to quantify peripheral visual field defects. Johnson showed a high correlation between visual field constriction (i.e. kinetic perimetry) and generalized sensitivity loss (i.e. static perimetry) in patients taking Vigabatrin.(138)

Patients are always excluded from these studies because they are unable to do Goldmann fields(136) or Humphrey fields. There is therefore a significant number of patients who are on Vigabatrin are who are unable to be monitored with visual field examination.

4.14 Risk factors

Vigabatrin was licensed in the UK in 1989. There were no reported cases of visual dysfunction until Eke et al showed visual field constriction in 3 patients in 1997. The discovery of visual field defects took 8 years. It is possible that patients need to be exposed for a minimum length of time before damage occurs. But one also has to consider that defects are often asymptomatic and that because this is a difficult group in which to measure visual fields, visual defects may have went unnoticed for such a long time.

In those patients on Vigabatrin with visual field defects Van der Torren and Johnson claim that there is no association with age, gender, duration of treatment or cumulative dosage and the severity of these defects. (134;138) However, Hardus claims those patients with the largest cumulative dose (>5kg) had a slightly higher incidence of visual field defects.(135) Manuchehri showed a correlation with visual field defects once a total ingested dose of at least 1.5kg was achieved.(139) He theorised that there was a certain minimum load that needed to be achieved before visual field defects occurred. Van der Torren however postulated that there is a correlation between the daily dose and visual field defects.(134)

Some studies have found an increased incidence in male patients tested with up to 2:1 relative risk. (126;128;140) Manuchehri found a correlation between number of cigarettes smoked and visual field defects.(139)

4.15 Other anti-epileptic drugs (AED)

Cases have been reported of visual field defects associated with other AED. These have included constricted fields with phenytoin(141), diazepam(142) and progabide.(104) Can such deficits be a relatively common side effect of anticonvulsant treatment or even a feature of the natural history of epilepsy? There have been attempts to quantify the prevalence of visual field defects in patients with epilepsy by some authors but there has been some difficulty in the design and in most studies other visual pathway pathology was present.(143) Some studies have shown that other anti-epileptic drugs can cause visual field defects identical to those reported with Vigabatrin.(121) However, one other study claims that there is very little visual field constriction associated with antiepileptic drugs other than Vigabatrin (0 out of 39 patients in one study).(124)

There was also recent concern that all AED with GABA-ergic action would cause peripheral visual field defects after a report on tiagabine (TGB) was published.(144) However, other studies have shown this is not the case. One study that has compared gabapentin (GBP) and topiramate (TPM) and Vigabatrin showed that Vigabatrin was the only drug to have concentration-related effects on enzymes and intermediates of the GABA shunt in rat brain and retina.(22) Vigabatrin produced a significant dose related increase in GABA concentrations and decrease in GABA-transaminase activity in all tissues investigated. This effect was most pronounced in the retina where Vigabatrin concentrations were 18.5-fold higher than those in the brain.(22) Hence if the reason for visual field defects is related to GABA concentration as is suggested by the authors then Vigabatrin causes much higher concentrations in the retina than GBP and TGB. Of course there may be other factors unrelated to GABA that are more important such as light toxicity (see chapter 3). Another study has showed that TGB does not precipitate any significant neuro-retinal toxicity and does not appear to accumulate in the retina.(21) The results of these pre-clinical investigations suggest that Vigabatrin and TGB are pharmacologically distinct compounds with different anti-convulsant, neuro-retinal toxicity and pharmacokinetic profiles. It is possible that they will ultimately prove to have different clinical efficacies and spectra of activity.(48)

Vigabatrin is not metabolised and is excreted unchanged in the urine and would theoretically not interact with any other drugs. One study has shown that patients using other enzyme inducing drugs show a shorter half life for Vigabatrin than healthy volunteers(145) but since the action of Vigabatrin depends on the rate of GABA-

transaminase being regenerated then other drugs are not that important in overall pharmacokinetics. Studies have shown that there is no significant contribution to visual field defects by any other concomitant antiepileptic drug.(135)

4.16 Continuing or stopping the drug – visual fields

Do visual field defects recover in patients who stop Vigabatrin? If loss is not reversible then do visual field defects stabilise or progress? (101; 127)

The response to stopping Vigabatrin has been reported to be variable. Krakow,Dieterle and Versino in several papers have reported that visual field defects improve(102;102;146;147) on stopping Vigabatrin while Nousiainen in another paper have reported that visual field defects do not improve in the majority of patients on stopping Vigabatrin (148).

Schmidt, Graniiewski-Wijnands and Paul in other studies claim that there is no deterioration in visual field defects on continuing the drug (128;129;149) and therefore a "maximum" defect is achieved, dependent probably on genetic make up. Hardus presents a convincing case otherwise showing a gradual, significant progression of visual field loss in patients who continue using Vigabatrin.(150)
Withdrawal of treatment in seizure-free individuals is sometimes not a preferred option as complications arise from failure to adequately manage these patients on alternative AED. Epilepsy control is important because uncontrolled seizures increase the risk of sudden unexpected death in epilepsy (SUDEP).(95;125)

Other studies surprisingly suggest otherwise. Out of 75 patients in one study who had stopped Vigabatrin due to a visual field abnormality or concern over this potential adverse effect, the seizure control was no different or had improved in 66 (88%), while it had deteriorated in only 7 (9%) as reported by Nicolson.(140) However, this was a retrospective study and did not state how long these patients were on Vigabatrin to be included.

4.17 Conclusion

More than 100 research papers have linked Vigabatrin use and visual field defects. However the prevalence is variable due to difficulties in testing these patients. Visual field

examination is subjective with poor reproducibility in this patient group. An improved method of monitoring visual problems is needed.

My hypothesis as to why visual field defects occur in patients on vigabatrin is as follows. Vigabatrin has many influences on the visual pathway. For the purpose of this discussion these changes are termed reversible and irreversible. Vigabatrin results in reversible actions that can be acute and chronic. Vigabatrin also has been shown to have irreversible actions that can be acute and chronic such as loss in ganglion cells seen in pathology reports(95). Vigabatrin raises GABA levels and GABA will have acute and chronic actions which are very difficult to distinguish from the actions of Vigabatrin. There are also unknown factors that Vigabatrin would affect. See Figure 4.13.1.1.

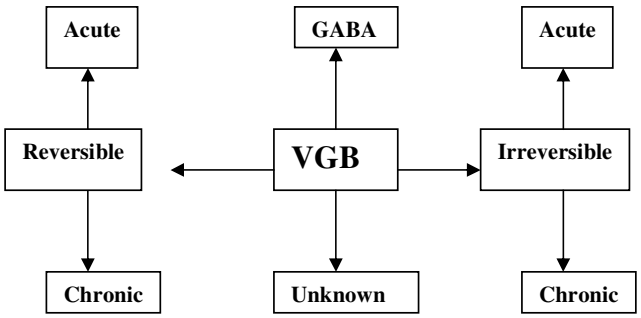


Figure 4.13.1.1 The multiple effects of Vigabatrin (VGB)

A review of the literature has not clearly defined into which "box" even visual field defects would go. Some papers claim that the visual field defects are irreversible whereas others claim that visual field defects are reversible. It is the same for other abnormalities detected in electrophysiological tests.(133;151) as will be discussed in Chapter 5. One hypothesis is that the wide field multifocal electroretinogram can better define the differences of these "boxes" with regards to management of these patients.

It is unclear what the contributing factors are to visual field defects associated with Vigabatrin use. What is clear is that only a certain number of people on Vigabatrin get visual field defects. Genetically determined variations in local tissue, drug deactivations or clearance, most probably in the retina may explain the random nature of Vigabatrin associated visual dysfunction.

But how does the prevalence of visual field defects in patients on Vigabatrin differ from other epileptic drugs? The incidence of symptomatic and asymptomatic visual field defects has not previously been accurately established and defined in patients with epilepsy. Several case reports have associated antiepileptic drugs other than Vigabatrin with visual field defects such as phenobarbitol and progabide(104). One study has a prevalence of 20% (out of 55 patients) but this was thought to be high due to occipital lobe lesions.(152) It is possible that the true incidence of pathological i.e. irreversible visual dysfunction is lower with Vigabatrin than previously thought. There was a 36% incidence of bilateral visual field defects in our patients with epilepsy not on Vigabatrin.

Because we can not accurately define field defects on different visits because of problems with reproducibility (for all the above reasons), it will be unclear if these visual field defects worsen or not thereby making managing these patients difficult.

Chapter 5

Vigabatrin and electrophysiology

5.1 Introduction

Electrophysiological tests are an attractive method of examining patients with epilepsy as they provide an objective measure of visual function. As previously discussed, patients with epilepsy have difficulty with attention and concentration and therefore subjective tests such as visual fields (kinetic or static) may be unreliable and have artifacts. Sadly, the literature does not agree on which electrophysiological tests are indicative of irreversible, pathological visual field defects that occur in patients on Vigabatrin. Reported abnormalities of electrophysiological tests will be reviewed in this chapter. If predictive retinal electrophysiological markers can be determined, it is possible that these changes can occur before visual field defects become irreversible, allowing an early review of treatment. Since electrophysiology is an objective measure of visual function it is vital in the monitoring of disease progression in patients with neuroretinal toxicity causing visual field defects.

Ocular electrophysiology comprises of a range of procedures that enable the visual pathway to be examined in an objective manner. Flash and/or pattern stimuli are presented to the patient and evoked responses are recorded by appropriate placement of electrodes. Various tests are performed to investigate different parts of the visual pathway. The electrooculogram (EOG) examines the retinal pigment epithelium. The ERG examines the global retinal responses of multiple cell types. The multifocal electroretinogram (mfERG)

examines focal areas of retina. The visual evoked potential (VEP) is an evoked electrophysiological potential that can be extracted, using signal averaging, from the electroencephalographic activity recorded at the scalp. The VEP can provide important diagnostic informationregarding the functional integrity of the visual system.The VEP examines the function of the optic nerves, optic radiations and occipital cortex.

Electrophysiological disturbances in patients receiving Vigabatrin indicate a retinal locus of abnormality. It has been proposed that Vigabatrin has many effects on visual electrophysiology. (148;153) One effect is a transient, reversible (physiological) reduction in the EOG Arden index. The EOG is affected when patients are actively taking VGB possibly due to physiologically elevated retinal GABA levels. The EOG Arden index returns to normal when the drug is discontinued(151;154). Another consequence is progressive ERG abnormalities which is thought to be associated with a risk of visual field loss and persists even when the drug is withdrawn.(43) However, the ERG abnormalities may not be synonymous with the mechanism that produces the visual field abnormality.(151)

The International Society for Clinical Electrophysiology of Vision (ISCEV) EOG measures the variation of the standing potential of the eye between light (500 cd/m^2) and dark conditions. The ratio of the voltages between light and dark is known as the Arden ratio. It is a measure of function of retinal pigment epithelial cells and their interaction with photoreceptors.

The ISCEV standard ERG measures the mass retinal response to a stimulus of light and is divided into 5 trials.

1. A rod response in the dark-adapted eye.
2. A maximal response in the dark adapted eye.
3. Oscillatory potentials.
4. A cone response in the light-adapted eye.
5. Responses to a rapidly repeated stimulus (flicker)

The visual evoked potential (VEP) is an evoked electrophysiological potential that can be extracted from the electroencephalographic activity recorded at the scalp with scalp electrodes.

5.2 Aetiology – electrophysiology

The origins of electrophysiological signals remain controversial. However some associations can be made with Vigabatrin effects on the retina.

Vigabatrin seems to have an effect in the outer retina. Reduced Arden ratios have been found in up to 70% of patients as reported by Besch(137) suggesting dysfunction of retinal pigment epithelium. A normal Arden ratio (light peak/dark trough) is greater than 1.5.

Vigabatrin appears to have an effect in the mid and inner retina.(115;155;156) Krauss has reported loss of oscillatory potentials suggesting involvement of amacrine cells.(115)

Decreased rod and cone b wave amplitude have been discovered by Van der Torren (134) suggesting dysfunction of Muller cells and bipolar cells.

Muller cells and bipolar cells are involved in the generation of the b wave. Muller cells contain retinal GABA-transaminase and actively perform transmitter recycling. Vigabatrin is thought to inhibit GABA-transaminase in Muller cells and bipolar cells(93) Therefore if Muller and bipolar cells accumulate Vigabatrin, then their GABA degrading enzyme would be inhibited, hence increasing GABA levels and therefore increases in GABA levels may lead to a decrease in b wave amplitude.(43).

Muller cell density decreases in the peripheral retina as compared to the central retina and this may be the reason that Vigabatrin can selectively damage the periphery. However this also applies to photoreceptor density.

5.3 Electrooculogram (EOG)

Studies claim that in patients on Vigabatrin, the Arden ratio is reduced by as much as 70% as reported by Arndt, Comaish and Hardus.(100;107;157) Researchers incuding Coupland, Lawden, and Harding claim that the Arden ratio of the EOG is affected only by the current use of Vigabatrin. (43;114;129;134;154) In one study Graniewski-Wijnands found that the EOG showed a statistically significant improvement after withdrawal from Vigabatrin. Abnormal EOG was present in 6/9 patients on Vigabatrin. All EOG became normal on stopping Vigabatrin.(129) Harding reported in another study in which clinically normal volunteers were given Vigabatrin for 9 days. None of these subjects had visual field

defects but all had reduced Arden index and decreased cone b wave latency that became normal on withdrawal of the drug.(151) Van der Torren showed a significant correlation with Arden ratio and cumulative Vigabatrin dose.(134) Conversely Arndt in one study has found a permanent change in EOG even after stopping Vigabatrin.(100) Van der Torren reported cumulative Vigabatrin dose had a significant correlation with EOG ratio and ERG rod and cone b wave amplitude.(134)

5.4 Electroretinogram (ERG)

5.4.1 Introduction

Vigabatrin causes abnormalities in the ERG. However Jensen has reported that abnormalities are detected in patients with and without visual field constrictions.(98) The incidence of ERG abnormalities varies from 30% to 90% (134) in patients on Vigabatrin with visual field defects . These changes have been detailed below.

5.4.2 Rod response

Decreased b wave amplitude have been reported by Van der Torren in one study(134). The incidence has ranged from 33% as reported by Coupland (43) to 38% as reported by Johnson.(138) Harding has also reported increased b wave latency in up to 50% of patients.(158)

5.4.3 Maximal

There have been reports of decreased amplitude of a wave by Hardus.(159)

5.4.4 Oscillatory potentials (OP)

Reduced oscillatory potential (OP) amplitudes have been described in several studies in up to 92% of patients including Krauss and Harding.(115;151) However, Daneshvar refutes this and have reported no change in OP but only 12 payients were tested in his study.(133)

5.4.5 Cone response

The incidence of decreased b wave amplitude has been reported to vary between 30% (Krauss) to 62% (Harding).(115;151) Studies show increased photopic b wave latency.(155);132;137) Arndt postulates in one of these studies that increased photopic b wave latency correlated significantly with severe visual field constriction and this parameter can be used to detect retinal toxicity.(132) Johnson disputes this by showing that photopic b wave latency has become less delayed on stopping Vigabatrin(138) without improvement in visual field defects and concluded there is no relationship between recovery of function and duration of treatment or cumulative dosage. Therefore the value of this test is debatable.

Miller found the cone single flash and flicker have been affected more than rod single flash.(44)

5.4.6 Flicker

Studies have reported a decrease in flicker amplitude in up to 92% of patients with a cutoff in amplitude of 70μV in patients on Vigabatrin(137;138). Ponjavic has shown that 100% of patients with visual field defects on Vigabatrin had decreased 30Hz flicker amplitude while none had decreased flicker amplitude who did not have visual field defects.(160) In another study Johnson found there was no improvement in amplitude even after discontinuation for 1 year.(138) Harding has reported delayed 30 Hz flicker in patients on Vigabatrin.(154)

5.4.7 Visual field constriction and ERG changes

Studies have shown that abnormal ERG potentials are significantly higher among patients with visual field defects than those without, in one study up to 90% of patients on Vigabatrin with visual field defects had ERG and EOG abnormalities. These included reduced ERG cone b wave amplitude, reduced OP amplitude, increased cone b wave latency (155) and reduced 30 Hz flicker amplitude which seemed to correlate with visual field loss(107) and was proposed could be used to detect retinal toxicity.(132)

However, Jensen postulates the findings of abnormal visual field defects may not be equal to abnormal ERG(98) and is supported by Lawden who has not found any link between visual field defects and ERG abnormalities.(114)

There has not been universal agreement to which ERG parameters are most sensitive and specific to visual field defects. Authors have disagreed and one of the common design flaws is insufficient control patients. However Harding has reported a study which have actively controlled for other antiepileptic drugs.(158)

Some studies claim that central, as well as peripheral retinal function is affected by Vigabatrin. Foveal ERG is proposed to test mainly central retina cone function. In one study 9 out of 11 eyes tested with foveal ERG showed normal or reduced amplitudes. However, it is difficult to position the stimulating beam precisely and steadily on the retina and these results are uncertain.(161)

5.5 Visual evoked potentials (VEP)

Multiple studies have reported abnormal VEP results associated with Vigabatrin use, though the prevalence has tended to be lower than that of visual field defects, abnormal ERG and abnormal EOG. The incidence of abnormal VEP has ranged from 7%(133) to 22%.(44) Abnormalities include decreased amplitude and increased latency of responses.

Because formal perimetry can rarely be done below a developmental age of 9 years a field specific VEP with a central (0 to 5) radius and peripheral (30 to 60) radius has been proposed(162) to be used in children (H-stimulus). Harding concluded that the different reversal rates of the central and peripheral checks allowed separate central and peripheral responses to be recorded by the electrodes on the skull. Though most of the children were able to comply with this test (35/39) only 12 children could have perimetry as well, giving values of 75% sensitivity and 87% specificity.(162)

5.6 Continuing or stopping the drug -electrophysiology

Electrophysiological tests measure the electrical signals generated by living cells of the eye. If use of Vigabatrin results in the death of these cells then the changes in electrophysiology would be irreversible. However if Vigabatrin use results in cell damage which can recover when Vigabatrin is stopped, then abnormal electrophysiological test results could be reversible.

EOG Arden index and ERG rod b-wave amplitude, rod b-wave latency time and cone ERG amplitude and latency showed a significant improvement when Vigabatrin was

discontinued in several studies.(100;138;151) However, visual field defects did not improve in these studies on discontinuing Vigabatrin(158;163). This recovery effect is a strong argument for the hypothesis that the reduction in EOG and ERG b-wave amplitude is a reversible effect. There was no statistical correlation between recovery of function and either duration of treatment or cumulative dosage.(138) Others have found no improvement in rod and cone ERG amplitudes after stopping Vigabatrin.(43;138;149)

The antiepileptic drugs carbamazepine and phenytoin have also been shown to decrease ERG rod and cone b wave and oscillatory potential amplitudes. Bayer and colleagues found that paradoxically that the addition of Vigabatrin to the medical regimen of these patients promoted the recovery of the b wave amplitude.(115)

5.7 Conclusion

Most researchers would agree that the EOG is only transiently affected by Vigabatrin usage (the Arden index recovers on stopping). ERG abnormalities have also been reported in patients with visual field defects on Vigabatrin. These have included decreased b wave amplitude (rod response), reduced oscillatory potentials, decreased b wave amplitude (cone response), increase b wave latency (cone response) and a decrease in a flicker amplitude. Reduced VEP have been reported with VGB. It is not clear if electrophysiological abnormalities can be predictive to visual field defects.

Chapter 6

Clinical findings

6.1 Introduction

A number of patients on Vigabatrin have visual complaints. These include decreased central visual acuity (VA) and flashing lights.(120) Patients also complain of decreased peripheral vision and have symptoms such as tunnel vision and bumping into objects. Some patients attribute decreased peripheral vision to clumsiness as a result of epilepsy. However many patients remain asymptomatic even though visual loss can be progressive. Peripheral visual field defects can be relevant to quality of life such as the ability to drive a car. This is one of the dilemmas in managing these patients on Vigabatrin. Many patients do not want to stop Vigabatrin even though there is visual dysfunction because they are seizure free.

Various reports have described fundus changes such as pale optic discs that may explain visual field defects associated with Vigabatrin. As previously discussed it is difficult to decide where the primary pathology is located due to Vigabatrin and what is secondary. Other reports have found no correlation between visual field defects and fundus changes.

6.2 Visual acuity

In one study central visual acuity remained stable in all patients as measured by Snellen visual charts.(130)

6.3 Colour vision

One study has reported colour defects ranging from 33% to 66% of people using various colour vision tests such as Isihara 38, Farnsworth D15-2 and Hardy Rand Rittler(161). One paper has reported a selective blue impairment that the author theorized was consistent with GABA-ergic inhibition at retinal level(164) while others have reported no change in colour vision on Vigabatrin with visual field defects.(130)

6.4 Ophthalmic findings

Studies have shown that abnormalities were found in up to 71% of subjects on Vigabatrin. These include retinal artery narrowing, epiretinal membrane, abnormal sheen or pigmentation in the macula, optic atrophy and a decrease in peri-papillary nerve fiber layer(44;126;165). Another study disputes this and has reported that there has not been any ophthalmic abnormality that could explain visual field loss.(135)

6.4.1 Optic atrophy

Several papers have reported incidences of optic atrophy with Vigabatrin use.(11;44) Indeed one of the few pathological reports available has documented loss of ganglion cells and optic atrophy.(95) However it is not clear if loss of ganglion cells is a primary phenomenon or one secondary to other retinal pathology.

One paper has reported a proposed a ‘characteristic’ finding associated with prolonged Vigabatrin use. This has been described as characteristic retinal atrophy with secondary “inverse” optic atrophy. The optic nerve is paler nasally as opposed to the more characteristic temporal pallor hence the term “inverse” However this finding was found in only 3 patients out of 138 on Vigabatrin.(96)

6.5 Studies in children

Visual field testing of children is often difficult and sometimes impossible. There have been reports of children with visual field defects in the literature.(166;166). The prevalence of visual field defects may be lower in children than in adults. (167)

In children the duration of AED therapy and the drug dose relative to body weight may differ considerably from those in adults and the maturing nervous system may respond to toxic substances in a very different manner. A major problem in estimating the prevalence

of visual field defects in children is the lack of ability to cooperate reliably in visual field testing due to young age or developmental disability.

Previous reports suggest that visual field defects do occur in some Vigabatrin treated children, however these studies have some practical problems: all study groups have been small and methods of visual field testing have varied even within one study(168-170). There are a lack of sufficient controls in studies(171) hampering the possibility of drawing conclusions that would be clinically relevant in children.(122)

There have been two reports of recovery of visual field in children who stopped Vigabatrin but this may be due to learning artifact. (172).

6.6 Conclusion

No consistent clinical observation has been reported which is specific to visual field defects associated with Vigabatrin. Other drugs have been recognised to cause retinal toxicity in the eye with characteristic clinical findings. By reviewing the retinal changes and test results of these drugs we may get an indication of the action of Vigabatrin in the retina.

Chapter 7

Retinal toxicity

7.1 Introduction

The development of retinal toxicity with medications has been an ongoing problem since Withering described digitalis-induced xanthopsia in 1785. Ocular complications due to pharmacologic agents are numerous.(173) This section describes the most commonly encountered retinopathies associated with drugs. Visual field defects seen with phenytoin, diazepam and progbabide are discussed in section 4.15.

7.2 Digitalis

It was suggested that the toxicity due to digitalis may be a result of inhibition of sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase). Isolated photoreceptors exhibited concentration-dependent reductions in the magnitude of the light response during digitalis exposure, suggesting a reduction in the normal dark current. Cones were about 50-fold more sensitive than rods.(174) Therefore chronic inhibition of Na^+, K^+ -ATPase might degrade photoreceptor polarisation with the greatest deterioration in the cone-mediated system. Digitalis toxicity is manifested as xanthopsia (yellow vision), scintillating scotoma, blurriness, colour vision defects, often in the yellow-blue axis and pericentral scotomas with normal-appearing retinas. The ERG abnormalities are decreased cone mediated amplitudes and increased photopic b-wave implicit time(174;175). Vision, colour vision and the ERG usually become normal with the cessation of therapy.(174;175)

7.3 Quinine

Over-dosage of quinine appears to be toxic specifically to retinal cells; photoreceptors, bipolar cells and ganglion cells. Occasionally bone spicule pigmentation occurs suggesting retinal pigment epithelium damage(176;177). The initial appearance of the fundus may be normal or there may be mild venous distention and retinal opacification. Over the ensuing months optic atrophy and vascular narrowing appears probably secondary to the retinal toxicity. Long term visual field constriction normally occurs(176;177). There seems to be a late decline in ERG b wave amplitude suggesting on-bipolar cell damage that may be due to toxicity or ischaemia secondary to retinal vascular narrowing. Increased ERG b wave latencies and absent oscillatory potentials have also been described.(178)

7.4. Tamoxifen

Histopathological examination of the retina of a patient with tamoxifen retinopathy revealed nerve fiber layer and inner plexiform intracellular lesions 3 to 35 μm in diameter which appear to be the product of neuronal degeneration.(179) Tamoxifen can cause a crystalline retinopathy.(179) Decreased visual acuity secondary to optic neuropathy has also been reported.(180) Visual evoked potentials (VEP) have been reported to be abnormal.(180) Reversibility of optic neuropathies has also been reported.(180)

7.5 Retinal artery emboli (talc and steroid retinopathy)

Embolic retinal vascular disease occurs from both chronic intravenous use of talc and cornstarch contained in illegal drugs and from facial injections of medication, usually steroids that are inadvertently injected intra-arterially.(181) Injected talc particles may gain access to the ocular circulation through congenital shunts or by the chronic use of crushed talc containing tablets in the presence of severe pulmonary obstructive disease. The particles lodge in the choriocapillaries and in the small vessels of the retina.(181) Embolisation of corticosteroid to the ipsilateral retinal choroidal circulation after injection of periocular and facial tissues is rare. These steroid emboli make their way to the ophthalmic artery through retrograde intra-arterial anastomatic connections after forceful injection into the vasculature.(182) Small talc particles can present as crystalline intravascular emboli and are often associated with good vision. However substantial ischemic damage to the macula can cause decreased visual acuity. Neo-vascularization at the disc and the retina can occur leading to vitreous haemorrhage and retinal detachment(181;183). Occasionally bone spicule pigmentation occurs suggesting retinal pigment epithelium damage is present. Embolisation of corticosteroid to the ophthalmic artery is rare but visually devastating when it occurs.(182)

7.6 Chloroquine and hydoxychloroquine

Chloroquine and hydoxychloroquine have been useful in treating malaria and, in larger doses, collagen vascular disease. They cause a dose related pigmented retinopathy. Both drugs apparently have a selected affinity for melanin, but the earliest histopathologic change, even before RPE damage appears to be membranous cytoplasmic bodies in ganglion cells and degenerative cells in photoreceptor outer segments followed by oedema of the retinal pigment epithelium. Such changes are typical of cationic ampiphilic (One end of the molecule is hydrophilic (`water loving', polar) and the other is hydrophobic (`water hating, non-polar)) drugs that interfere with phospholipid breakdown, probably by damaging lysosomes.(184)

Another factor compounding the toxicity of chloroquine and hydoxychloroquine is their very slow excretion rate. Small amounts of chloroquine are detectable in blood and urine as long as 5 years after the drug is discontinued.(185) This prolonged retention of the drug probably accounts for the reports of progressive and delayed onset retinopathy despite discontinuation of therapy.

Hydroxychloroquine seems to be less toxic than chloroquine.(186) In general toxicity correlates with total dosage, although this may be less so in patients less than 40 years old who may have toxicity from lower doses.(186)

The characteristic ocular signs of ocular toxicity include corneal whorl deposition, poliosis, and especially bulls' eye maculopathy. The maculopathy begins as a pigmentary mottling that progresses to become a pericentral ring of depigmentation that is often horizontally oval. There is also often peripheral pigmentary retinopathy with an associated loss of peripheral visual field, occasionally leading to a mistaken diagnosis of retinitis pigmentosa or rod/cone dystrophy. Visual acuity normally decreases with worsening of the maculopathy. Other tests may show variable results especially in early, mild involvement including abnormal colour vision.(187) There may be central, pericentral and peripheral visual defects(184;188). Immediate cessation of chloroquine or hydroxychloroquine therapy when toxicity is noted may produce clinical improvements, but the slow excretion of these drugs usually results in further progression of symptoms. Careful clinical evaluation remains imperative because there is no treatment for the retinal toxicity. EOG Arden ratio can be reduced in patients with retinal toxicity with chloroquine and hydroxychloroquine.(187) The ERG has been recorded to have reduced a and b wave amplitudes and increased latency as well as decreased oscillatory potentials.(189)

Long-term hydroxychloroquine use may be associated with mfERG abnormalities. The mfERG appears to detect retinal physiological change earlier than visual acuity testing, color vision testing or Amsler grid testing.(190;191)

7.8 Conclusion

Retinal toxicity can be caused by a variety of drugs, commonly digitalis, quinine, chloroquine and hydroxychloroquine. The effect of AED such as Carabazepine, Phenytoin and Taiagabine are discussed in section 4.15. Different mechanisms have been proposed such as the inhibition of Na^+, K^+-ATPase in the case of digitalis and disruption of membranous cytoplasmic bodies in ganglion cells and degenerative cells in photoreceptor outer segments with hydroxychloroquine. Electrophysioloical tests provide an objective measure of visual function and are often used in diagnosis and monitoring of disease progression.

Chapter 8

8.0 Multifocal Electroretinogram (mfERG)

8.1 Introduction

Recording of electrical impulses from the human eye was first reported in Scotland in 1877 independently by Dewar and McKendrick and the electroretinogram (ERG) has since become a useful diagnostic tool in ophthalmology, providing information on retinal integrity.(192) The ERG is a global retinal response produced by a summation of all the electrical responses of the different cells within the layers of the retina. The ERG is therefore unable to detect localised areas of retinal dysfunction. Recent advances in electrophysiological techniques have enabled topographical maps of retinal function to be constructed, using a technique called multifocal electroretinography (mfERG), which was first described by Sutter and Tran.(193)

MfERG enables the simultaneous recording of a collection of focal electrical impulses from the retina that correspond to localised areas of retinal function. This electro-diagnostic technique facilitates a more in depth study of the normal physiology of the human retina and leads to better understanding of the effect of disease processes on retinal function. In contrast to the standard ERG, the method of stimulation and the signal averaging process employed enables mfERG to provide high resolution spatial and temporal information on retinal processing.

The mfERG allows for the simultaneous recording of many focal retinal responses in a relatively brief recording period.

Since the first introduction to mfERG by Sutter and Tran in 1992(194), many commercial (VERIS™, RetiScan™, Metrovision™ and AccuMap™) and non-commercial systems have become available.(3;195) The discussion of the mfERG technique in this chapter will concentrate on the VERIS™ and the non-commercial system developed in the Electro-diagnostic Imaging Department in Glasgow(3;195). In general, all systems apply the same basic technique to obtain the mfERG response. The systems stimulate the retina using a

binary, aperiodic flash stimulus consisting of multiple, independent hexagonal scaled elements. The on or off state of each element is controlled by a group of pseudorandom binary sequences called m-sequences. M-sequences are unique mathematically and allow various discrete, focal retinal areas to be stimulated, independently form one another. M-sequences also allow the collection of these focal bits of retinal information from one "raw" signal collected from the eye.

8.2 Technique

Patient preparation will be described in the Methods section of this thesis

8.2.1 Stimulus

The technique of applying m-sequences to the recovery of small signals from noise has been used extensively in engineering and physics since the early 1960's and was first applied for the recovery of the ERG in the early 1970's and 1980's (196-200). The technique was further developed to provide multiple focal responses from the retina simultaneously.(201)

The mfERG evokes these electrophysiological responses using a stimulus generally consisting of multiple hexagonal scaled elements, which are independently switched between low or high luminance (black or white). See Figure 8.2.1.1

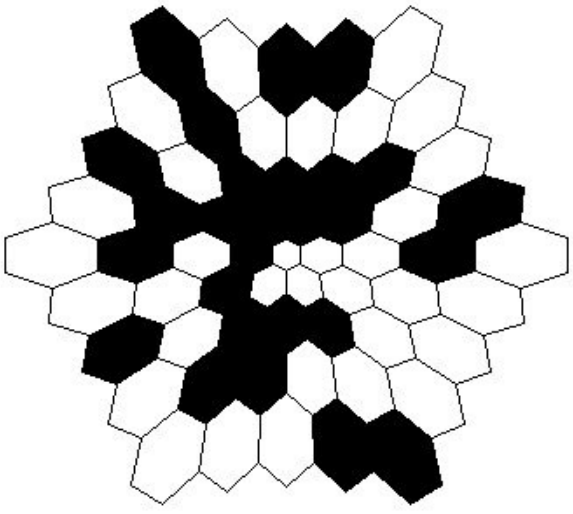


Figure 8.2.1.1 The hexagonal multifocal electroretinogram stimulus

The stimulus delivery system can be a standard cathode ray tube (CRT) device, liquid crystal display (LCD), light emitting diode (LED) or scanning laser ophthalmoscope (SLO). In this study a custom built electrophysiological system was used to stimulate 90 degrees of the visual field. This enabled wide field stimulation using a digital polysilicon projection system on a back projected screen. The main advantage of this technique is that peripheral retinal function can be assessed. This wide field stimulation is unique as no other multifocal system can stimulate more than 60 degrees of the visual field. The wide field system has been shown useful in the assessment of early retinal dystrophy and in selected cases of retinal toxicity(202;202-208;208-213). Patients on Vigabatrin appear to have selective peripheral retinal toxicity. Therefore wide field assessment has been a key element in the investigation of these patients in this study.

The luminance of each element is controlled by m-sequences. A different sequence drives each element within the array. The sequences consist of an array of '0's and '1's. The stimulus is designed so that these sequences will switch the elements on and off at its driving frequency. In the case of the most commonly used stimulator (a computer monitor as with VERIS™) this driving frequency will generally be around 75 times per second (75Hz). Thus when the stimulus is active, it appears as a random flickering pattern.

Typically this stimulus consists of either 61 or 103 elements. The scaling of each element is derived empirically to recover equivalent response amplitudes from all stimulated areas of the retina. This empirical scaling is influenced by photoreceptor topography, adaptation variation across the retina and the luminance topography of the stimulus. The intensity field of stimulation of the display varies depending on the stimulator used. Luminance intensity has ranged from 100-1000 cd/m^2 and a variety of stimulus sizes ranging from 30-120 degrees of the visual field have been reported.

8.2.2 The recording procedure

As discussed previously the luminance of each element within the stimulus is controlled by individual m-sequences. These sequences consist of an array of '0's and '1's. The stimulus is designed so that these sequences will modulate the luminance (i.e. switch the elements on and off) at its driving frequency. In the case of the most commonly used stimulator (a computer monitor) this driving frequency will generally be around 75 times per second (75Hz). Thus when the stimulus is active, it appears as a random flickering pattern.

Although each element independently stimulates a focal area of the retina, the raw (uncorrelated) response recovered will represent the summation of retinal responses generated at each individual area. Since each element is driven by its own independent orthogonal (modifying one sequence does not affect any other sequence) m-sequence this 'fingerprint' sequence can be cross-correlated against the recovered mass response. The cross-correlation process in this binary system simply involves adding the relevant section of the global response when a particular stimulus element was at 'on' and subtracting the global response when the stimulus element was 'off'. By repeating this process for each element at each stage of the recording process only the physiological responses that were modulated (and so related) to the sequence will be recovered. This provides the means of extracting the isolated response from the 'global' response. Most modern computer systems with an appropriate signal processing card can acquire, digitise, store in memory and carry out this processing in real-time and will produce a map of retinal function in around 8 minutes (see figure 8.2.2.1). This array of responses is usually termed the 'ERG map' or 'trace array'.

As the mfERG technique is still developing there are no international standards for the measurement of mfERG responses, although the International Society for Clinical Electrophysiology of Vision (ISCEV) does provide some basic guidelines. (214)

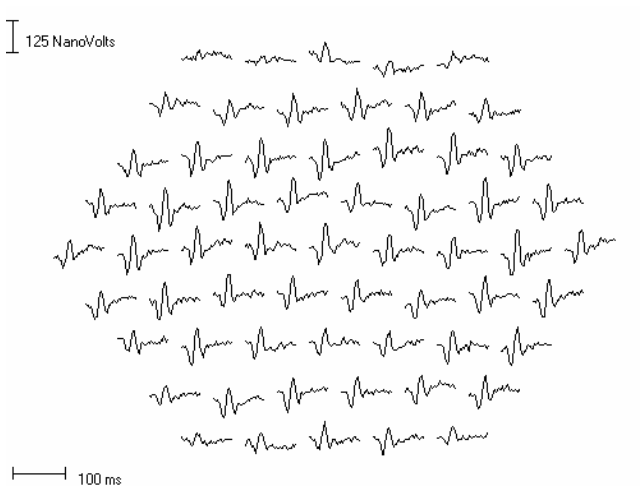


Figure 8.2.2.1 The mfERG Response

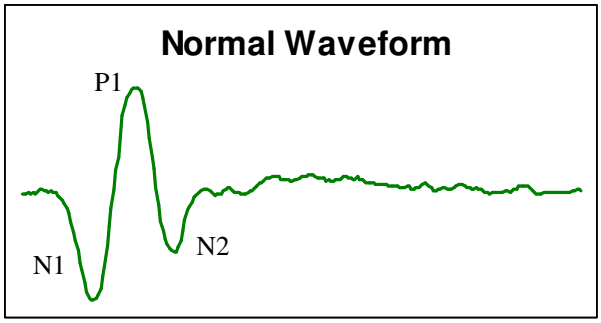


Figure 8.2.2.2 Focal waveforms in the mfERG response

There are multiple waveforms in each multifocal response. Conventionally these are named N1, first negative deflection, P1, first positive deflection and N2, second negative

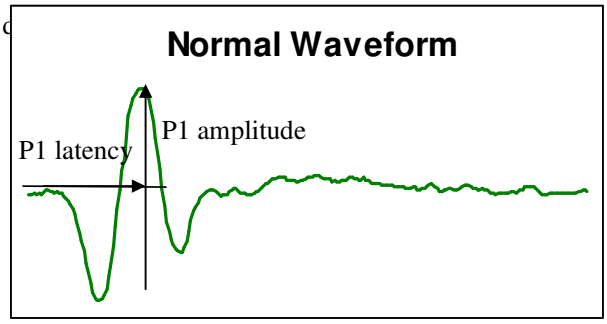


Figure 8.2.2.3 Parameters used to measure waveforms in mfERG response

Multiple measures of retinal function can be calculated using the waveforms. Illustrated in figure 8.2.2.3 are the parameters used to measure P1 latency and P1 amplitude. The commonest way of analysing mfERG waveforms is by looking at P1 amplitude and latency.

There are two responses that can be recorded from the mfERG. The first order response, which reflects responses evoked when presented with a high luminance and the second order response, which reflects responses evoked when presented with a change in luminance. In reality both 1^{st} and 2^{nd} order responses are derived from the same subcomponents which are merely added and subtracted differently (215;216). Other authors believe that the 2^{nd} order responses are non-linear or from the inner retina. Evidence from animal investigations does not clarify the contributions from the inner retina to a specific order of the response. It is also sometimes difficult to translate results from the animal model to humans.

8.3 Clinical Application

8.3.1 Introduction

There has been a huge amount of published data on the mfERG. It is useful to categorise the clinical conditions into five categories.

8.3.2 Vascular diseases of the retina

Diabetes

It has been shown that there is a reduction in first order mfERG responses before clinical changes were apparent and that implicit (latency) timing delays of the mfERG responses were a more useful indicator of diabetic macular oedema than mfERG amplitude changes(217).

Branch Retinal Artery Occlusion

A small study on 3 patients showed a reduction in amplitude and delay in implicit time of the first order P1 and N1 mfERG responses in the affected quadrant compared with the vertically symmetrical unaffected quadrant(218).

Central Retinal Vein Occlusion (CRVO)

The mfERG is a useful investigative tool for differentiating CRVO in the acute phase. There is significant difference in the P1 amplitude and P1 latency between ischaemic and non-ischaemic CRVO(219).

8.3.3 Retinitis Pigmentosa (RP)

Implicit timing delays of the mfERG responses in patients with RP could be a useful indicator of the disease and a useful parameter for monitoring the progression of RP. At advanced stages of RP, the standard Ganzfield ERG responses can be unrecordable. The spatial resolution of mfERG facilitates the recording of local electrical responses from the central retina in patients with advanced RP(220).

8.3.4 Macular disease

Age Related Macular Degeneration (ARMD)

MfERG has been shown to be a sensitive tool in the assessment of patients with pre or early ARMD. In one study P1 amplitude and P1 latency of central mfERG responses were

significantly reduced and delayed in pre-ARMD and early ARMD eyes and also in the fellow asymptomatic eyes when compared to age-matched controls. Interestingly significant delays of the peripheral retinal mfERG responses were obtained from patients with ARMD using wide field mfERG suggesting that ARMD globally affects retinal function.(221)

Stargardt's Macular Dystrophy (SMD)

Macular mfERG response amplitudes were significantly reduced in patients with SMD and central mfERG amplitude reductions were detected even in patients with normal visual acuity and normal visual fields.(222)

Best's Disease (BMD)

Central mfERG amplitude reductions that correlated significantly with visual acuity loss, were observed in a population of 18 patients with BMD, however, the mfERG reductions were much more marked than those observed in eyes with ARMD or Stargardts macular dystrophy(223).

Central Serous Retinopathy

The Electrodiagnostic Imaging Unit, Glasgow has tested 6 patients diagnosed clinically and angiographically with unilateral CSR, using multifocal electroretinography (unpublished data). They found that mfERG abnormalities of reduced amplitudes with or without implicit time delays were localised only to the areas clinically affected by the CSR and they did not find mfERG abnormalities in clinically normal areas of the affected eyes. Indeed, the electroretinographic responses from the clinically uninvolved eye were normal, supporting earlier work. Conversely, mfERG abnormalities observed in clinically unaffected areas of eyes with CSR and also in the contralateral normal eye despite the former findings and suggest a systemic aetiology to CSR suggesting that there is a pan-retinal functional effect. The cause of this is unknown.

8.3.5 Retinal toxicity

MfERG was found to be a sensitive indicator of retinal dysfunction in patients with chloroquine toxicity. The technique was more sensitive at detecting abnormalities of retinal

function than standard ERG or routine clinical tests. (62) However, only three patients were assessed in this small study.

The first reported case of a patient on Vigabatrin with visual field defects examined with mfERG was in 1998.(156) This case report concluded that both the ERG and mfERG were normal in a 17 year old on Vigabatrin for 18 months. The paper did not state if the patient was examined prior to Vigabatrin treatment so he may have had visual field constriction prior to starting Vigabatrin. The mfERG was performed using a conventional stimulus with only 50 degrees field of view and therefore the peripheral retina was not examined by mfERG.(156)

The next reported case series of two patients in 1999 reported that there was a marked reduction in amplitude in peripheral responses of the mfERG with macular sparing.(114) Other studies have confirmed reduced mfERG amplitude, sometimes globally, including one study where 12 out of 20 patients had reduced amplitude in first order kernel with conventional CRT monitors using a VERIS system with a 50 degree horizontal and 40 degree vertical visual stimulus.(114;137;155) Some studies have stated that the pattern of reduced amplitude on mfERG was predominantly bi-nasal.[155]

One study in 12 patients has found no difference in amplitude of mfERG responses in those patients with visual field defects compared to controls.(160) The range of amplitude with mfERG is wide and may not represent the most sensitive indicator of retinal pathology associated with Vigabatrin.

The first report in the literature of the use of the wide field multifocal electroretinogram (WF-mfERG) was made in the literature in 2001.(2) This case report indicated that the WF-mfERG had good correlation with visual field loss in a patient on Vigabatrin. Retinal function as measured by the WF-mfERG was normal in the central retina. A delay in implicit timings occurred with eccentricity in both eyes.(2)

A larger report in 32 adults on Vigabatrin was published in 2003.(3) These patients were matched with a cohort of patients who had never received Vigabatrin for age, sex and other anti-epileptic medication. There was no significant change in visual acuity or colour vision between the groups. 59% of the Vigabatrin group had visual field defects and none of the controls. Using WF-mfERG, all patients on Vigabatrin with visual field defects showed abnormalities (100% sensitivity) and only 2 out of 13 patients without a field defect

showed retinal abnormalities (86% specificity). The most consistent overall predictor of bilateral visual field defects was the difference between central and peripheral implicit time. See Figure 8.1 and 8.2

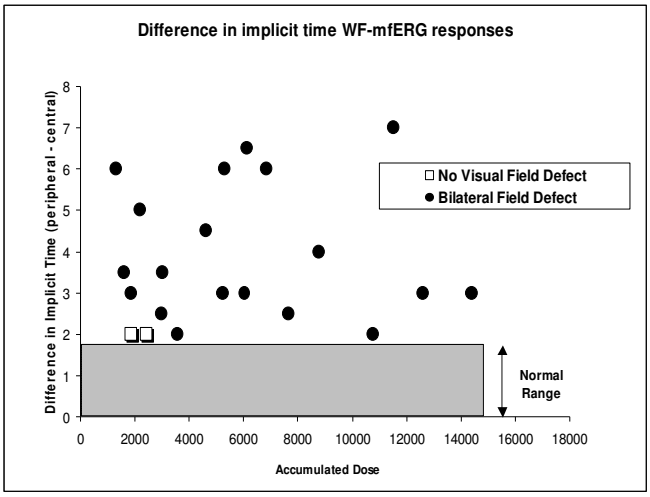


Figure 8.1 Plot of difference between central and peripheral implicit time of WF-mfERG responses in patients currently taking Vigabatrin Note the high correlation of WF-mfERG abnormalities in patients with bilateral visual field defects. Also there appears no correlation of visual defect with accumulated dose.

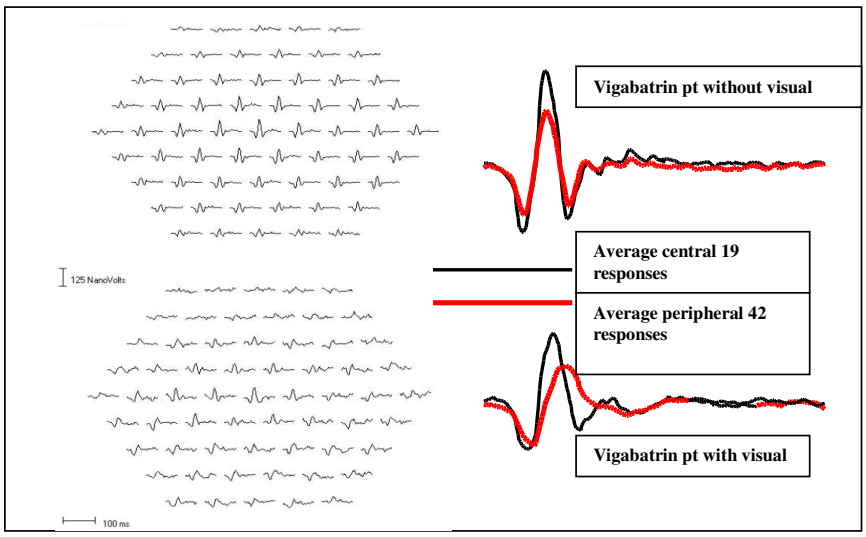


Figure 8.2 showing the difference in WF-mfERG between two patients with and without visual field defects. In the patient with visual field defects on Vigabatrin the peripheral responses are greater than 2msec delayed compared to the central responses.

8.4 Conclusion

Vigabatrin (VGB) was the first in a series of new antiepileptic agents that arose from a period of unprecedented drug development for epilepsy in the 1980s and 1990s. It was launched in the UK and Ireland in 1989 and exerts its effects by irreversible inhibition of the transaminase enzyme responsible for inactivation of the inhibitory neurotransmitter GABA(46) VGB is an effective adjunctive treatment for complex partial seizures with or without secondary generalisation in adults as shown by Marson(224) and may be the monotherapy of choice in some children with infantile spasms as reported by Chiron.(82) The drug is now licensed in more than sixty countries. Recently, VGB has received "fast track" designation from the U.S. Food and Drug Administration for the treatment of cocaine and methamphetamine dependence.

The initial barrier to marketing approval for epilepsy in the USA was an observation of white matter vacuolisation by Gibson following chronic VGB administration to experimental animals.(88) This pathology has never been reproduced in humans.(225) However, these concerns were compounded in 1997 with initial reports of bilateral visual field constriction in VGB-treated epilepsy patients by Eke.(11) Kalviainen suggested that this may be an issue for up to 40% of exposed individuals(120), despite the dearth of prospective studies or consideration of the inherent variability in the techniques employed in the assessment of visual fields.(97)

As discussed in previous chapters, there have been limitations investigating patients on Vigabatrin with visual field defects (with selective peripheral retinal toxicity) with ERG alone as it is a global retinal response and is affected by the reversible actions of Vigabatrin and increased GABA levels.

The wide-field multifocal electroretinogram (WF-mfERG) is a novel ophthalmological tool that encompasses up to 90° of the visual field and can thereby identify and differentiate dysfunction in both central and peripheral retina as described by Parks & Keating.(195) This is in contrast to standard multi-focal electroretinography that reports only 40-50° of the central field. In comparison to perimetric methods for the assessment of visual fields, WF-mfERG permits investigation of causative electrophysiology rather than just symptomatology. We have previously employed WF-mfERG to identify retinal dysfunction and by implication toxicity in VGB-treated epilepsy patients and demonstrated

a partial concordance with data obtained from traditional perimetry(2;3). The current study was designed to distinguish retinal dysfunction from visual field constriction in a larger cohort of epilepsy patients in relation to the pharmacology of their antiepileptic medications.

Chapter 9

Materials and Methods

9. 1 Introduction

Vigabatrin is an effective anti-epileptic drug for refractory partial epilepsy and the drug of choice for infantile spasms. Vigabatrin seems to selectively affect the outer retina in causing peripheral visual field defects. There are limitations in the current evaluation of these patients. Visual fields are subjective. Patients with epilepsy often have poor concentration and attention, making repeat visual fields poorly repeatable and reproducible. It is difficult to determine if there is progression of a vision defect if patients continue Vigabatrin. The ERG, though objective lacks spatial resolution. It is affected by the physiological effect of Vigabatrin itself and does not give a guideline to management. Conventional mfERG does not have a wide enough field of view to assess peripheral peripheral vision as the maximum area of examination is 60 degrees. Most other studies do not seem to have adequately controlled for epilepsy and other epilepsy drugs in the examination of the visual system. During the study I was surprised to find even if patients have documented visual field defects, patients seemed to want to continue taking Vigabatrin.

9.2 Aims

The aim of this study is to provide essential data to improve the management of patients taking Vigabatrin. This will include accurately quantifying the extent of retinal defects in patients, assessing visual and epilepsy-related quality of life, and identifying possible factors that may increase an individual's risk of developing retinal defects (i.e. other AED, occupation (indirect measure of light levels), site of epileptiform activity, smoking, alcohol etc). The study also seeks to establish whether other GABA-ergic AED are implicated in causing retinal toxicity.

9.3 Patients

Two hundred and eighty three patients, aged 16 years or over, with partial-onset seizures attending either the Epilepsy Unit (Western Infirmary), Glasgow, Scotland or the Institute of Neurological Sciences (Southern General Hospital), Glasgow, Scotland were invited to participate in the study 2002 and 2006. Only patients that had read the patient information sheet and signed the consent form were recruited into the study. (see appendix 1) Each was currently taking, or had previously taken, Vigabatrin or alternative GABA-ergic or non-GABA based AED for at least one year. All patients had CT and/or MRI scanning and were excluded if they had visual pathway pathology. Patients were not included if they had photosensitive epilepsy, significant retinal and/or optic disc abnormalities, including glaucoma, not associated with Vigabatrin therapy, were at risk of developing angle closure glaucoma, a previous temporal lobectomy or who are pregnant Two patients who subsequently developed occipital infarction were excluded from analysis.

Twenty one patients recruited were excluded from analysis for the following reasons: ten patients had a subsequent diagnosis of glaucoma (6 patients) or were found to have raised intraocular pressure and cupped optic discs (4 patients), two patients had a previous history of optic neuritis and were found to have pale optic discs on examination, four patients were unable to do visual field examination and WF-mfERG (there were no patients who could do a visual field examination but not do WF-mfERG examination), one patient had a previous history of retinal vasculitis and had retinal scars on examination, one patient had a previous history of optic atrophy with bilateral pale optic disc and three patients refused to re-attend after equipment failure.

Current Vigabatrin n=56	Previous Vigabatrin n=49	Other GABA-ergic n=46	GABA naïve n=53

Three patients were excluded from analysis as they did not have at least 6/6 best corrected visual acuity in both eyes. These included a decrease in central visual activity due to ophthalmic pathology such as opacity in the visual axis i.e. cataract (2 patients) and corneal dystrophy (1 patient). Fifty four patients failed to attend. One patient did not have repeat measurements as she had become pregnant. Two hundred and four patients were placed into four groups for analysis. Patients were matched for age, sex, duration of epilepsy and AED in each of the groups.

The patients were divided into the following groups.

1. Current Vigabatrin users. Patients had been on Vigabatrin for at least 2 years.

2. Previous Vigabatrin users. Patients had used Vigabatrin for at least 1 year but had been off Vigabatrin for at least 2 years.

3. Other GABA-ergic users. Patients had used another AED with GABA-ergic action.

4. GABA naïve users. Patients had never used AED with GABA-ergic action.

The final numbers that were analysed in the various groups were as follows.

Groupings were performed to robustly control for the prevalence of visual field defects in patients with epilepsy not on Vigabatrin and for GABA-ergic AED. The groupings also allowed analysis to identify possible factors that may increase an individual's risk of developing retinal defects.

Table 9.3.1 Numbers of patients in each group analysed

9.4 Methods

Ethical approval was obtained from The West Ethical Committee, West Glasgow Hospitals University NHS Trust, (see Appendix 1)

This research project complied with the Declarations of Helsinki.

9.4.1 Medical history

Demographic data such as age and address were noted. Patients were asked about current eye complaints, for example flashing lights, eye pain, floaters or decreased central vision. Decreased peripheral vision with symptoms such as bumping into objects was noted if volunteered and specifically asked for if not. Past ophthalmological history that can cause decreased peripheral visual field defects such as glaucoma or cataract was enquired about. Epileptic history included aetiological factors e.g. birth trauma, duration of epilepsy, type of epilepsy, time since last fit, normal frequency of fits per month and past and current AED. If patients used to be or were currently on Vigabatrin, the dosage and duration of therapy were calculated. Medical conditions that affect the eye or brain such as diabetes, hypertension or brain tumours were verified. EEG findings and MRI/CT scan results were recorded. A note was made of any family history, smoking (cigarettes per day), alcohol use (units per week), diet (scale 0 to 5, 0 being the worse possible diet and 5 being the best possible diet) and occupation.

9.4.2 LogMAR crowded test visual acuity (Keeler, Windsor, UK.)

An assessment of a patient's visual acuity gave a subjective measure of central vision. The logMAR flip chart has six selected letters which are of approximately equal legibility with all letters being symmetrical about the vertical mid-line. The following six letters were used X, V, O, H, U and Y. Each line in the chart contained 4 of the above letters to ensure a constant visual demand at each acuity level (as opposed to a Snellen chart which has different numbers of letters per line). This ensured that the only variable is the change in visual angle of the letters and permits low levels of the letter acuity to be measured with the same precision as higher acuity levels. Measured visual acuities ranged from 3/19 to 3/1.5 (equivalent to 6/38 – 6/3) at 3 m allowing parametric statistical analysis of the complete distribution of acuity scores. The range could have been extended as required by changing the test distance. A regular geometric progression of letter sizes was employed whose ratio is equal to $^{10}\sqrt{10}$ or (0.1 log units) i.e. each new line in the chart was 0.1 log

units smaller than the preceding one. Letters in each row were larger than those in the following smaller row by a factor of approximately 1.26.

Artefacts introduced through memorisation and intersession variability were also an important consideration and patients were closely monitored while reading the logMAR chart.

The test was performed in an evenly well lit room at a test distance of 3m. The initial letter acuity level was determined using the screening cards, which were cards 1 to 3 in each of the crowded tests charts. Patients were encouraged to respond to each letter in the series until an error was made. The last successful response is used to determine the starting point for the measurement of line acuity. The appropriate card was then selected and the patient asked to identify each of the four letters presented. If the patient was able to correctly identify two or more letters on a line then the next card in the series was presented.

The score for each eye was calculated using a single letter scoring system. Each line on the chart represents change of 0.1 log unit in the acuity level with each letter having a value of 0.025 log unit, an example: a patient who reads correctly all of the letters on line 5 (0.4 log unit) and 1 letter on line 6 (-0.025 log unit for a single letter) was awarded a final score of 0.375 log unit and a patient reading only 3 letters on line 5 (0.4 log unit) would have had the score for the missed letter (0.025 log unit) added to the line score giving a final score of 0.425 log unit. See Figure 9.4.2.1

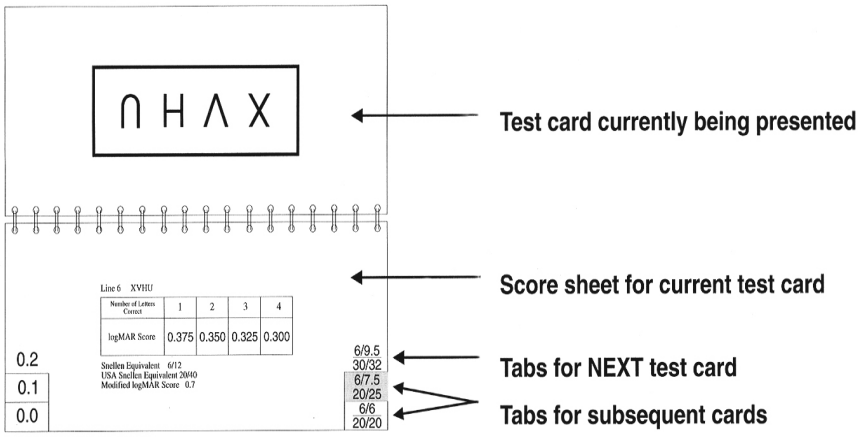


Figure 9.4.2.1 the logMAR test card

The advantage of scoring each individual letter is that the scale is made four times finer than scoring simply by line. Comparison with Snellen are provided below (Table 9.4.2)

Snellen (UK)	Snellen (USA)	logMAR
6/38	20/127	0.8
6/30	20/100	0.7
6/24	20/80	0.6
6/19	20/63	0.5
6/15	20/50	0.4
6/12	20/40	0.3
6/9.5	20/32	0.2
6/7.5	20/25	0.1
6/6	20/20	0.0
6/5	20/17	-0.1
6/3.75	20/12.5	-0.2
6/3	20/10	-0.3

Table 9.4.2.1 Comparison between LogMAR and Snellen visual acuity

The logMAR scoring system designates 6/6 a score of '0' and 6/60 a score of '1', with visual acuities less than 6/6 carrying a negative sign. Improvements in acuity result in a decrease in the score.

9.4.3 Colour vision using Hardy-Rand-Rittler (HRR) pseudoisochromatic plates (Richmond International, Boca Raton, Florida USA)

The HRR pseudoisochromatic plates were used as a qualitative diagnostic test to classify;

1. The type of colour vision defect whether protan or deutan, tritan or tetartan.
2. The degree of the defect whether mild, moderate or severe.

HRR plates have been shown to be effective in detecting acquired colour defects whereas other pseudoisochromatic plates such as Ishihara have been shown to detect predominantly congenital colour blindness.(226)

The first four plates were demonstration plates and were not scored. These plates were used to detect malingerers or patients who were totally colour blind. Patients were allowed to name the symbols as they wished e.g. for “O” they may have said circle, ball or zero. Patients were instructed that symbols may appear in any of the four corners of the page and were asked to name each symbol and then trace them out. Patients were not allowed to trace out symbols before the symbol was named. Patients were then instructed that the test was made up of circles, triangles and crosses with two, one or none on a page. Some of them would be harder to see as they may be less strong in colour (see Figure 9.4.3.1).

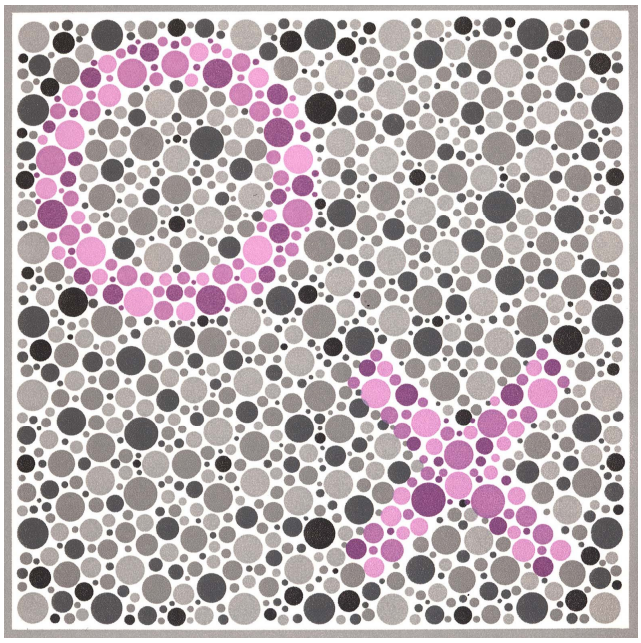


Figure 9.4.3.1 HRR screening plate. The correct response is “0” top left, “X” bottom right.

The next six plates presented were screening plates. Only patients’ immediate responses were recorded. Plates were presented every 5 seconds. If patients correctly identified the objects in all six plates then they had normal colour vision and no more colour vision testing was done. If plate 1 or 2 was not correctly identified then the patient has defective blue-yellow colour vision (see figure 9.4.3.2) and plates 17 to 20 were then presented. If any of plates 3 to 6 were not correctly identified then the patient had defective red green colour vision and plates 7 to 16 were then presented (see figure 9.4.3.3).

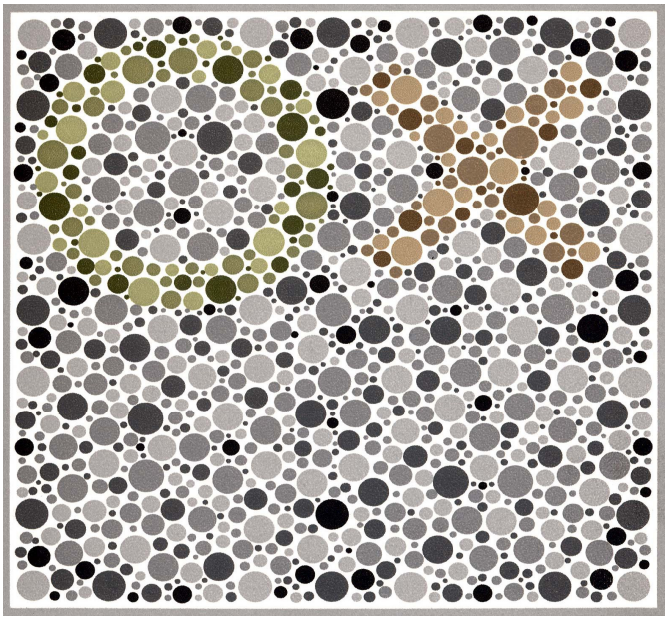


Figure 9.4.3.2 Plate 1 in HRR to test for blue – yellow colour defects

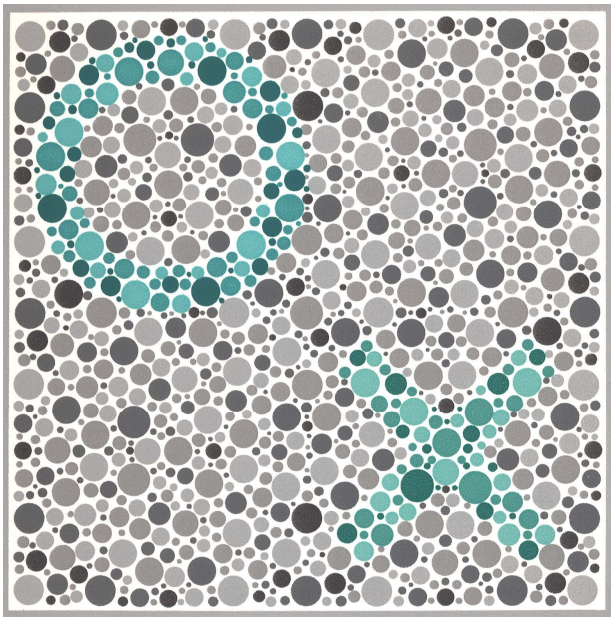


Figure 9.4.3.3 Plate 10 in HRR to test for mild red green colour defects.

For diagnosis of the type and extent of defects, plates 7 to 20 were used (see figure 9.4.3.4 An error was a failure to see all symbols or citing an incorrect name or location of any symbol or an incorrect location.

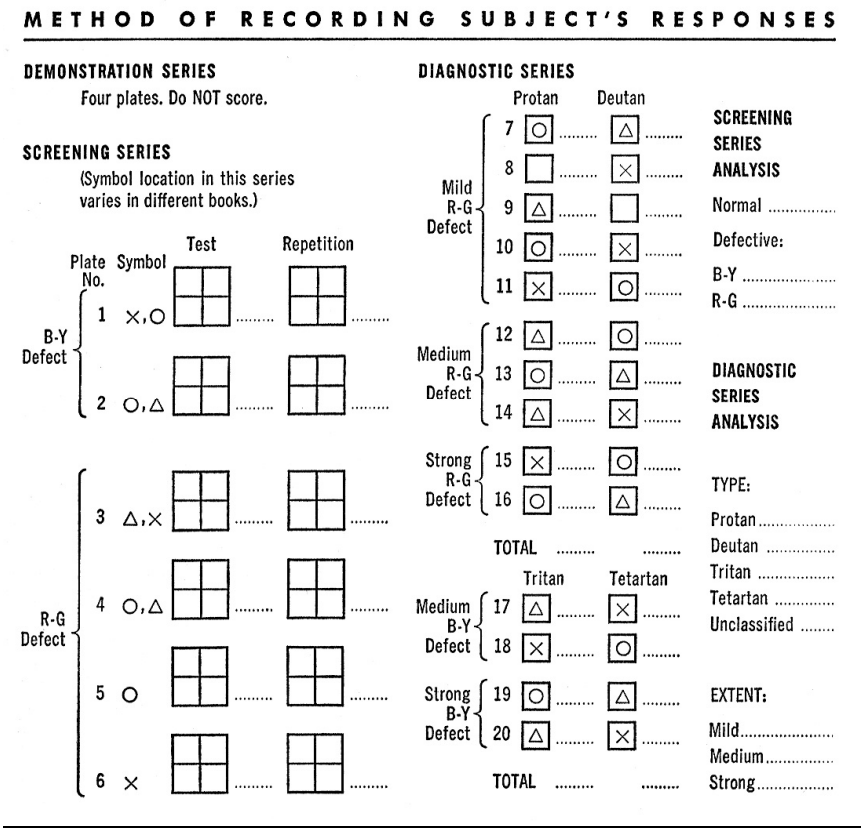


Figure 9.4.3.4 Scoring sheet for HRR
(taken from Hardy-Rand Rittler scoring manual)

Normal colour vision

Patients with normal colour vision had correct responses to all six screening plates or made an error in the screening plates but none in the diagnostic plates, and had been given the screening plates again and made no error.

Defective Colour Vision

Red green deficiency patients were labeled depending on their responses to plates 7 to 16 as protan (difficulty seeing red) or deutan (difficulty seeing blue). Blue yellow deficiency patients were labeled depending on their responses to plates 17 to 20 as tritan (difficulty seeing blue) or tetaran (difficulty seeing yellow).

Extensive scattered errors throughout the various groups were likely due to malingering or total colour blindness. Three degrees of extent of defect were recognized: mild, medium and strong.

9.4.4 Pupil examination

The size and shape of the pupils and their reaction to light and accommodation were noted. The swinging flashlight test was performed to examine for a relative afferent pupillary defect (RAPD). The patient was asked to fix his vision on an object in the distance. A strong light was shone in the right eye. The normal response is a bilateral contraction of both pupils. On moving the light to the left eye the normal response is no change in pupil size. If a patient had a RAPD then when the light was shone into the affected eye both pupils would dilate. Then on return of the light to the non-affected eye, both pupils would contract. RAPD occurs with unilateral retinal or optic nerve disease.

9.4.5 Slit lamp examination

The slit lamp is a device in which a focused, high intensity light beam (that can be narrowed into a slit) is used to illuminate the structures of the eye while the examiner looks at these structures with a magnifying scope.

The eyelids were examined for lesions of the margins and subcutaneous tissues. The areas of the lacrimal sacs were palpated and an attempt made to express any contents up through the canaliculi and puncta. The lids were then everted, and the palpebral and bulbar conjunctivae and the fornices were inspected for foreign bodies, signs of inflammation (eg, follicular hypertrophy, exudate, hyperemia, or edema), or other abnormalities.

The cornea was closely inspected. If pain and photophobia made it difficult for the patient to open their eye, topical anesthesia could be added before examination by instilling one drop of 0.5% w/v proxymetacaine hydrochloride BP and 0.25% w/v Fluorescein Sodium BP. These drops allow the easier examination of corneal abrasions or ulcers more apparent. The patient would be asked to blink several times to spread the dye into the tear film and then the eye would be examined under good magnification and cobalt blue illumination. Areas where the corneal or conjunctival epithelium is absent would stain green.

Once it was determined that patients were not at risk of developing narrow angle glaucoma and after visual field testing pupils were dilated with 1 drop of 1% tropicamide w/v BP.

Examination of the eye with dilated pupils showed opacities of the cornea, lens, and vitreous as well as lesions of the retina and optic nerve in some patients.

9.4.6 Intraocular pressure measurement (IOP)

Intraocular pressure (IOP) was indirectly measured using a Goldmann applanation tonometer on the slit lamp. This is an instrument that measures intraocular pressure by determination of the force necessary to flatten a corneal surface of constant size and eliminates the effects of scleral resistance. The device used a simple weighted lever system and eccentrically placed weights were varied until the applanated area of the cornea was flattened. This was a small corneal area (3mm) and the test was not uncomfortable for patients. Fluorescein dye with topical anaesthesia had already been instilled into the conjunctivval sac before measurement of IOP.

The weight required to flatten the cornea was directly converted to mm Hg by the device using the equation:

P = W/A where P = Intraocular pressure
W = weight applied
A = area flattened.

The procedure was repeated several times until two consecutive readings within 0.5 mm Hg were obtained. The normal range of IOP is 8 to 21mmHg.

9.4.7 Visual fields examination

The visual field was examined by automated static, three zone, suprathreshold perimetry using the Humphrey® Visual Field Analyzer (Humphrey systems Inc., Dublin, California, USA). This test was chosen as it is relatively quick to perform, is less likely to be influenced by fatigue than threshold testing (which takes longer to perform), encompasses a similar retinal field to the 90° WF mfERG and has been recommended as a screening instrument in Vigabatrin related visual field assessment.(126) Also, the visual field defects seen in patients with Vigabatrin are absolute scotomas. The added time to do a threshold test in this patient group was thought to be not worthwhile.

The Humphrey visual field device consists of a projection bowl on which test stimuli can be presented onto the surface using light projections. The bowl design ensures even background illumination of a known intensity which was consistent between repeated measurements over the period of this study.

Static suprathreshold perimetry employs a stimulus intensity that should be seen everywhere in the visual field; i.e. it is above the predicted threshold value for each location. The stimulus that is presented is 6dB brighter than the expected age-dependent threshold at each point. The suprathreshold stimulus of light was presented as a small stationary spot of white light for a short period of time superimposed on a white background of uniform brightness. A hill of vision was assigned to the patient based on the patient's age.

A three zone test strategy was used. Every missed point is measured again at maximum intensity at 10,000 apostilbs to determine if the defect is absolute. The printout displays (X) for relative defects. Using this strategy, large areas of the visual field can be quickly examined.

The 120 stimulus locations are located within an eccentricity of 50° nasally, 60° temporally, 40° superiorly and 55° inferiorly (see Figure 9.4.7.1.). The stimulus size subtended 0.43 degrees, was $4mm^2$ and was white in colour. The stimulus duration was 200 milliseconds and the background luminance of the bowl was 31.5 apostilbs for all visual field examinations. The normal test speed setting was used which automatically adjusted for slow responding patients. The fixation target used was a small yellow light in the centre of the bowl.

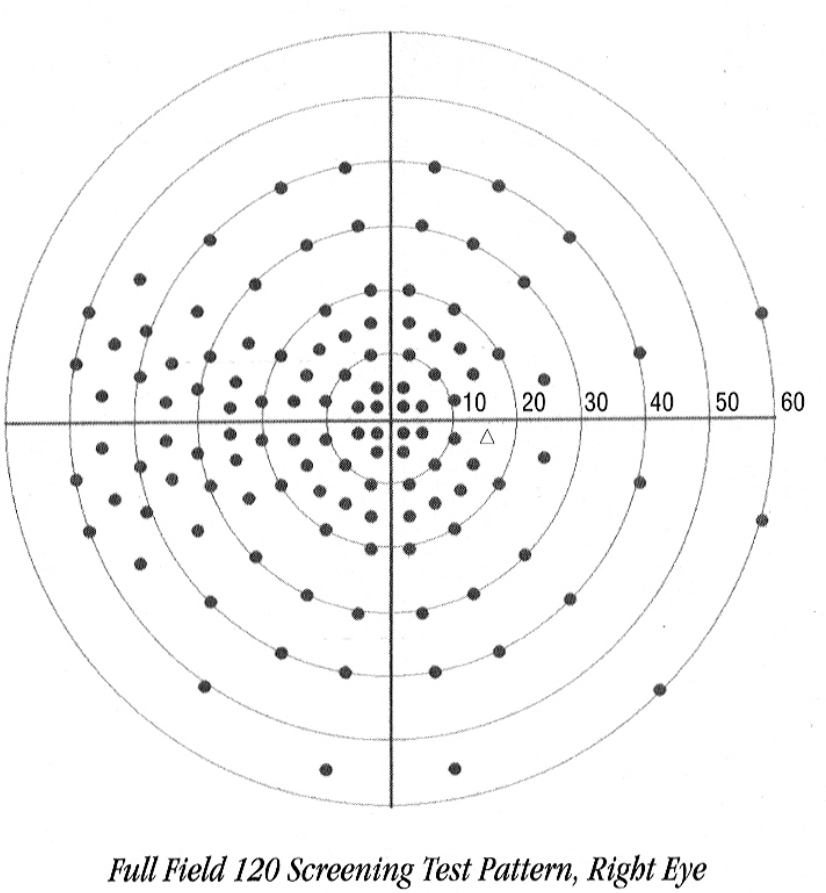


Figure 9.4.7.1 Stimulus locations for 120 degree visual field
(Taken from Humphrey® Field Analyzer II–i series User Manual)

The test procedure was explained to all patients clearly. All questions were answered before starting. The following instructions were given;

"This test will measure your central and side vision. It is always important that you look straight ahead at the steady yellow light. (The yellow fixation light was shown.) Other lights will flash one at a time off to the side. Some will be bright, some dim. Press the button whenever you see one of these lights. (The response button is presented to the patient.) You are not expected to see all of the lights so do not worry if you think you have missed some. If you want to rest, hold down the button, the test will resume when you release the button. We test one eye at a time. Blink normally so that your eye does not get dry."

The non-test eye was patched with temporary adhesive eye patches so that vision was completely blocked. The table, seat height and chin rest height were adjusted so that the

patient was comfortable and relaxed while holding the button. The patient placed their chin on the appropriate side of the chin rest with their forehead against the forehead rest. The patient was aligned on the video eye monitor so that the pupil was centred on the target. The blinds were closed so that the room was dimly lit.

The blind spot was monitored to determine reliability. The test programme periodically presented 5% of stimuli to the patient's blind spot. Only if the patient indicated seeing the blind spot stimulus would the instrument record a fixation loss. If the patient was fixating well then they would not see the blind spot check stimulus. The blind spot test stimulus matches the test stimulus size i.e. $4mm^2$. A high fixation loss score indicated that the patient did not fixate well or that the blind spot was incorrectly located. The printout showed the total number of fixation losses followed by the total number of stimuli presented within the blind spot.

Trial lens correction was used in all patients requiring near vision correction.

Classification	Temporal	Nasal	Superior	Inferior
Normal	>60°	>50°	>40°	>55°
Mild	50 – 60°	36-50°	36-40°	45-55°
Moderate	30-50°	20-35°	20-35°	25-45°
Severe	<30°	<20°	<20°	<25°

Table 9.4.7.1 Classification of degree of visual field loss is dependent on proximity to fixation of a cluster of four or more visual field defects. Values are degrees from fixation.

All visual fields were assessed masked to drug history by two experienced Ophthalmologists (PG and FD) with much experience of automated perimetry. Automated static threshold perimetry is a demanding visual task particularly in patients with cognitive impairment. Therefore patients who exhibited visual fields that manifested >50% fixation losses were deemed unreliable i.e. a greater margin of error was allowed in this patient group because of attention problems, normally only up to 33% of fixation losses are allowed.

Using a modification of a previously described visual field defect classification by Wild (126), a cluster of four or more relative or absolute defects was described as an abnormal field defect. These defects were further classified as mild, moderate or severe depending on the proximity of the defect to fixation in each of the retinal quadrants. See Table 9.4.7.1

Examples are given below of no, mild, moderate and severe visual field defects. See figure 9.4.7.2 – 9.4.7.5

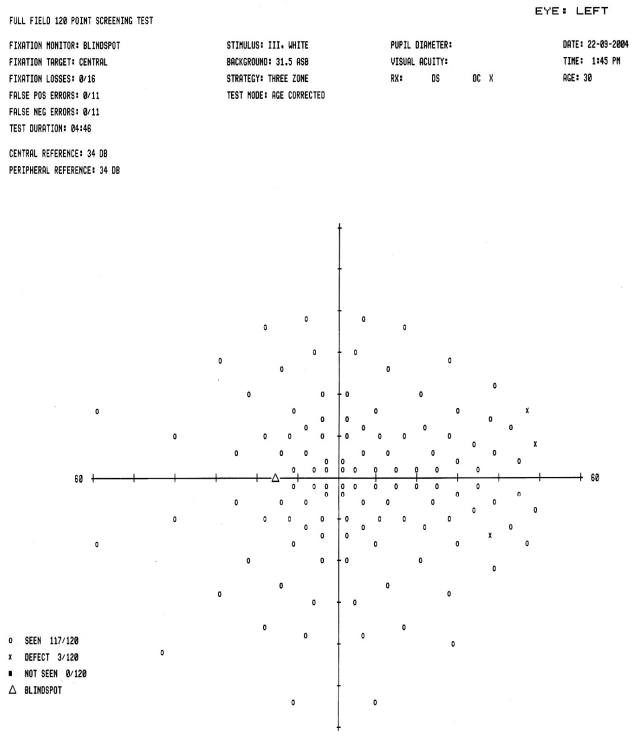


Figure 9.4.7.2 No field defect (Humphrey 120 degree screening test)

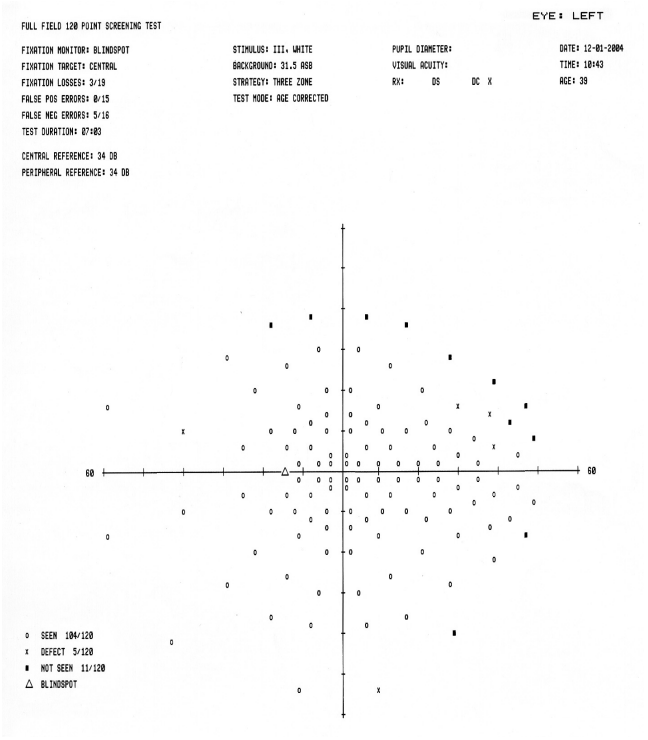


Figure 9.4.7.3 Mild field defect (Humphrey 120 degree screening test)

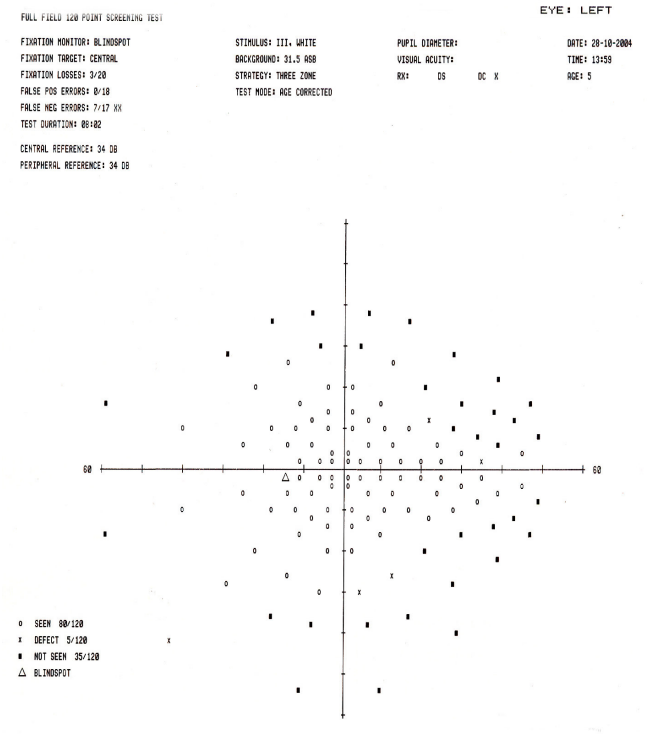


Figure 9.4.7.4 Moderate field defect (Humphrey 120 degree screening test)

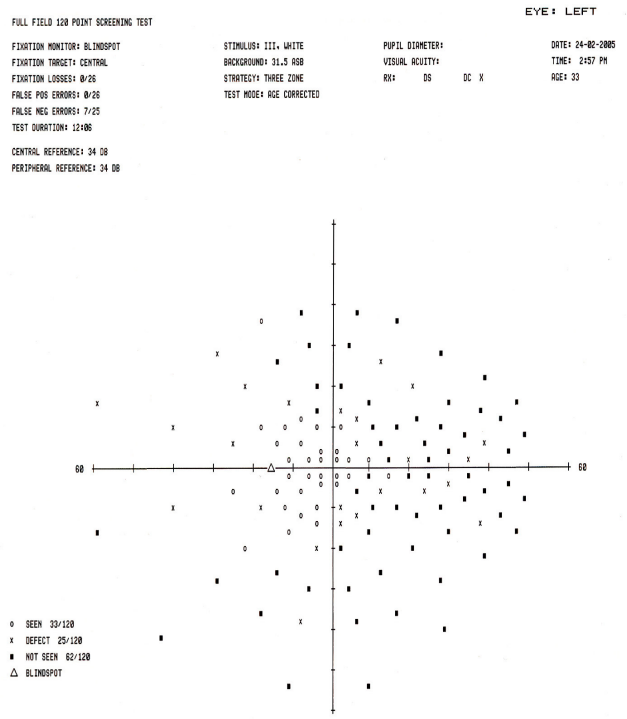


Figure 9.4.7.5 Severe field defect (Humphrey 120 degree screening test)

9.4.8 Preparation for Electrophysiology

Patients are seated comfortably. Clear explanations for the test are given. Topical anesthesia and dilation were achieved using one drop of 0.5% w/v proxymetacaine hydrochloride BP and 2 drops of 1% tropicamide w/v BP into each eye. Reference skin electrodes were placed at the outer canthi of each eye and a ground or indifferent electrode was placed on the forehead using Neuroline® disposable skin electrodes. Contact DTL® electrodes were placed along the lower cornea of both eyes.

9.4.9 Electroretinograms (ERG)

ERG were performed in all patients to identify global retinal function.

The ERG response is dependent on a number of variables including the type of electrode used. It is therefore important that every individual laboratory or clinic establish their own normative data. See figure 9.4.9.1 for our normative data set for the Espion Diagnosys electrophysiological system using DTL® and Neuroline® electrodes.

	Amplitudes (micro Volts)	Implicit times (ms)
Rod	**72-367**	**74-102**
Max A	**165-291**	**15-17**
Max B	**241-709**	**34-59**
Osc Pot	**36-112**	**15-20**
Cone A	**17-55**	**7-13**
Cone B	**68-222**	**22-31**
Flicker	**25-150**	**21-31**

Table 9.4.9.1 Normative data for Electro-diagnostic Imaging Unit

By appropriate selection of background light levels, stimulus luminance, dark or light adaptation it is possible to obtain a set of responses which give objective and complementary information on the integrity of retinal processing. The examples shown in this section were recorded from a patient in group 4 of this study using the disposable DTL Fibre electrode. In the description of the responses a Standard Flash is defined as a stimulus luminance level of 3.0 $Cd.m^2$.

Response 1- The Rod Response

This response was recorded using a dim flash of light in dark adapted eyes. The period of dark adaptation was 20 minutes. The stimulus intensity was 0.01 cd/m^2. Serial averaging of a number of responses was performed but inter stimulus duration was not less than 2 seconds to avoid light adapting the retina. A typical response is shown in Figure 9.4.9.2.The positive wave is known as the b-wave and is generated by the on-bipolar cells in the retina. As signals are passed to the on –bipolar cells from the rod system, a normal waveform indicates intact rod and on-bipolar cell function. The key measurement was the amplitude from baseline to the peak of the response. Time to peak was also of interest.

Response 2-The Maximal Response

This response was also performed on a dark adapted eye. In this case a bright flash of $3cd/m^2$ was used to evoke a response that is generated by both rod and cone systems. As this was a more intense flash of light inter stimulus duration was not less than 15 seconds to avoid light adapting the retina. An example is shown in Figure 9.4.9.2. The trough is known as the a-wave and is generated by off–bipolar cells with a small contribution directly from the photoreceptors. The positive component is the b-wave and this is mainly generated by off-bipolar cells. The a-wave amplitude is measured from the baseline to the trough and the b-wave amplitude from the a-wave trough to the response peak.

Response 3-Oscillatory Potentials

Oscillatory potentials are small oscillations on the rising edge of the b-wave. Stimulation was the same as for the maximal response but in order to emphasise the high frequency oscillations, a different amplifier filter bandwidth was used. Instead of 0.5 to 300 Hz a restricted bandwidth of 75 Hz – 300 Hz was used. This removed the slow frequency component giving the oscillatory potentials as illustrated in Figure 9.4.9.2. The oscillatory potentials are believed to originate in the inner retina with horizontal and amacrine cells the most likely generators.

Response 4-Cone Response

A 10 minute period of light adaptation to a background luminance of 30 cd/m^2 was done before this photopic measurement was performed. 3 cd/m^2 was used and an example response is shown in Figure 9.4.9.2. This response is dominated by the cone pathway with the a-wave generated by the off-bipolar cells and the b-wave the on-bipolar cells. Waveform measurements are the same as in previous examples.

Response 5-Flicker Response

A pure response from the cone pathway was obtained using a fast flickering stimulus. In this case, the Standard Flash was used at a stimulation rate of 30 Hz. The rod system cannot respond at these frequencies therefore the flicker response is a pure cone pathway response. A normal flicker response is shown in Figure 9.4.9.2.

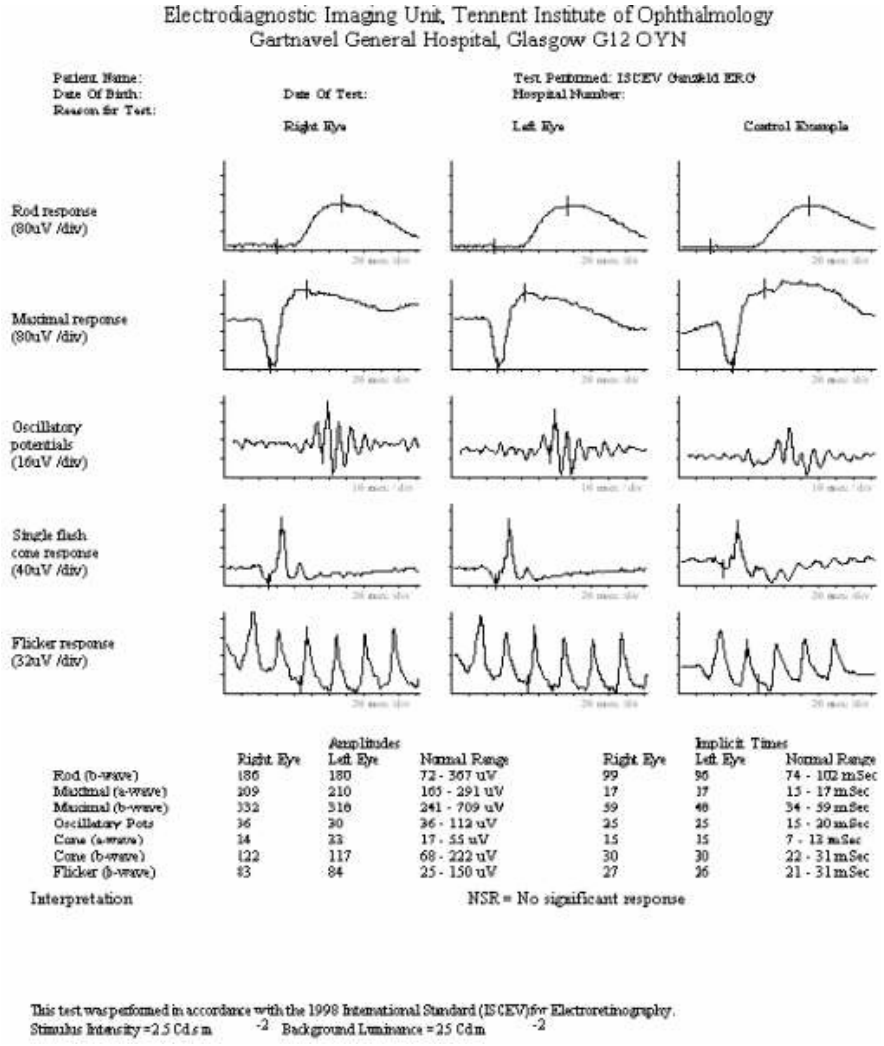


Figure 9.4.9.1 Normal ERG

(taken from Electro-diagnostic Imaging Unit, Glasgow)

A summary table of stimulus intensity, background intensity and frequency is given below for the ERG parameters in this study.

Parameter	Flash intensity (cd/m^2)	Background intensity (cd/m^2)	Flash Frequency (Hz)
Rod	0.01	0	1
Maximal	3	0	1
Oscillatory potential	3	0	1
Cone	3	30	1
Flicker	3	30	30.3

Table 9.4.9.2 Stimulus intensity, background intensity and frequency of the ERG stimulus

9.4.10 Wide field multifocal ERG (WF-mfERG)

The WF-mfERG was performed in all patients immediately after the ERG was performed. The electrodes used for the ERG were also used to record the WF-mfERG response.

The WF-mfERG was recorded using a custom built electrophysiological system. Wide field stimulation was achieved using a digital polysilicon projection system at a refresh rate of 75Hz. Maximal stimulus luminance was 1500 candelas per m^2. An array of sixty one empirically scaled hexagons was used to stimulate 90 degrees of the visual field. The hexagons were scaled with eccentricity to take into account photoreceptor topography, photo-adaptive response profile and projection luminance gradient. Each hexagon OFF and ON state (black and white, 97% contrast) was controlled by a binary m sequence (explained in the introduction section).The duration of overall recording period was eight minutes, segmented into sixteen intervals each lasting thirty seconds. An amplifier gain of 100,000 with an ADC digitisation rate of 1200Hz and a dual high/low pass filter of 3-300Hz and 10-100Hz was used

Wf-mfERG responses were grouped concentrically into central (60 degrees) and peripheral (61 to 90 degrees) for analysis. See figure 9.4.10.1

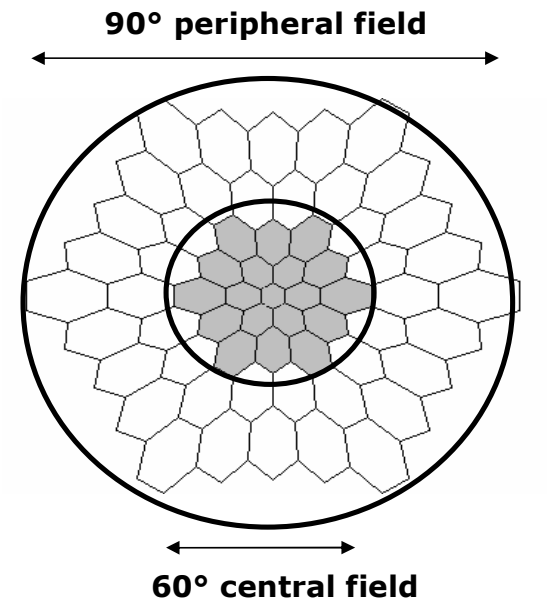


Figure 9.4.10.1 Groupings of central and peripheral responses for analysis of the WF-mfERG.

Responses were compared between the four patient groups for N1, P1 and N2 amplitude and latency. From previous studies the most consistent overall predictor of bilateral field defects was the difference between central and peripheral implicit times.(3) See figure 9.4.10.2.

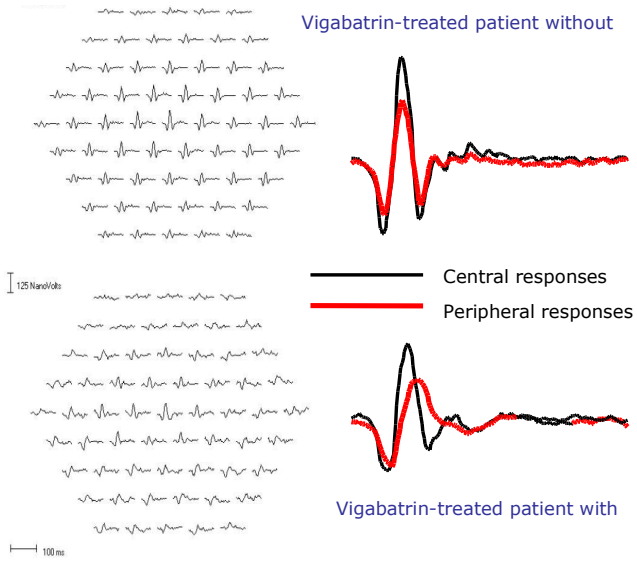


Figure 9.4.10.2 Typical examples showing responses from a patient on Vigabatrin with visual field defects compared to a patient on Vigabatrin without visual field defects. The traces from each retinal area are on the left while summed responses are on the right. In the patient on Vigabatrin with visual field defects the peripheral responses are delayed compared to the central responses.

9.4.11 Quality of life in epilepsy questionnaire (QOLIE 31 P)

The Quality of Life in Epilepsy Inventory (QOLIE-31 P) contains seven multi-item scales that question the following health parameters: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life.(227) A QOLIE-31 P overall score was obtained using a weighted average of the multi-item scale scores. The QOLIE-31 P also included a single item that assesses overall health. The additional 7 preference items are scored separately and not combined with the main score.

Pre-coded numeric values for responses on some QOLIE-31 P items are in the direction such that a higher number reflects a more favorable health state. For example, a circled response of '10' for item 1 corresponds to "Best Possible Quality of Life", while a circled response of '0' corresponds to "Worst Possible Quality of Life." However, pre-coded numeric values for some other items on the QOLIE-31 P are in the direction such that a lower number reflects a more favorable health state. For example, a circled response of '1' for item 14 corresponds to more favorable quality of life, while a value of '5' on this item

corresponds to less favorable quality of life. As these examples also demonstrate, different items in the QOLIE-31 P have different ranges of precoded numeric values. After coding higher scores always reflect better quality of life (see appendix 3).

A QOLIE-31 P overall score was derived by weighting and summing QOLIE-31 scale scores. QOLIE-31 P scale weights were derived from a regression analysis that used a summary score from the OOLIE-89. The QOLIE-31 overall score was calculated by summing the product of each scale score times its weight and summing over all scales.

The QOLIE 31 P questionnaire and QOLIE 31 P scoring manual are in appendix 2.

9.4.12 Visual function questionnaire (VFQ-25)

The VFQ-25 is the product of an item-reduction analysis of the longer field test version of the survey called the 51-item National Eye Institute Vision Function Questionnaire (NEI-VFQ).(228) The survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. Questions included in the VFQ-25 represent the content identified during a series of condition-specific focus groups with patients who had age-related cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, or CMV retinitis. The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question.

The VFQ-25 generates the following vision-targeted sub-scales: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and color vision , and ocular pain. Additionally, the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in population-based studies.

The VFQ-25 was scored by a two-step process. In step 1 original numeric values from the survey were re-coded following the scoring rules outlined in appendix 3. All items were scored so that a high score represented better functioning. Each item was then converted to a 0 to 100 scale so that the lowest and highest possible scores were set at 0 and 100 points

respectively. In this format, scores represented the achieved percentage of the total possible score, e.g. a score of 50 represented 50% of the highest possible score. In step 2, items within each sub-scale were averaged together to create the 12 sub-scale scores. Appendix 4 indicates which items contributed to each specific sub-scale. Items that were left blank (missing data) were not taken into account when calculating the scale scores. Sub-scales with at least one item answered could be used to generate a sub-scale score. Hence, scores represented the average for all items in the sub-scale that the respondent answered. To calculate an overall composite score for the VFQ-25 the vision-targeted sub-scale scores were simply averaged excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we gave equal weight to each sub-scale whereas averaging the items would have given more weight to scales with more items.

9.4.13 Digital fundus photograph

Every patient had digital fundus photography using the Oculab® digital imaging system with a Zeiss® F450 camera. Two photographs were taken: one with 50 degrees of view encompassing the optic nerve, macula and superior and inferior arcades, the other a 30 degree close up of the macula. The fundus photographs of all patients were reviewed by two experienced Ophthalmologists (PG) and (FD) who were blinded to the other's assessment. Only agreed clinical findings were included in analysis.

9.5 Statistical analysis

Statistical analysis was performed following advice from the Robertson Centre for Biostatistics, University of Glasgow.

Baseline demographics (visit 1) and clinical characteristics were summarised by drug group. Continuous variables were reported as mean (standard deviation (SD)) or median (as appropriate) and range (minimum-maximum). Categorical variables are reported as number and percentage. The proportion of patients in each of the drug groups with bilateral visual field defects at visit 1 was compared using the chi-squared test. Unilateral visual field defects and bilateral and unilateral abnormal WF-mfERG were compared in a similar manner. Kappa statistics and corresponding 95% confidence intervals were reported for the agreement between visual field defects and abnormal WF-mfERG for both bilateral and unilateral effects.

ERG investigation variables at visit 1 were compared between patients with and without bilateral visual field defects using Wilcoxon rank sum tests. Results are given for all patients and for each of the 4 drug groups separately. Each variable is also summarised by mean (SD) and median (Interquartile range (IQR)).

The Wilcoxon signed rank test was used to compare the change in the difference between central implicit time and peripheral implicit time at visit 2 from visit 1 for all patients and by each of the 4 drug groups separately. The proportion of patients with visual field defects and abnormal mf ERG were compared between visit 1 and visit 2 using McNemar tests. Spearman's rank-correlation coefficient was used to asses the association between number of monthly seizures and degree of Ptosis.

The influence of baseline patient and clinical characteristics on bilateral visual field defects were examined using logistic regression models. Each of the variables was added into the model univariately, then a multivariate stepwise model was constructed retaining only variables significant at $p<0.05$. Odds ratios, 95% confidence intervals and corresponding p-values are reported.

Analysis of variance (ANOVA) was used to compare QOLIE-31 total score and subscales at visit 1 for the 4 groups.

All statistical analyses were performed using SAS for windows version 8.2. All available data was used for each measurement.

Chapter 10

INITIAL RESULTS

10.1 Baseline Demographics

Patients with epilepsy were grouped into four groups. Group 1 consisted of patients with epilepsy who had been Vigabatrin for at least 2 years and is named Vigabatrin group. Group 2 consisted of patients with epilepsy on Vigabatrin for at least 2 years and off Vigabatrin for at least 2 years and is named ex-Vigabatrin group. Group 3 consisted of patients with epilepsy on another anti-epileptic drug with a GABA-ergic action other than Vigabatrin and is named GABA group. Group 4 consisted of patients with epilepsy who have never been on Vigabatrin or GABA-ergic drugs and is named the non-GABA group.

Patients were matched for age, sex and duration of epilepsy as far as possible and baseline demographics support this. (see Table 1) Since we had a limited population, sex of the patient was not as important as other epilepsy drugs or duration of epilepsy. Average monthly seizure frequency was 1 for Vigabatrin and ex-Vigabatrin groups and 0 for other GABA groups and other non-GABA group but ranged from 0 to 750 per month across all groups.

The mean length of Vigabatrin therapy in Vigabatrin Group was 5.7 years, range 2 years to 8 years. The mean Vigabatrin load was 5788g with the range 2765g to 21056g.

A number of patients in each group described decreased visual acuity on ophthalmic history. Three patients were excluded from analysis as they did not have at least 6/6 best corrected visual acuity in both eyes. These included a decrease in central visual activity due to ophthalmic pathology such as opacity in the visual axis i.e. cataract (2 patients) and corneal dystrophy (1 patient). Similarly, anyone who had peripheral visual field defects which could be explained by ophthalmic pathology such as glaucoma, occipital lobe stroke or cataract was excluded from analysis (12 patients). Every patient had MRI scans of their visual pathway and were not included if there were any structural lesion that could affect the visual pathway (7 patients).

There was an equal distribution of significant medical diseases between the groups. Hypertension was the most common associated medical disease in all groups (n = 16). The most common associated familial diseases were epilepsy and glaucoma and were distributed between the groups.

By far, the most common additional anti-epileptic drug was carbamazepine (n = 126). There was a consistent distribution of anti-epileptic drugs across all groups. However on average patients in the Vigabatrin group and

the ex-Vigabatrin group had used a greater variety of anti-epileptic drugs than those in the GABA group and the non-GABA group. This was expected as Vigabatrin is used mainly to treat refractory seizures in this patient population by the Epilepsy Unit, Western Infirmary Glasgow. Taking this into account, patients were matched as best possible for other anti-epileptic drugs used among the four groups as well as age, sex and duration of epilepsy. Patients in the Vigabatrin group and the ex-Vigabatrin group seemed to smoke more and drink less on average than patients in the GABA group and the non-GABA group, see Table 1. The GABA group and non-GABA group had the highest employment rate reflecting good seizure control. Monthly seizure frequency was on average 0.

Characteristics	Vigabatrin (n=56)	Ex-Vigabatrin (n=49)	GABA (n=46)	Non-GABA (n=53)
Continuous variables				
Age (years)	39.9 (13.0), [12.1-70.5]	43.9 (14.6), [16.4-81.3]	46.7 (14.8), [16.3-79.8]	43.8 (16.0), [17.4-85.8]
Duration of epilepsy (years)	20.4 (9.9), [5.1-51.5)	24.4 (12.2), [4.2-55.0]	19.3 (12.8), [1.4-50.6]	13.3 (10.0), [2.0-39.6]
Female	29 (51.8)	35 (71.4)	25 (54.4)	36 (67.9)
Monthly seizure frequency Median [range]	1 [0-90]	2 [0-750]	0 [0-84]	0 [0-30]
Length of Vigabatrin therapy (years)	7.7 (3.7), [2.2-9.0]	1.75(0.35) [1.0-1.9.0]	-	-
Actual load Vigabatrin (g) median [range]	5788 [2765, 21056]	(not enough data)	-	-
Categorical variables				
Ophthalmology history				
Myopia	3 (5.4)	3 (6.1)	2 (4.4)	4 (7.6)
Presbyopia	0 (0)	2 (4.1)	10 (21.7)	9 (17.0)
Decreased central visual acuity	5 (8.9)	7 (14.3)	9 (19.6)	7 (13.2)
Medical history of :				
Asthma	2 (3.6)	2 (4.1)	2 (4.4)	7 (13.2)
Diabetes	2 (3.6)	3 (6.1)	0 (0)	2 (3.8)
Hypertension	1 (1.8)	5 (10.2)	3 (6.5)	7 (13.2)
Ischaemic heart disease	5 (8.9)	2 (4.1)	2 (4.4)	1 (1.9)
Family history of:				
Epilepsy	3 (5.4)	8 (16.3)	1 (2.2)	7 (13.2)
Glaucoma	2 (3.6)	4 (8.2)	5 (10.9)	1 (1.9)
Other anti-epileptic drugs:				
ACETAZOLAMIDE	5 (8.9)	7 (14.3)	0 (0)	0 (0)
CARBAMAZEPINE	38 (67.9)	39 (79.6)	24 (52.2)	25 (47.2)
CLOBAZAM	10 (17.9)	17 (34.7)	5 (10.9)	0 (0)
GABAPENTIN	11 (19.6)	20 (40.8)	6 (13.0)	0 (0)
LEVETIRACETAM	8 (14.3)	19 (38.8)	16 (34.8)	0 (0)
LAMOTRIGINE	18 (32.1)	28 (57.1)	17 (37.0)	29 (54.7)
OXCARBAZEPINE	2 (3.6)	6 (12.2)	3 (6.5)	1 (1.9)
PHENOBARBITONE	8 (14.3)	12 (24.5)	7 (15.2)	0 (0)
PHENYTOIN	24 (42.9)	21 (42.9)	11 (23.9)	5 (9.4)
TIAGABINE	5 (8.9)	11 (22.4)	2 (4.4)	0 (0)
TOPIRAMATE	15 (26.8)	26 (53.1)	6 (13.0)	0 (0)
VALPROATE	18 (32.1)	25 (51.0)	25 (54.4)	0 (0)
Current smoker	14 (25.0)	15 (30.6)	8 (17.4)	12 (22.6)
Drinks alcohol	2 (3.6)	5 (10.2)	8 (17.4)	16 (30.2)
Employment:				
Employed/student	25 (44.6)	18 (36.7)	23 (50)	38 (71.7)
Retired	7 (12.5)	7 (14.3)	13 (28.3)	7 (13.2)

Unemployed	24 (42.9)	24 (49.0)	10 (21.7)	8 (15.1)

Table 10.1.1 Baseline demographics and clinical characteristics by patient drug group. Data are presented as mean (SD), [Range] for continuous variables and number (%) for categorical variables unless otherwise stated.

10.2 Wide field multifocal electroretinogram (WF-mfERG) and visual field defects.

As discussed previously, a typical WF-mfERG response from a Vigabatrin patient with no field abnormality and one with a moderate bilateral field abnormality is shown below. Note the delay (>2ms) between central and peripheral WF-mfERG response peaks in the patient with a moderate bilateral visual field defect. A bilateral delay of greater than 2 milliseconds was the defining feature of retinal toxicity in this patient group. However, all parameters of anatomical and functional assessment of vision, such as fundus examination, visual field assessment and ERG in all patient groups were also analyzed and compared.

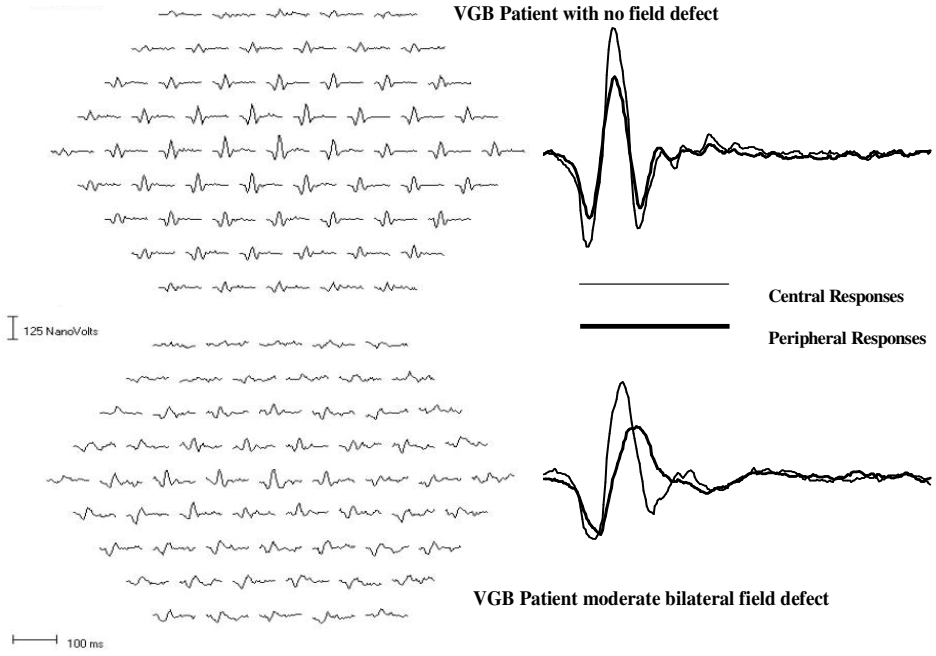


Figure 10.2.1 WF-mfERG differences in patients with and without visual field defects

Table 10.2.1 summarises the comparison between bilateral visual field defects and abnormal WF-mfERG responses in all groups.

	Vigabatrin (n=56)	Ex-Vigabatrin (n=49)	GABA (n=45)	non-GABA (n=53)	Chi-squared test p-value (overall)
Bilateral visual field defects (mild, moderate and severe)	33 (64.7)	21 (45.6)	13 (30.2) *	11 (21.2)* ‡	<0.0001
Bilateral abnormal WF mf ERG	27 (48.2)	11 (22.4) ±	0 (0)* †	0 (0)* †	<0.0001

Table 10.2.1 Bilateral visual field defects and abnormal WF-mfERG by patient drug groups.

Date is presented as number (%). N is the maximum number in each group. All available data used.

*p<0.001 for pairwise comparison with Vigabatrin.

± p<0.01 for pairwise comparison with Vigabatrin.

† p<0.001 for pairwise comparison with Ex-Vigabatrin.

‡ p<0.01 for pairwise comparison with Ex-Vigabatrin.

Note: Due to multiple tests only p<0.01 (i.e. 0.05/6 =0.01) is considered to be statistically significant.

Immediately, there are several striking observations. Only patients in Vigabatrin group and ex-Vigabatrin groups had abnormal bilateral WF-mfERG abnormalities on testing. Therefore, patients not exposed to Vigabatrin did not have abnormal bilateral WF-mfERG. This result is statistically significant. In contrast, in all groups a number of patients had bilateral visual field defects. In fact, the percentage in the groups not exposed to Vigabatrin was much higher than expected in the GABA group (30.2%) and non-GABA group (21.2%). This result was statistically significant. Therefore, we surmise that not all bilateral visual field defects can be attributed to a retinal abnormality i.e. retinal toxicity. These results are presented graphically in Figure 10.2.2.

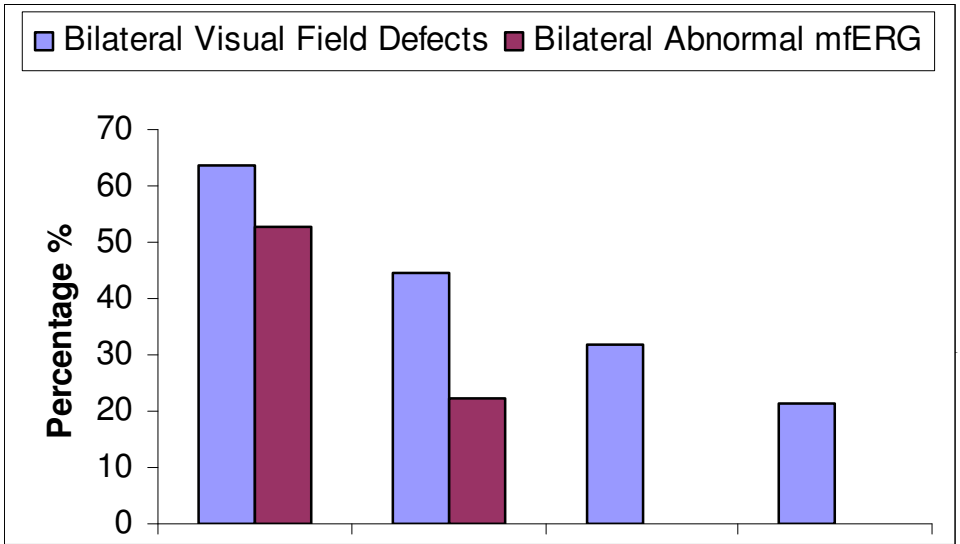


Figure 10.2.2 Graph to show percentage of bilateral visual field defects and abnormal bilateral WF-mfERG in each group.

It is important to note that all patients analysed had normal visual pathways on MRI scanning hence no structural cause for visual field defects. Patients in all groups had visual field defects even those not on Vigabatrin. Therefore, visual field defects may not be specific to retinal toxicity associated with Vigabatrin.

Let us assume that the visual field test is not as specific for retinal toxicity as compared to WF-mfERG (thus using the WF-mfERG as the "gold standard"), visual field defects has still proven to be sensitive in Vigabatrin group as only 2 patients out of 33 with abnormal WF- mfERG did not have bilateral abnormal visual field defects (93.9% sensitivity). Specificity was 87.9%.

It is also interesting that ex-Vigabatrin users still have abnormal WF-mfERG and visual field defects (up to two years after stopping Vigabatrin) suggesting irreversible damage in some patients and on-going retinal toxicity.

Analysis was also done comparing right and left eye visual field defects and WF-mfERG and is illustrated below in Tables 10.2.2 and 10.2.3.

	Vigabatrin (n=56)	Ex-Vigabatrin	GABA (n=46)	non-GABA (n=53)	Chi-squared test p-value

		(n=49)			(overall)
Left eye visual field defects	37 (72.6)	22 (47.8)	19 (43.2) ±	17 (32.7)*	0.0006
Left eye abnormal WF mf ERG	32 (57.1)	12 (24.5) *	3 (6.5) *	3 (5.7) *‡	<0.0001

Table 10.2.2: Left eye visual field defects and abnormal WF-mfERG by patient drug groups.

Date is presented as number (%). N is the maximum number in each group. All available data used.

*p<0.001 for pairwise comparison with Vigabatrin.

± p<0.01 for pairwise comparison with Vigabatrin.

† p<0.001 for pairwise comparison with Ex-Vigabatrin.

‡ p<0.01 for pairwise comparison with Ex-Vigabatrin.

	Vigabatrin (n=56)	Ex-Vigabatrin (n=49)	GABA (n=45)	Non GABA(n=53)	Chi-squared test p-value (overall)
Right eye visual field defects	40 (76.9)	23 (48.9) ±	18 (40.9) *	19 (36.5)*	0.0002
Right eye abnormal mf ERG	29 (51.8)	14 (28.6) *	1 (2.2) *†	1 (1.9) *†	<0.0001

Table 10.2.3: Right eye visual field defects and abnormal WF-mfERG by patient drug groups.

Data is presented as number (%). N is the maximum number in each group. All available data used.

*p<0.001 for pairwise comparison with Vigabatrin.

± p<0.01 for pairwise comparison with Vigabatrin.

† p<0.001 for pairwise comparison with Ex-Vigabatrin.

‡ p<0.01 for pairwise comparison with Ex-Vigabatrin

Retinal toxicity should largely be present in both eyes to the same degree if this is due to systemic toxicity. Interestingly, the presence of unilateral visual field defects is greater than in all groups. (Bilateral; GABA group 30.2%, non-GABA group 21.2%, Left; GABA group 43.2%, non-GABA group 32.7%, Right GABA group 40.9%, non-GABA group 36.5%). There is greater variability in the groups when eyes are examined singly and could

be due to the inherent poor attention and concentration in all patients with patients with epilepsy.

There were greater numbers of patients with epilepsy with abnormal bilateral visual field defects than abnormal bilateral WF-mfERG. The WF-mfERG is an objective test. There will be patients with epilepsy who will do poorly on visual field tests because of poor attention and concentration, but by chance will have acceptable false negative and false positive rates. The data is suggesting that visual fields are not as specific to retinal toxicity as WF-mfERG.

There are abnormal bilateral WF-mfERG results in both right and left eyes in other GABA and other non-GABA groups suggesting bilateral abnormal WF-mfERG rather than individual WF-mfERG are more specific to retinal toxicity associated with Vigabatrin.

Evaluating new technologies or tests raises the question of whether differences are due to the technology or the interpreters. Kappa is widely used to measure inter-observer variability, that is, how often 2 or more observers agree in their interpretations. Simple agreement, the proportion of agreements between yes and no is a poor measure of agreement because it does not correct for chance. Kappa is the preferred statistic because it accounts for chance. In statistical inference, one wishes to estimate population parameters using observed sample data. A confidence interval gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data.

Table 10.2.4 shows agreement between abnormal WF-mfERG and visual field defects using Kappa statistics and corresponding 95% confidence intervals.

Abnormal WF-mfERG		Visual field defects		Kappa (95% CI)
		Yes	No	
All patients	Yes	33	3	0.43 (0.31, 0.55)
	No	45	111	
Vigabatrin only	Yes	23	2	0.53 (0.31, 0.75)
	No	10	16	
Ex-Vigabatrin only	Yes	10	1	0.45 (0.22, 0.69)
	No	11	24	
GABA	Yes	0	0	N/A
	No	13	30	
non-GABA	Yes	0	0	N/A
	No	11	41	

Table 10.2.4: Agreement between bilateral visual field defects and abnormal WF mf-ERG

Note: Values of between 0.41-0.60 moderate agreement and values between 0.61-0.80 good agreement (see Altman D G Practical Statistics for Medical Research 1991)

There is moderate agreement in Vigabatrin and ex-Vigabatrin groups. This was expected since visual fields measure a complex interplay between the retina, visual pathway, processing areas of the brain, concentration and hand co-ordination whereas WF-mfERG measures central and peripheral retinal function. This is the real strength of the WF-mfERG in patients with epilepsy in this project. The WF-mfERG is an objective way to measure retinal function without interference in test results due to the cognitive problems of epilepsy.

Similar results are detected on comparing individual eyes, see Tables 10.2.5 and 10.2.6.

Abnormal Wf-mfERG		Visual field defects		Kappa (95% CI)
		Yes	No	
All patients	Yes	43	4	0.42 (0.30, 0.53)
	No	52	94	
Vigabatrin only	Yes	27	2	0.50 (0.27, 0.73)
	No	10	12	
Ex-Vigabatrin only	Yes	12	0	0.56 (0.34, 0.77)
	No	10	24	
Other GABAergic	Yes	2	1	N/A
	No	17	24	
Other non-GABAergic	Yes	2	1	N/A
	No	15	34	

Table 10.2.5: Agreement between left eye visual field defects and abnormal WF mf-ERG

Note: Values of between 0.41-0.60 moderate agreement and values between 0.61-0.80 good agreement (see Altman D G Practical Statistics for Medical Research 1991).

Abnormal mf ERG		Visual field defects		Kappa (95% CI)
		Yes	No	
All patients	Yes	40	3	0.36 (0.26, 0.47)
	No	60	92	
Vigabatrin only	Yes	26	1	0.41 (0.20, 0.63)
	No	14	11	
Ex-Vigabatrin only		13	1	0.53 (0.30, 0.75)
Yes		10	23	
	No			
Other GABAergic	Yes	1	0	N/A
	No	17	26	
Other non-GABAergic	Yes	0	1	N/A
	No	19	32	

Table 10.2.6: Agreement between right eye visual field defects and abnormal bilateral WF mf-ERG.

Note: Values of between 0.41-0.60 moderate agreement and values between 0.61-0.80 good agreement (see Altman D G Practical Statistics for Medical Research 1991).

There has been controversy surrounding drug load as a contributory factor in the development of retinal toxicity. Bilateral abnormal WF-mfERG is compared to drug load of Vigabatrin in Vigabatrin and ex-Vigabatrin groups in Table 10.2.7.

Group	**Bilateral abnormal WF-mfERG**				Wilcoxon p-value
	Yes		No		
	N	Median [Range], g	N	Median [Range], g	
Vigabatrin & Ex-Vigabatrin	31	9012 [512-21056]	40	5065 [180-16875]	0.0035
Vigabatrin	27	9416 [893-21056]	29	5201[180-16875]	0.0081
Ex-Vigabatrin	4	7690 [512-9100]	11	4745 [3000-8612]	0.41

Table 10.2.7 Comparison of actual load (g) of Vigabatrin by abnormal bilateral WF-mfERG

Note: For ex-Vigabatrin only 15/49 (31%) with information had actual load calculated.

The results show that in both Vigabatrin group and ex-Vigaabtrin group patients who developed bilateral abnormal WF-mfERG had a higher median load of Vigabatrin. Vigabatrin group patients with abnormal WF-mfERG had a median dose of 9416g whereas those patients with normal WF-mfERG had a median dosage was 5201. Ex-Vigabatrin group patients with abnormal WF- mfERG had a median dose of 7690g whereas patients with normal WF-mfERG had a median dosage of 4745g.

An arbitrary threshold of 8000g VGB was established, which did not correlate with the prevalence of visual field defects (x^2=2.710, p=0.100), but above which WF-mfERG abnormalities were significantly (x^2=9.046, p=0.003) more common.

The accumulated load of Vigabatrin seems to be a significant factor in the development of retinal toxicity. Difficulties in identifying patients with retinal toxicity in previous studies may be due to the poor specificity of the tests used.

It was often difficult in the ex-Vigabatrin group to work out actual drug loads as varying concentrations of Vigabatrin were given over varying times and often changes were not documented and so results were analysed only for confirmed drug loads.

Comparison of actual load (g) of Vigabatrin to bilateral visual field defects with bilateral visual field defects is shown in Table 10.2.8.

Group	**Bilateral visual field defects**				Wilcoxon p-value
	Yes		No		
	N	Median [Range], g	N	Median [Range], g	
Vigabatrin & Ex-Vigabatrin	41	8225 [180-21056]	24	4878 [1500-16875]	0.058
Vigabatrin	33	8910 [180-21056]	18	4820 [1500-16875]	0.070
Ex-Vigabatrin	8	6527 [512-9100]	6	4878 [3000-8612]	0.75

Table 10.2.8 Comparison of actual load (g) of Vigabatrin by bilateral visual field defects
Note: For Ex-Vigabatrin group only 14/46 (52%) with information on visual field defects had actual load recorded.

Note: even though visual field defects were classified as mild, moderate and severe the numbers were not enough to perform statistical analysis in Tables 10.2.4 to 10.2.8. Yes/No to visual field defects were used for analysis.

10.3 Comparison of WF-mfERG variables between patients with and without bilateral visual field defects.

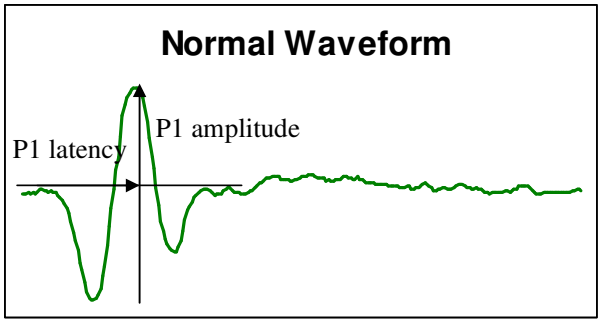


Figure 10.3.1 a single WF-mfERG tracing.

Table 10.3.1 explains the WF-mfERG terms.

Investigation variable	Explanation
Right P1 amp-c	Right 1st positive peak average of central amplitude responses
Right N1 imp-c	Right 1st negative trough average of central implicit times responses
Right P1 imp-c	Right 1st positive peak average of central implicit times responses
Right N1/P1-c	Ratio of 1st negative trough to positive peak of central responses

Right P1 amp-p	Right 1st positive peak average of peripheral amplitude responses
Right N1 imp-p	Right 1st negative trough average of peripheral implicit times responses
Right P1 imp-p	Right 1st positive peak average of peripheral implicit times responses
Right N1/P1	Ratio of 1st negative trough to positive peak of peripheral responses
Left P1 amp-c	Left 1st positive peak average of central amplitude responses
Left N1 imp-c	Left 1st negative trough average of central implicit times responses
Left P1 imp-c	Left 1st positive peak average of central implicit times responses
Left N1/P1-c	Left of 1st negative trough to positive peak of central responses
Left P1 amp-p	Left 1st positive peak average of peripheral amplitude responses
Left N1 imp-p	Left 1st negative trough average of peripheral implicit times responses
Left P1 imp-p	Left 1st positive peak average of peripheral implicit times responses
Left N1/P1	Left 1st negative trough to positive peak of peripheral responses

Table 10.3.1 Explanation of WF-mfERG terms

Table 10.3.2 summarizes the comparison of WF-mfERG variables between patients with and without bilateral visual field defects analyzing right and left eyes separately.

Investigation variable	Visual field defects (n= 78)		No visual field defects (n=114)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right P1 amp-c	50.7 (24.3)	46 [35-60]	65.4 (28.2)	56 [46-82]	0.0002
Right N1 imp-c	25.0 (2.0)	25 [24-26]	24.7 (2.7)	24 [23-25]	0.13
Right P1 imp-c	40.5 (2.7)	40 [39-41]	40.5 (2.9)	40 [39-41]	0.57
Right N1/P1-c	2.4 (0.5)	2.3 [2.0-2.7]	2.4 (0.5)	2.4 [2.2-2.6]	0.22
Right P1 amp-p	31.1 (14.3)	28 [21-39]	46.5 (18.0)	42 [34-57]	<0.0001
Right N1 imp-p	26.6 (2.1)	27[25-28]	26.2 (2.6)	26 [25-27]	0.017
Right P1 imp-p	43.0 (3.2)	43 [41-45]	41.3 (2.6)	41 [40-42]	<0.0001
Right N1/P1	2.1 (0.8	1.9 [1.7-2.2]	2.3 (0.4)	2.3 [2.0-2.4]	<0.0001
Left P1 amp-c	49.9 (22.7)	45 [36-62]	65.8 (27.8)	60 [46-83]	<0.0001
Left N1 imp-c	24.9 (2.2)	25 [24-25]	24.5 (1.8)	24 [23-25]	0.092
Left P1 imp-c	40.6 (2.8)	40 [39-41]	40.3 (2.5)	40 [39-41]	0.33
Left N1/P1-c	2.2 (0.5)	2.2 [2.0-2.4]	2.4 (0.7)	2.4 [2.2-2.6]	0.0016
Left P1 amp-p	30.8 (14.3)	28 [21-38]	46.0 (18.5)	44 [33-57]	<0.0001
Left N1 imp-p	26.5 (2.0)	26 [25-28]	26.0 (1.9)	25 [25-27]	0.020
Left P1 imp-p	43.2 (3.2)	43 [41-45]	41.2 (2.5)	41 [40-42]	<0.0001
Left N1/P1	2.1 (1.2)	1.9 [1.7-2.3]	2.2 (0.3)	2.2 [2.0-2.4]	0.0001

Table 10.3.2 Comparison of WF-mfERG variables between all patients with and without bilateral visual field defects in 4 groups

Significant positive correlation occurred with Right P1 amp-p, Right P1 imp-p, Right N1/P1, Left P1 amp-c, Left P1 amp-p, Left P1 imp-p (P1- 1st positive wave, N1- first negative wave, imp- implicit time, amp – amplitude, -p – peripheral, -c- central see Figure 10.3.1). It is important to note that these variables are not specific to any group and by extension not specific to patients with epilepsy who were on Vigabatrin. Right N1/P1 and left N1/P1 show p-values of <0.0001 indicating peripheral retinal function is decreased in patients with visual field defects.

Analysis of Groups 1 to 4 with regard to WF-mfERG variables with and without bilateral visual field defects are summarised in Table 10.3.3 (Vigabatrin), Table 10.3.4 (ex-Vigabatrin), Table 10.3.4 (GABA) and Table 10.3.5 (non-GABA). There is no other significant parameter of the WF-mfERG that correlates with bilateral visual field defects.

Investigation variable	Visual field defects (n= 33)		No visual field defects (n=26)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right P1 amp-c	60.6 (25.8)	58 [42-74]	80.3 (31.9)	92 [52-99]	0.035
Right N1 imp-c	25.0 (1.4)	25 [24-26]	24.9 (2.2)	24 [24-25]	0.36
Right P1 imp-c	40.1 (1.9)	40 [39-40]	40.3 (3.0)	39 [39-40]	0.38
Right N1/P1-c	2.2 (0.4)	2.2 [1.9-2.5]	2.3 (0.2)	2.3 [2.1-2.5]	0.55
Right P1 amp-p	35.9 (15.5)	33 [25-48]	56.2 (22.5)	58 [42-72]	0.0027
Right N1 imp-p	27.4 (1.8)	28 [26-29]	26.7 (2.1)	26 [25-28]	0.080
Right P1 imp-p	43.8 (2.9)	44 [42-45]	41.5 (2.8)	40 [40-42]	0.0063
Right N1/P1	1.8 (0.2)	1.8 [1.6-2.0]	2.0 (0.3)	2.1 [1.8-2.3]	0.0043
Left P1 amp-c	57.9 (23.9)	56 [40-75]	76.2 (31.9)	79 [45-95]	0.049
Left N1 imp-c	25.0 (1.6)	25 [24-25]	25.1 (2.1)	24 [24-26]	0.65
Left P1 imp-c	40.3 (2.3)	40 [39-42]	40.8 (3.1)	40 [39-42]	1.00
Left N1/P1-c	2.1 (0.5)	2.1 [1.8-2.3]	2.2 (0.3)	2.2 [2.1-2.5]	0.17
Left P1 amp-p	34.6 (14.8)	32 [22-46]	54.7 (24.0)	54 [38-75]	0.0047
Left N1 imp-p	27.1 (1.8)	27 [25-29]	26.8 (2.6)	26 [25-28]	0.26
Left P1 imp-p	44.0 (3.0)	44 [42-45]	42.4 (3.3)	42 [40-43]	0.028
Left N1/P1	1.9 (0.4)	1.8 [1.7-2.0]	2.0 (0.2)	2.0 [1.8-2.1]	0.035

Table 10.3.3 Comparison of WF-mfERG variables between Vigabatrin patients with and without bilateral visual field defects

Investigation variable	Visual field defects (n= 21)		No visual field defects (n=28)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right P1 amp-c	41.8 (16.8)	43 [33-50]	53.6 (19.1)	50 [44-56]	0.021
Right N1 imp-c	25.1 (2.7)	25 [23-26]	24.8 (1.2)	25 [24-25]	0.71
Right P1 imp-c	39.7 (2.2)	40 [39-41]	40.5 (2.3)	40 [39-41]	0.49
Right N1/P1-c	2.6 (0.6)	2.5 [2.1-2.8]	2.4 (0.3)	2.5 [2.2-2.6]	0.47
Right P1 amp-p	24.0 (10.3)	20 [16-32]	38.0 (10.4)	37 [31-44]	0.0006
Right N1 imp-p	26.2 (2.0)	25 [25-27]	26.0 (1.7)	26 [25-27]	0.86
Right P1 imp-p	42.4 (2.8)	43 [41-44]	41.3 (1.9)	41 [40-42]	0.023
Right N1/P1	2.1 (0.9)	1.8 [1.7-2.0]	2.2 (0.4)	2.3 [2.0-2.4]	0.019
Left P1 amp-c	40.4 (16.1)	39 [30-46]	56.0 (17.4)	53 [48-62]	0.0021
Left N1 imp-c	24.4 (1.7)	25 [23-25]	24.4 (1.6)	24 [23-25]	0.80

Left P1 imp-c	40.0 (2.4)	40 [39-40]	40.1 (2.3)	40 [39-41]	0.86
Left N1/P1-c	2.4 (0.7)	2.3 [2.0-2.6]	2.4 (0.3)	2.4 [2.2-2.6]	0.56
Left P1 amp-p	23.5 (12.4)	21 [13-27]	38.9 (9.8)	40 [33-45]	0.0002
Left N1 imp-p	26.3 (1.9)	26 [25-28]	25.7 (1.6)	26 [25-27]	0.29
Left P1 imp-p	42.3 (2.8)	43 [40-44]	41.1 (2.1)	41 [40-42]	0.13
Left N1/P1	2.4 (2.2)	1.7 [1.6-2.1]	2.2 (0.3)	2.2 [2.0-2.3]	0.011

Table 10.3.4 Comparison of WF-mfERG variables between ex-Vigabatrin patients with and without bilateral visual field defects

Investigation variable	Visual field defects (n= 13)	No visual field defects (n=32)	Wilcoxon p-value

	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right P1 amp-c	39.5 (18.3)	44 [29-91]	61.5 (25.0)	56 [44-79]	0.0090
Right N1 imp-c	24.3 (1.4)	24 [24-95]	24.9 (4.3)	24 [23-25]	0.69
Right P1 imp-c	41.3 (3.2)	40 [40-29]	41.1 (4.1)	40 [39-41]	0.61
Right N1/P1-c	2.4 (0.4)	2.3 [2.2-28]	2.5 (0.7)	2.4 [2.0-2.7]	0.91
Right P1 amp-p	28.2 (12.6)	29 [17-47]	45.9 (18.8)	43 [29-56]	0.0090
Right N1 imp-p	25.5 (2.0)	25 [25-25]	26.4 (4.2)	25 [24-27]	0.99
Right P1 imp-p	42.3 (4.0)	41 [40-43]	41.7 (3.8)	41 [40-43]	0.55
Right N1/P1	2.7 (1.2)	2.4 [2.1-2.8]	2.2 (0.3)	2.2 [2.0-2.4]	0.35
Left P1 amp-c	42.1 (14.6)	46 [37-32]	63.3 (27.2)	58 [45-85]	0.029

Left N1 imp-c	24.7 (3.1)	25 [23-27]	24.4 (1.8)	24 [23-25]	0.78
Left P1 imp-c	41.0 (3.3)	40 [39-45]	40.2 (2.5)	40 [39-41]	0.81
Left N1/P1-c	2.3 (0.5)	2.3 [2.1-2.5]	2.6 (1.2)	2.4 [2.2-2.6]	0.30
Left P1 amp-p	29.8 (11.0)	30 [20-52]	47.5 (21.4)	41 [32-62]	0.018
Left N1 imp-p	25.2 (1.6)	25 [25-25]	25.9 (2.2)	25 [25-27]	0.54
Left P1 imp-p	42.2 (3.3)	42 [40-41]	40.9 (2.7)	40 [39-42]	0.29
Left N1/P1	2.3 (0.4)	2.3 [2.1-2.6]	2.2 (0.3)	2.2 [2.0-2.4]	0.35

Table 10.3.5 Comparison of WF-mfERG variables between GABA patients with and without bilateral visual field defects

Investigation variable	Visual field defects (n= 11)	No visual field defects (n=42)	Wilcoxon p-value

	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right P1 amp-c	51.9 (28.4)	41 [35-59]	69.0 (30.5)	57 [48-92]	0.050
Right N1 imp-c	25.2 (2.8)	24 [24-29]	24.5 (2.1)	24 [23-25]	0.90
Right P1 imp-c	42 (3.9)	40 [39-45]	40.1 (2.2)	40 [39-40]	0.18
Right N1/P1-c	2.1 (0.3)	2.2 [1.9-2.4]	2.4 (0.4)	2.4 [2.2-2.6]	0.035
Right P1 amp-p	33.9 (14.7)	26 [25-38]	47.7 (17.2)	42 [38-57]	0.0054
Right N1 imp-p	26.6 (2.3)	26 [25-28]	25.8 (1.5)	25 [25-27]	0.46
Right P1 imp-p	43.0 (3.8)	41 [40-47]	50.0 (1.9)	41 [40-42]	0.27
Right N1/P1	2.2 (0.2)	2.2 [2.1-2.4]	2.4 (0.4)	2.4 [2.1-2.5]	0.39

Left P1 amp-c	54.0 (29.8)	38 [36-71]	68.9 (30.1)	65 [45-86]	0.075
Left N1 imp-c	25.9 (3.0)	25 [24-30]	24.4 (1.6)	25 [23-25]	0.19
Left P1 imp-c	42.3 (3.7)	41 [40-46]	40.2 (2.5)	40 [39-42]	0.067
Left N1/P1-c	2.2 (0.2)	2.2 [2.1-2.4]	2.4 (0.5)	2.4 [2.2-2.6]	0.070
Left P1 amp-p	34.6 (16.0)	29 [26-48]	45.4 (16.2)	44 [34-52]	0.034
Left N1 imp-p	26.8 (2.7)	26 [26-29]	25.8 (1.6)	25 [25-57]	0.19
Left P1 imp-p	43.7 (4.0)	42 [41-47]	41.0 (2.0)	41 [40-42]	0.026
Left N1/P1	2.2 (0.4)	2.1 [1.9-2.5]	2.3 (0.4)	2.2 [2.1-2.4]	0.29

Table 10.3.6 Table shows comparison of ERG variables between other non-GABA patients with and without bilateral visual field defects

10.4 Visual field defects and ERG

Table 10.4.1 summarizes the comparison of ERG variables between patients with and without bilateral visual field defects analyzing right and left eyes separately. Significant positive correlation occurred between bilateral visual field defects and oscillatory amplitudes, cone amplitude and flicker amplitude.

Analysis of Groups 1 to 4 of to ERG variables with and without bilateral visual field defects are summarised in Table 10.4.2 (Vigabatrin Group), Table 10.4.3 (ex-Vigabatrin Group), Table 10.4.4 (GABA Group) and Table 10.4.5 (non-GABA Group).

The conventional ERG responses, OP amplitude, cone B amplitude and flicker amplitude displayed a correlation with visual field abnormalities, but again not specifically with bilateral visual field defects in those exposed to Vigabatrin. This was surprising. A possible explanation is that some of the parameters of the ERG were affected by the

physiological neurological dampening caused by anti-epileptic drugs but were not specific to the pathological retinal toxicity.

Investigation variable	Visual field defects (n= 78)		No visual field defects (n=114)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	149.3 (66.1)	138 [100-187]	180.8 (75.2)	166 [133-216]	0.0021
Left rod amp	140.8 (57.4)	138 [97-181]	180.9 (78.3)	168 [131-217]	0.0003
Right rod lat	90.2 (13.6)	91 [82-99]	86.8 (12.3)	86 [79-96]	0.025
Left rod lat	88.9 (13.9)	89 [79-100]	86.6 (12.2)	86 [79-94]	0.14
Right max A amp	184.1 (92.9)	164 [122-235]	185.4 (60.4)	180 [144-227]	0.28
Left max A amp	180.9 (72.4)	180 [128-237]	186.8 (64.3)	178 [138-221]	0.67
Right max A lat	18.3 (6.2)	17 [16-19]	17.2 (2.7)	16 [16-17]	0.060
Left max A lat	17.5 (3.6)	17 [16-18]	17.0 (2.8)	16 [16-17]	0.068
Right max B amp	299.4 (137.7)	265 [198-380]	331.6 (134.9)	306 [232-419]	0.076
Left max B amp	299.4 (131.0)	266 [188-390]	337.9 (138.4)	310 [245-398]	0.038
Right max B lat	45.5 (9.6)	45 [38-51]	44.4 (8.0)	46 [37-50]	0.64
Left max B lat	45.6 (7.9)	46 [38-52]	44.7 (7.5)	47 [38-51]	0.51

Right op amp	25.1 (14.5)	23 [16-31]	36.4 (16.8)	34 [24-45]	<0.0001
Left op amp	24.2 (12.5)	22 [14-30]	37.5 (17.2)	37 [24-46]	<0.0001
Right op lat	21.8 (3.6)	22 [18-25]	22.4 (3.6)	24 [19-25]	0.39
Left op lat	21.8 (3.4)	22 [19-25]	22.4 (3.5)	24 [19-25]	0.31
Right cone A amp	23.5 (11.3)	22 [16-29]	26.1 (10.1)	25 [19-32]	0.036
Left cone A amp	23.9 (14.4)	22 [15-29]	26.9 (10.2)	26 [19-32]	0.0063
Right cone A lat	12.7 (3.2)	13 [10-15]	12.2 (3.4)	13 [10-15]	0.61
Left cone A lat	12.7 (3.7)	13 [10-15]	12.4 (3.3)	13 [9-15]	0.69
Right cone B amp	78.9 (29.0)	76 [56-100]	107.8 (36.9)	102 [84-126]	<0.0001
Left cone B amp	82.9 (35.0)	81 [59-103]	112.5 (41.3)	108 [82-142]	<0.0001
Right cone B lat	29.0 (4.0)	30 [26-32]	28.8 (3.4)	29 [26-31]	0.47
Left cone B lat	29.1 (3.8)	30 [26-32]	28.9 (3.2)	30 [26-31	0.46
Right flicker amp	68.8 (33.8)	64 [46-89]	87.2 (30.8)	84 [61-107]	<0.0001
Left flicker amp	70.1 (41.3)	64 [49-81]	93.6 (56.6)	82 [61-114]	<0.0001
Right flicker lat	26.0 (4.3)	26 [24-29]	26.1 (2.7)	26 [24-28]	0.90
Left flicker lat	26.3 (3.5)	26 [24-29]	25.9 (2.8)	26 [24-28]	0.46

Table 10.4.1: Table shows comparison of ERG variables between patients with and without bilateral visual field defects.

N is the maximum number in each group. All available data is used.

Investigation variable	Visual field defects (n= 33)		No visual field defects (n=18)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	156.5 (65.1)	145 [105-179]	212.3 (87.83)	200 [149-274]	0.018
Left rod amp	153.6 (57.5)	152 [110-185]	208.4 (80.9)	184 [156-281]	0.024
Right rod lat	90.3 (9.3)	92 [82-97]	82.6 (13.8)	82 [69-90]	0.060
Left rod lat	89.7 (11.0)	92 [81-100]	82.6 (14.7)	83 [74-94]	0.096
Right max A amp	223.0 (80.8)	224 [146-272]	238.1 (77.5)	233 [202-299]	0.60
Left max A amp	220.2 72.6)	216 [173-260]	229.6 (79.4)	201 [171-281]	0.65
Right max A lat	16.8 (2.3)	17 [16-18]	17.1 (2.1)	17 [16-18]	0.94
Left max A lat	16.6 (2.6)	17 [16-18]	17.1 (3.0)	17 [16-17]	0.97
Right max B amp	373.0 (134.9)	358 [271-475]	445.4 (173.5)	438 [299-588]	0.18
Left max B amp	366.0 (122.0)	379 [256-432]	435.5 (167.9)	428 [290-529]	0.17
Right max B lat	42.6 (11.8)	39 [36-45]	38.6 (8.8)	38 [36-42]	0.60

Left max B lat	40.9 (7.6)	38 [36-43]	38.8 (9.2)	38 [36-43]	0.85
Right op amp	24.6 (15.2)	22 [13-33]	37.3 (17.4)	39 [24-49]	0.014
Left op amp	23.9 (14.0)	22 [12-31]	37.4 (18.5)	37 [22-49]	0.013
Right op lat	20.3 (3.4)	19 [18-21]	18.4 (2.4)	18 [17-18]	0.0033
Left op lat	20.5 (3.4)	19 [18-22]	19.2 (2.9)	18 [17-22]	0.077
Right cone A amp	24.5 (9.9)	23 [17-31]	26.3 (9.6)	26 [22-34]	0.38
Left cone A amp	24.1 (8.9)	24 [19-29]	24.3 (7.8)	23 [19-28]	0.91
Right cone A lat	11.2 (2.6)	11 [10-14]	9.8 (2.8)	9 [8-11]	0.053
Left cone A lat	11.2 (3.3)	10 [10-13]	10.4 (3.0)	10 [9-11]	0.31
Right cone B amp	80.1 (33.4)	75 [56-100]	108.4 (35.9)	109 [93-114]	0.0051
Left cone B amp	82.5 (34.0)	80 [59-103]	104.1 (36.6)	104 [73-119]	0.040
Right cone B lat	27.5 (4.0)	27 [25-31]	26.8 (3.0)	26 [25-28]	0.43
Left cone B lat	27.6 (3.6)	28 [26-31]	27.2 (3.5)	26 [25-28]	0.44
Right flicker amp	68.9 (35.5)	60 [46-87]	77.7 (28.0)	81 [53-91]	0.17
Left flicker amp	70.4 (47.9)	59 [49-73]	81.1 (38.8)	74 [55-107]	0.17
Right flicker lat	24.8 (3.3)	24 [22-28]	24.8 (2.2)	24 [24-25]	0.71
Left flicker lat	25.4 (3.8)	24 [23-29]	24.7 (1.9)	24 [24-25]	0.79

Table 10.4.2 Table shows comparison of ERG variables between Vigabatrin patients with and without bilateral visual field defects.

N is the maximum number in each group. All available data is used.

Investigation variable	Visual field defects (n= 21)		No visual field defects (n=25)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	126.4 (54.0)	112 [97-152]	160.4 (74.5)	148 [116-191]	0.044
Left rod amp	115.0 (43.7)	104 [87-136]	161.5 (89.4)	157 [122-181]	0.010
Right rod lat	86.9 (12.3)	90 [78-92]	88.0 (13.3)	88 [79-93]	1.00
Left rod lat	89.6 (14.0)	89 [78-98]	86.4 (13.0)	85 [80-93]	0.38
Right max A amp	133.5 (42.9)	144 [110-170]	156.9 (48.1)	147 [134-188]	0.20
Left max A amp	139.3 (52.5)	143 [103-178]	163.4 (45.3)	158 [133-178]	0.13
Right max A lat	18.3 (3.4)	18 [16-19]	17.1 (2.4)	16 [16-17]	0.096
Left max A lat	18.7 (3.8)	17 [16-21]	16.7 (2.8)	16 [15-17]	0.020
Right max B amp	235.1 (100.6)	223 [158-258]	271.4 (90.6)	263 [216-319]	0.086
Left max B amp	222.9 (112.0)	184 [163-240]	282.3 (130.2)	252 [212-319]	0.017
Right max B lat	46.5 (7.9)	47 [40-51]	48.0 (6.7)	49 [45-53]	0.39

Left max B lat	48.2 (6.1)	49 [45-52]	47.6 (5.6)	49 [45-51]	0.70
Right op amp	21.4 (6.9)	22 [17-27]	30.5 (14.0)	27 [23-39]	0.022
Left op amp	20.0 (8.9)	19 [14-24]	32.3 (17.8)	27 [21-42]	0.0054
Right op lat	23.0 (3.0)	24 [21-25]	23.7 (3.1)	24 [24-25]	0.94
Left op lat	23.3 (3.2)	24 [24-25]	23.9 (2.8)	24 [24-25]	0.70
Right cone A amp	18.6 (7.3)	18 [16-22]	24.6 (8.0)	24 [21-28]	0.016
Left cone A amp	20.5 (15.0)	17 [13-23]	25.7 (10.1)	23 [18-30]	0.016
Right cone A lat	13.1 (3.2)	14 [11-15]	13.4 (3.1)	14 [12-15]	0.67
Left cone A lat	13.1 (3.1)	14 [12-15]	13.2 (2.8)	14 [12-15]	0.90
Right cone B amp	73.2 (27.3)	65 [50-93]	98.4 (30.9)	93 [80-116]	0.0079
Left cone B amp	70.8 (28.7)	68 [47-88]	100.4 (32.7)	101 [80-115]	0.0035
Right cone B lat	30.6 (3.5)	31 [29-33]	29.1 (4.3)	31 [29-31]	0.24
Left cone B lat	30.6 (3.2)	31 [29-33]	29.8 (2.6)	30 [30-31]	0.29
Right flicker amp	62.1 (32.8)	63 [34-77]	79.5 (27.8)	73 [56-98]	0.038
Left flicker amp	62.5 (34.4)	60 [40-69]	102.2 (95.2)	84 [62-103]	0.011
Right flicker lat	27.6 (3.1)	28 [26-30]	26.8 (2.5)	27 [26-28]	0.29
Left flicker lat	27.3 (3.2)	28 [26-30]	26.5 (2.6)	27 [26-28]	0.33

Table 10.4.3: Table shows comparison of ERG variables between ex-Vigabatrin patients with and without bilateral visual field defects.

N is the maximum number in each group. All available data is used.

Investigation variable	Visual field defects (n= 13)		No visual field defects (n=30)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	142.5 (73.7)	138 [90-169]	171.0 (73.5)	162 [111-209]	0.26
Left rod amp	125.4 (50.5)	141 [111-145]	181.8 (84.1)	154 [128-226]	0.066
Right rod lat	95.5 (22.8)	101 [95-108]	88.1 (12.3)	87 [80-99]	0.026
Left rod lat	86.9 (21.8)	89 [82-98]	87.2 (13.6)	86 [79-92]	0.57
Right max A amp	130.7 (56.8)	120 [111-148]	184.8 (54.0)	182 [139-227]	0.0087
Left max A amp	150.4 (62.3)	147 [133-183]	189.5 (70.3)	184 [131-238]	0.15
Right max A lat	18.5 (4.3)	18 [16-21]	17.2 (3.0)	16 [15-18]	0.26
Left max A lat	17.8 (4.4)	17 [16-22]	16.6 (2.1)	16 [16-17]	0.18
Right max B amp	197.2 (73.8)	188 [145-207]	324.4 (140.0)	291 [199-427]	0.0036
Left max B amp	235.4 (84.0)	235 [182-283]	346.0 (148.8)	308 [250-398]	0.016

Right max B lat	47.8 (7.4)	50 [44-53]	41.7 (8.0)	40 [34-49]	0.024
Left max B lat	49.5 (7.6)	51 [47-54]	43.8 (8.0)	43 [36-52]	0.073
Right op amp	22.8 (11.0)	21 [16-30]	39.7 (21.2)	36 [24-51]	0.0096
Left op amp	24.1 (7.8)	22 [19-30]	40.4 (17.1)	38 [29-52]	0.0031
Right op lat	23.1 (4.0)	24 [20-25]	21.8 (3.8)	24 [20-25]	0.52
Left op lat	21.8 (2.6)	23 [20-24]	21.6 (3.8)	23 [18-25]	0.98
Right cone A amp	24.6 (17.0)	22 [16-27]	22.8 (7.8)	21 [17-28]	0.84
Left cone A amp	27.0 (24.5)	26 [12-28]	25.8 (9.4)	28 [18-31]	0.21
Right cone A lat	14.5 (3.5)	14 [12-16]	11.3 (3.9)	12 [7-15]	0.036
Left cone A lat	14.2 (4.3)	15 [14-16]	11.6 (4.1)	10 [9-15]	0.074
Right cone B amp	73.4 (24.5)	73 [57-93]	101.7 (32.8)	100 [78-125]	0.013
Left cone B amp	83.3 (31.4)	81 [67-106]	114.6 (43.3)	120 [82-146]	0.023
Right cone B lat	29.8 (3.9)	31 [28-32]	28.6 (3.6)	29 [26-31]	0.24
Left cone B lat	29.6 (4.2)	31 [28-32]	28.3 (3.8)	28 [25-31]	0.32
Right flicker amp	77.4 (39.0)	67 [54-91]	83.1 (30.4)	76 [61-96]	0.62
Left flicker amp	82.4 (38.4)	79 [62-95]	93.5 (44.7)	78 [60-115]	0.66
Right flicker lat	25.5 (7.4)	28 [24-29]	25.9 (3.4)	25 [23-28]	0.48
Left flicker lat	26.1 (3.8)	27 [24-28]	26.2 (3.4)	25 [23-29]	0.97

Table 10.4.4: Table shows comparison of ERG variables between GABA patients with and without bilateral visual field defects.

N is the maximum number in each group. All available data is used.

Investigation variable	Visual field defects (n= 11)		No visual field defects (n=41)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	179.4 (73.2)	187 [133-216]	186.5 (68.1)	162 [149-238]	0.96
Left rod amp	169.6 (68.8)	181 [100-233]	179.9 (63.4)	170 [132-215]	0.91
Right rod lat	89.7 (13.0)	89 [82-95]	86.8 (10.9)	86 [79-95]	0.50
Left rod lat	87.4 (11.6)	87 [79-96]	87.9 (9.1)	88 [80-95]	0.76
Right max A amp	227.2 (148.1)	171 [154-243]	180.2 (49.7)	178 [151-221]	0.60
Left max A amp	178.1 (57.9)	201 [135-224]	180.3 (54.4)	181 [151-210]	0.80
Right max A lat	21.9 (4.6)	16 [15-22]	17.2 (3.0)	16 [15-17]	0.61
Left max A lat	17.9 (4.4)	16 [16-17]	17.5 (3.1)	16 [15-17]	0.89
Right max B amp	321.6 (142.5)	294 [206-410]	323.7 (106.2)	315 [244-374]	0.86
Left max B amp	321.1 (135.2)	315 [238-378]	322.9 (96.9)	325 [269-390]	0.62

Right max B lat	49.3 (4.2)	50 [47-52]	46.7 (6.5)	47 [43-50]	0.12
Left max B lat	50.6 (4.1)	52 [49-53]	46.4 (5.7)	49 [42-51]	0.0078
Right op amp	36.5 (21.5)	35 [19-43]	37.3 (14.0)	36 [28-44]	0.54
Left op amp	33.1 (15.0)	35 [21-44]	38.6 (16.3)	38 [26-49]	0.30
Right op lat	22.7 (3.3)	24 [20-25]	23.8 (2.9)	24 [23-25]	0.59
Left op lat	22.7 (3.1)	24 [21-25]	23.6 (2.8)	24 [23-25]	0.53
Right cone A amp	28.9 (11.3)	27 [19-34]	29.3 (11.9)	28 [20-35]	0.89
Left cone A amp	26.1 (11.1)	25 [17-33]	29.6 (11.6)	28 [23-35]	0.37
Right cone A lat	14.3 (2.8)	14 [12-16]	13.3 (2.8)	14 [12-15]	0.42
Left cone A lat	14.8 (38)	15 [12-17]	13.3 (2.5)	14 [12-15]	0.32
Right cone B amp	92.8 (19.5)	99 [79-107]	117.8 (42.0)	108 [88-151]	0.13
Left cone B amp	105.8 (45.1)	99 [68-131]	122.0 (45.0)	108 [89-149]	0.31
Right cone B lat	29.6 (3.8)	30 [29-32]	29.5 (2.2)	30 [29-31]	0.71
Left cone B lat	29.7 (3.8)	31 [29-32]	29.4 (2.7)	30 [29-31]	0.51
Right flicker amp	71.1 (25.2)	73 [48-95]	99.2 (31.4)	103 [68-130]	0.016
Left flicker amp	69.4 (36.6)	64 [40-89]	93.8 (37.3)	95 [66-120]	0.061
Right flicker lat	26.8 (2.9)	26 [24-30]	26.4 (2.3)	27 [26-28]	0.90
Left flicker lat	26.8 (2.4)	27 [25-30]	25.9 (2.8)	27 [24-28]	0.54

Table 10.4.5: Table shows comparison of ERG variables between other non-GABA patients with and without bilateral visual field defects.

N is the maximum number in each group. All available data is used.

10.5 Comparison of ERG and WF-mfERG variables between patients with and without bilateral abnormal mf ERG.

Table 10.5.1 summarizes the comparison of ERG and WF-mfERG variables between patients with and without bilateral abnormal WF-mfERG analysing right and left eyes separately. This was done to identify any other factors that might be significant in identifying retinal toxicity.

Investigation variable	Abnormal WF-mfERG (n= 38)		No abnormal WF-mfERG (n=165)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	140.2 (57.2)	128 [96-175]	171.2 (74.8)	158 [117-209]	0.014
Left rod amp	143.2 (52.2)	132 [98-183]	167.6 (75.4)	157 [121-210]	0.048
Right rod lat	90.8 (11.9)	92 [82-97]	88.2 (13.2)	88 [80-98]	0.28
Left rod lat	93.6 (13.9)	94 [83-104]	86.9 (12.7)	86 [79-95]	0.0076

Right max A amp	204.0 (81.1)	199 [145-250]	177.2 (73.5)	165 [131-219]	0.054
Left max A amp	206.6 (80.0)	210 [147-253]	177.2 (65.2)	168 [133-216]	0.031
Right max A lat	17.6 (3.1)	17 [16-19]	17.8 (4.8)	17 [16-18]	0.16
Left max A lat	17.8 (3.5)	18 [16-19]	17.3 (3.2)	16 [16-18]	0.13
Right max B amp	322.0 (132.2)	296 [241-386]	311.7 (136.6)	278 [207-389]	0.45
Left max B amp	318.7 (121.5)	302 [235-407]	318.0 (139.2)	285 [214-390]	0.71
Right max B lat	42.1 (7.5)	40 [36-51]	45.6 (8.7)	47 [39-51]	0.023
Left max B lat	42.6 (7.8)	41 [36-50]	45.9 (7.6)	48 [40-51]	0.019
Right op amp	21.7 (10.4)	22 [14-28]	33.2 (17.3)	30 [21-41]	0.0002
Left op amp	21.0 (10.6)	21 [12-25]	34.1 (16.8)	33 [21-44]	<0.0001
Right op lat	20.7 (3.6)	20 [18-23]	22.5 (3.5)	24 [20-25]	0.0072
Left op lat	21.4 (3.7)	20 [18-25]	22.4 (3.4)	24 [19-25]	0.17
Right cone A amp	22.1 (7.5)	22 [16-27]	25.3 (11.1)	24 [17-31]	0.16
Left cone A amp	23.8 (13.2)	22 [16-28]	26.0 (12.2)	26 [17-31]	0.10
Right cone A lat	12.2 (3.1)	12 [10-15]	12.6 (3.4)	14 [10-15]	0.41
Left cone A lat	12.2 (3.3)	12 [10-15]	12.6 (3.4)	14 [10-15]	0.38
Right cone B amp	72.6 (27.2)	68 [50-96]	100.2 (36.3)	97 [76-117]	<0.0001
Left cone B amp	71.9 (25.3)	72 [49-91]	105.2 (41.6)	99 [77-131]	<0.0001
Right cone B lat	29.2 (4.2)	30 [26-32]	28.9 (3.5)	30 [26-31]	0.51
Left cone B lat	29.3 (3.6)	30 [26-32]	29.0 (3.4)	30 [26-31]	0.55
Right flicker amp	62.1 (31.3)	54 [35-85]	82.8 (32.5)	77 [58-102]	0.0004
Left flicker amp	60.3 (29.0)	57 [39-72]	87.6 (54.1)	79 [56-107]	0.0002
Right flicker lat	26.2 (3.5)	27 [24-29]	26.1 (3.4)	26 [24-28]	0.89
Left flicker lat	26.6 (3.7)	27 [24-29]	26.0 (3.0)	26 [24-28]	0.29
Right P1 amp-c	53.5 (24.2)	47 [35-70]	59.8 (27.8)	52 [42-75]	0.15
Right N1 imp-c	25.4 (1.92)	25 [24-26]	24.7 (2.5)	24 [23-25]	0.0058
Right P1 imp-c	40.0 (1.8)	40 [39-41]	40.6 (3.0)	40 [39-41]	0.83
Right N1/P1-c	2.2 (0.4)	2.2 [2.0-2.4]	2.4 (0.5)	2.4 [2.1-2.6]	0.010
Right P1 amp-p	29.8 (13.4)	28 [19-36]	42.1 (18.3)	40 [28-52]	<0.0001
Right N1 imp-p	27.6 (1.9)	28 [26-29]	26.1 (2.4)	26 [25-27]	<0.0001
Right P1 imp-p	44.2 (2.2)	44 [43-46]	41.6 (3.0)	41 [40-42]	<0.0001
Right N1/P1-p	1.8 (0.4)	1.7 [1.6-1.9]	2.3 (0.6)	2.2 [2.0-2.4]	<0.0001
Left P1 amp-c	50.3 (23.1)	44 [36-66]	60.3 (27.2)	54 [42-77]	0.026
Left N1 imp-c	25.0 (1.6)	25 [24-26]	24.5 (2.1)	24 [23-25]	0.023
Left P1 imp-c	40.3 (2.4)	40 [39-42]	40.5 (2.7)	40 [39-41]	0.93
Left N1/P1-c	2.0 (0.6)	2.1 [1.8-2.3]	2.4 (0.6)	2.4 [2.1-2.6]	<0.0001
Left P1 amp-p	28.1 (12.7)	26 [21-34]	41.9 (18.4)	40 [29-52]	<0.0001
Left N1 imp-p	27.4 (1.8)	27 [26-29]	25.9 (2.0)	26 [25-27]	<0.0001
Left P1 imp-p	44.5 (2.9)	44 [43-45]	41.5 (2.7)	41 [40-43]	<0.0001
Left N1/P1-p	1.9 (0.5)	1.7 [1.6-2.0]	2.2 (0.8)	2.2 [1.9-2.4]	<0.0001

Table 10.5.1 Table shows comparison of ERG and WF-mfERG variables between patients with and without bilateral abnormal WF-mfERG. N is the maximum number in each group.

Parameters of the ERG that correlate with the presence of bilateral abnormal WF-mfERG were oscillatory potential amplitude and cone amplitude. Vigabatrin clearly exerts an effect on the global retinal response. It is unsure why these two parameters are the only ones affected.

There may be other parameters of the WF-mfERG that indicates bilateral abnormalities other than the difference in P1 implicit times between central and peripheral responses. Each of the parameters of the WF-mfERG was analysed to see if it corresponded to bilateral abnormalities. These included the peripheral P1 amplitude, peripheral N1 implicit

time, peripheral N1/P1 and central N1/P1. Mostly peripheral parameters are affected in patients with retinal toxicity. This is likely to be due to selective peripheral toxicity. However, central N1/P1 is also significant for retinal toxicity. Other investigators have surmised that Vigabatrin affects the retina uniformly but there are reduced cells peripherally then these are affected first and therefore a field defect results. The central responses of the WF-mfERG are reduced suggesting that there is involvement of the central retina and could be 'physiological' or 'pathological'.

Analysis of Groups 1 to 4 with regard to ERG and WF-mfERG variables with and without bilateral abnormal WF-mfERG are summarised in Table 10.5.2(Vigabatrin group) and Table 10.5.3 (ex-Vigabatrin group). In group 1 patients, peripheral implicit time and peripheral N1/P1 in right eyes with bilateral abnormal WF-mfERG.

Investigation variable	Abnormal WF-mfERG (n= 27)		No abnormal WF mf-ERG (n=29)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	145.7 (60.2)	145 [96-175]	198.9 (81.2)	186 [132-266]	0.017
Left rod amp	150.3 (55.4)	134 [104-185]	192.7 (73.9)	178 [152-246]	0.025
Right rod lat	91.5 (11.9)	93 [82-99]	86.4 (12.5)	86 [80-98]	0.21
Left rod lat	92.6 (13.9)	94 [82-103]	85.1 (12.9)	84 [77-94]	0.070

Right max A amp	232.0 (76.3)	224 [171-276]	217.3 (81.7)	224 [144-286]	0.49
Left max A amp	237.2 (68.6)	241 [195-269]	208.0 (81.4)	200 [138-263]	0.22
Right max A lat	16.9 (2.2)	17 [16-18]	17.4 (2.5)	17 [16-18]	0.70
Left max A lat	17.0 (2.8)	17 [15-18]	17.1 (3.1)	17 [16-18]	0.70
Right max B amp	359.9 (131.7)	334 [256-433]	412.2 (166.6)	409 [271-512]	0.36
Left max B amp	361.1 (113.0)	351 [256-425]	404.5 (162.2)	395 [283-487]	0.37
Right max B lat	40.3 (6.6)	39 [35-44]	42.1 (13.3)	39 [36-45]	0.64
Left max B lat	40.0 (6.3)	37 [36-44]	41.0 (10.1)	38 [36-43]	0.51
Right op amp	20.2 (11.2)	20 [10-29]	34.7 (18.7)	33 [21-49]	0.0052
Left op amp	21.0 (11.8)	22 [11-25]	35.3 (17.6)	36 [22-49]	0.0029
Right op lat	19.7 (2.5)	19 [18-21]	20.0 (3.7)	18 [18-22]	0.62
Left op lat	20.2 (2.7)	19 [18-21]	20.0 (3.6)	18 [18-22]	0.30
Right cone A amp	22.4 (7.6)	23 [16-30]	26.9 (10.8)	26 [21-34]	0.15
Left cone A amp	24.3 (10.7)	23 [19-28]	25.0 (9.6)	24 [19-29]	0.65
Right cone A lat	11.3 (2.8)	11 [9-14]	10.4 (2.8)	10 [8-11]	0.16
Left cone A lat	11.5 (3.3)	11 [10-14]	10.6 (3.2)	10 [9-11]	0.17
Right cone B amp	70.0 (26.0)	72 [50-90]	106.2 (35.0)	106 [87-114]	0.0003
Left cone B amp	71.0 (24.7)	70 [54-87]	105.1 (36.4)	102 [77-120]	0.0007
Right cone B lat	28.0 (4.1)	28 [25-32]	26.8 (3.4)	26 [25-29]	0.20
Left cone B lat	28.2 (3.5)	29 [26-31]	27.0 (3.6)	26 [25-29]	0.15
Right flicker amp	60.8 (32.0)	52 [35-85]	80.1 (31.8)	80 [53-94]	0.016
Left flicker amp	59.7 (31.1)	57 [37-72]	84.4 (50.2)	73 [55-107]	0.020
Right flicker lat	25.1 (3.1)	24 [22-28]	24.8 (3.0)	24 [23-26]	0.71
Left flicker lat	25.7 (3.7)	24 [23-29]	24.6 (2.8)	24 [23-26]	0.36
Right P1 amp-c	57.1 (25.5)	49 [40-70]	75.1 (29.3)	70 [55-98]	0.019
Right N1 imp-c	25.2 (1.5)	25 [24-26]	24.8 (1.8)	25 [24-25]	0.11
Right P1 imp-c	40.2 (1.9)	40 [39-41]	40.2 (2.6)	40 [39-40]	0.45
Right N1/P1-c	2.2 (0.3)	2.1 [1.9-2.4]	2.3 (0.3)	2.3 [2.0-2.6]	0.065
Right P1 amp-p	32.0 (14.2)	28 [22-39]	52.8 (20.0)	54 [41-64]	0.0003
Right N1 imp-p	27.8 (1.8)	28 [27-29]	26.7 (1.9)	26 [25-28]	0.0098
Right P1 imp-p	44.5 (2.2)	45[43-46]	41.5 (3.0)	40 [40-42]	<0.0001
Right N1/P1-p	1.6 (0.2)	1.6 [1.4-1.8]	2.1 (0.2)	2.1 [1.9-2.3]	<0.0001
Left P1 amp-c	53.4 (23.9)	48 [37-67]	73.1 (27.2)	72 [56-90]	0.010
Le41ft N1 imp-c	25.1 (1.7)	25 [24-26]	24.8 (2.0)	24 [24-25]	0.20
Left P1 imp-c	40.4 (2.4)	40 [39-42]	40.5 (2.6)	40 [39-41]	0.82
Left N1/P1-c	2.0 (0.4)	2.0 [1.8-2.2]	2.3 (0.4)	2.2 [2.1-2.5]	0.0057
Left P1 amp-p	30.4 (13.2)	28 [21-35]	52.0 (20.2)	51 [40-66]	0.0002
Left N1 imp-p	27.5 (1.9)	27 [26-29]	26.5 (2.2)	26 [25-28]	0.021
Left P1 imp-p	45.0 (2.9)	45 [43-47]	42.1 (2.5)	42 [40-43]	0.0004
Left N1/P1-p	1.8 (0.3)	1.7 [1.5-1.9]	2.0 (0.3)	2.0 [1.8-2.2]	0.0006

Table 10.5.2: Table shows comparison of ERG and WF-mfERG variables in Group 1 patients with and without bilateral abnormal mf ERG N is the maximum number.

Investigation variable	Abnormal mf ERG (n=11)		No abnormal mf ERG (n=38)		Wilcoxon p-value
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Right rod amp	126.9 (48.7)	114 [90-165]	146.3 (70.9)	132 [104-181]	0.41
Left rod amp	125.8 (40.6)	121 [95-139]	143.3 (80.3)	144 [94-165]	0.42
Right rod lat	88.9 (12.3)	89 [80-92]	87.7 (12.7)	90 [78-94]	0.92
Left rod lat	96.2 (14.1)	98 [85-110]	86.1 (12.2)	86 [79-93]	0.042

Right max A amp	135.3 (43.1)	144 [107-174]	145.1 (49.4)	140 [126-172]	0.68
Left max A amp	131.4 (52.4)	132 [103-152]	156.3 (46.7)	154 [120-180]	0.15
Right max A lat	19.3 (4.4)	18 [16-21]	17.3 (2.3)	16 [16-18]	0.078
Left max A lat	19.6 (4.5)	18 [16-23]	17.0 (2.7)	16 [16-18]	0.041
Right max B amp	229.0 (78.5)	241 [139-269]	255.9 (99.4)	250 [177-310]	0.58
Left max B amp	214.6 (68.1)	188 [163-284]	260.1 (133.2)	229 [174-309]	0.35
Right max B lat	46.4 (8.2)	51 [38-54]	47.8 (6.8)	48 [43-52]	0.95
Left max B lat	49.0 (7.5)	51 [43-54]	47.6 (5.0)	49 [45-51]	0.25
Right op amp	25.3 (7.4)	25 [21-28]	26.1 (13.2)	24 [18-30]	0.89
Left op amp	20.9 (7.6)	21 [14-30]	27.9 (16.7)	24 [15-37]	0.26
Right op lat	23.4 (4.6)	24 [19-26]	23.4 (2.6)	24 [23-25]	0.88
Left op lat	24.4 (4.3)	25 [24-26]	23.2 (2.6)	24 [23-25]	0.10
Right cone A amp	21.4 (7.4)	22 [16-26]	21.6 (8.5)	22 [16-25]	0.90
Left cone A amp	22.4 (18.6)	17 [15-20]	23.6 (10.4)	22 [17-30]	0.21
Right cone A lat	14.2 (3.1)	15 [12-16]	13.0 (3.0)	14 [12-15]	0.27
Left cone A lat	13.7 (2.8)	14 [13-15]	13.0 (2.9)	14 [12-15]	0.52
Right cone B amp	79.0 (30.3)	67 [50-112]	88.9 (31.6)	88 [63-110]	0.36
Left cone B amp	74.1 (27.7)	82 [47-94]	90.3 (34.5)	90 [64-115]	0.19
Right cone B lat	32.1 (2.7)	33 [30-34]	26.2 (3.9)	30 [29-31]	0.020
Left cone B lat	32.0 (2.1)	32 [30-34]	29.7 (2.8)	30 [29-31]	0.022
Right flicker amp	65.4 (30.8)	77 [34-90]	72.8 (30.7)	66 [51-94]	0.58
Left flicker amp	61.8 (24.4)	60 [40-76]	89.4 (82.0)	76 [55-97]	0.15
Right flicker lat	29.1 (2.6)	30 [27-31]	26.7 (2.5)	27 [26-28]	0.016
Left flicker lat	28.8 (2.6)	29 [27-31]	26.4 (2.7)	27 [25-29]	0.028
Right P1 amp-c	44.8 (19.2)	43 [32-50]	48.1 (18.7)	48 [39-54]	0.37
Right N1 imp-c	25.8 (2.8)	25 [24-26]	24.7 (1.6)	25 [24-25]	0.24
Right P1 imp-c	39.6 (1.4)	40 [39-41]	40.3 (2.5)	40 [39-41]	0.78
Right N1/P1-c	2.4 (0.4)	2.3 [2.0-2.7]	2.5 (0.5)	2.5 [2.2-2.7]	0.47
Right P1 amp-p	24.6 (9.6)	20 [16-34]	33.0 (12.3)	32 [27-41]	0.068
Right N1 imp-p	27.0 (2.0)	27 [25-29]	26.0 (1.6)	26 [25-27]	0.16
Right P1 imp-p	43.4 (2.3)	43 [42-44]	41.3 (2.2)	41 [40-42]	0.017
Right N1/P1	2.1 (0.5)	1.8 [1.6-2.7]	2.2 (0.7)	2.1 [1.8-2.4]	0.41
Left P1 amp-c	42.4 (19.8)	37 [29-53]	49.1 (18.2)	48 [38-59]	0.22
Left N1 imp-c	24.9 (1.4)	25 [24-25]	24.0 (2.3)	24 [23-25]	0.21
Left P1 imp-c	40.0 (2.4)	40 [39-40]	40.2 (2.4)	40 [39-41]	0.98
Left N1/P1-c	2.1 (0.3)	2.2 [1.8-2.3]	2.5 (0.5)	2.5 [2.2-2.6]	0.022
Left P1 amp-p	22.4 (9.7)	21 [12-32]	33.7 (13.3)	35 [23-45]	0.018
Left N1 imp-p	27.1 (1.8)	27 [25-29]	25.7 (1.5)	26 [25-27]	0.044
Left P1 imp-p	43.4 (2.7)	43 [42-44]	41.2 (2.2)	41 [40-42]	0.024
Left N1/P1	2.1 (0.8)	1.9 [1.6-2.6]	2.3 (1.6)	2.1 [1.7-2.3]	0.69

Table 10.5.3: Table shows comparison of ERG and WF-mfERG variables between ex-Vigabatrin with and without bilateral abnormal WF-mfERG. N is the maximum number.

10.6 Difference in visual field defects between visit 1 and visit 2.

Table 10.6.1 illustrates the difference in visual field defects between visit 1 and visit 2.

Visit 1		Visit2	
		Yes	No
All patients	Yes	31	6
	No	3	49
Vigabatrin only	Yes	18	0
	No	2	8
Ex-Vigabatrin only	Yes	8	1
	No	1	9
GABA	Yes	2	0
	No	0	16
non-GABA	Yes	3	5
	No	0	16

Table 10.6.1: Comparison of number of patients with bilateral visual field defects at visit 1 and visit 2

In group 1, 18 patients had visual field defects at visit 1 and visit 2. There were no patients with a visual field defects at visit 1 without a visual field defects at visit 2. Two patients with no visual field defects at visit one had a visual field defects at visit 2. This statistic may suggest 2 got worse based on visual field defects. 8 patients without visual field defects at visit 1 also had no visual field defects at visit 2. So in summary all patients with a visual field defects on visit 1 had a visual field defects on visit 2. Only 2 patients seem to get worse. These statistics were not significant.

Similar findings were found in group 2. However 1 patient with a visual field defects at visit 1 did not have visual field defects at visit 2. Similarly in group 4, 5 patients with visual field defects at visit 1 did not have visual field defects at visit 2. This illustrates the lack of consistency of the visual field test as varying results are obtained at different visits.

Table 10.6.2 and Table 10.6.3 summarizes with right and left eye visual field defects at visit 1 and visit 2. Results follow the same trend but are more consistent showing that bilaterally is more sensitive.

Visit 1		Visit2	
		Yes	No
All patients	Yes	40	9
	No	4	37
Vigabatrin only	Yes	20	1
	No	3	4
Ex-Vigabatrin only	Yes	10	0
	No	1	8
Other GABAergic	Yes	5	3
	No	0	11
Other non-GABAergic	Yes	5	5
	No	0	14

Table 10.6.2: Table shows comparison of number of patients with left eye visual field defects at visits 1 and 2.

Visit 1		Visit2	
		Yes	No
All patients	Yes	37	11
	No	5	37
Vigabatrin only	Yes	22	2
	No	0	5
Ex-Vigabatrin only	Yes	8	1
	No	1	9
Other GABAergic	Yes	2	2
	No	1	13
Other non-GABAergic	Yes	5	6
	No	3	10

Table 10.6.3: Table shows comparison of number of patients with right eye visual field defects at visit 1 and visit 2

10.7 Difference in WF-mfERG between visits 1 and 2.

See Table 10.7.1.

Visit 1		Visit2	
		Yes	No
All patients	Yes	17	0
	No	1	75
Vigabatrin only	Yes	13	0
	No	1	15
Ex-Vigabatrin only	Yes	4	0
	No	0	19
Other GABA	Yes	0	0
	No	0	17
non-GABA	Yes	0	0
	No	0	24

Table 10.7.1 Comparison of number of patients with bilateral abnormal WF-mfERG at visit 1 and visit 2

In the Vigabatrin group 13 patients had abnormal WF-mfERG on visit 1 and 2. One patient who had a normal WF-mfERG on visit 1 had an abnormal WF-mfERG on visit 2. There were no patients with abnormal WF-mfERG on visit one who did not have an abnormal WF-mfERG on visit 2. 15 patients did not have an abnormal WF-mfERG on visit 1 or 2. In the ex-Vigabatrin group 4 patients had an abnormal WF-mfERG on visit one and 2 and 19 patients did not have an abnormal WF-mfERG on visit 1 and 2. In the other groups all the patients did not have an abnormal WF-mfERG on visit 1 and 2.

Table 10.7.2 and Table 10.7.3 shows of the comparison of patients with left and right eye abnormal WF-mfERG at visit 1 and visit 2.

Visit 1		Visit2	
		Yes	No
All patients	Yes	18	9
	No	1	70
Vigabatrin only	Yes	14	3
	No	0	13
Ex-Vigabatrin only	Yes	4	1
	No	0	18
GABA	Yes	0	3
	No	1	15
non-GABA	Yes	0	2
	No	0	24

Table 10.7.2: Comparison of number of patients with left eye abnormal mf ERG at visit 1 and visit 2

For left eyes 14 patients had abnormal WF-mfERG on visit 1 and 2 and 13 did not have abnormal WF-mfERG on visit 1 and 2. However 3 patients did not have abnormal WF-mfERG on their 2nd visit even though they did on visit 1. The numbers for the ex-Vigabatrin group are 4 patients with abnormal WF-mfERG on visit 1 and 2 and 18 did not have abnormal WF-mfERG on visit 1 and 2. 1 patient did not have abnormal WF-mfERG on their 2nd visit even though they did on visit 1.

Visit 1		Visit2		P-value*
		Yes	No	
All patients	Yes	17	5	1.00
	No	4	68	
Vigabatrin only	Yes	13	2	1.00
	No	3	11	
Ex-Vigabatrin only	Yes	4	2	0.50
	No	0	17	
GABA	Yes	0	1	1.00
	No	1	15	
non-GABA	Yes	0	0	-
	No	0	25	

Table 10.7.3: Comparison of number of patients with right eye abnormal WF mf-ERG at visit 1 and visit

For right eyes 13 patients had abnormal WF-mfERG on visit 1 and 2 and 11 did not have abnormal WF-mfERG on visit 1 and 2. However 2 patients did not have abnormal WF-mfERG on their 2nd visit even though they did on visit 1 and 3 patients did not have abnormal WF-mfERG on visit 1 but had on visit 2. The numbers for the ex-Vigabatrin group are 4 patients with abnormal WF-mfERG on visit 1 and 2 and 17 did not have abnormal WF-mfERG on visit 1 and 2. 2 patients did not have abnormal WF-mfERG on their 2nd visit even though they did on visit 1.

10.8 Predictors of visual field defects are abnormal wide field multifocal electroretinograms

Predictors of visual field defects are shown below in Table 10.8.1. Predictors of abnormal wide field multifocal electroretinograms are shown below in Table 10.8.2.

Baseline characteristics	Univariate model		Multivariate stepwise model	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Continuous variables*				
Age (5 years)	0.98 (0.89, 1.08)	0.64		
Duration of epilepsy (5 years)	1.05 (0.92, 1.19)	0.45		
Monthly seizure frequency (5 seizures)	0.99 (0.96, 1.03)	0.59		
Categorical variables				
Drug group:				
Vigabatrin	Referent	<0.0001	Referent	0.0001
Ex-Vigabatrin	0.46 (0.20, 1.04)		0.29 (0.11, 0.73)	
GABA	0.24 (0.10, 0.56)		0.23 (0.09, 0.57)	
Other non-GABA	0.15 (0.06, 0.35)		0.13 (0.05, 0.33)	
Female	0.78 (0.43, 1.41)	0.40		
Current smoker	1.23 (0.62, 2.41)	0.55		
Drinks alcohol	0.45 (0.19, 1.07)	0.071		
Employment:				
Employed/student	Referent	0.0085		
Retired	2.15 (0.94, 4.88)			
Unemployed	2.71 (1.40, 5.27)			
Ophthalmology history of:				
Myopia	0.47 (0.12, 1.78)	0.27		
Presbyopia	0.89 (0.35, 2.26)	0.80		
Decreased central VA	0.97 (0.41, 2.29)	0.95		
Medical history of :				
Asthma	0.91 (0.29, 2.88)	0.87		
Diabetes	1.48 (0.29, 7.53)	0.64		
Hypertension	1.99 (0.71, 5.60)	0.19	3.38 (1.08, 10.59)	0.037
IHD	12.91 (1.58, 105.47)	0.017	10.53 (1.19, 93.55)	0.035
Family history of:				

Epilepsy	0.71 (0.25, 1.98)	0.51		
Glaucoma	2.15 (0.66, 7.04)	0.21		
Other antiepileptic drug				
ACETAZOLAMIDE	1.82 (0.53, 6.12)	0.34		
CARBAMAZEPINE	0.87 (0.48, 1.57)	0.64		
CLOBAZAM	2.37 (2.06, 5.39)	0.036		
GABAPENTIN	2.28 (1.08, 4.79)	0.030		
LEVETIRACETAM	1.04 (0.52, 2.11)	0.90		
LAMOTRIGINE	0.90 (0.51, 1.61)	0.73		
OXCARBAZEPINE	1.82 (0.53, 6.12)	0.34		
PHENOBARBITONE	1.70 (0.71, 4.08)	0.23		
PHENYTOIN	1.19 (0.63, 2.24)	0.59		
TIAGABINE	1.15 (0.41, 3.23)	0.79		
TOPIRAMATE	1.63 (0.82, 3.25)	0.16		
VALPROATE	1.64 (0.90, 2.99)	0.11		

Table 10.8.1 Univariate and multivariate logistic regression for predictors bilateral visual field defects.Odds ratios (95% CI) represent 5 units increase. Note for odds ratios if the 95% CI contains 1 then variable is non-significant.

Baseline characteristics	Univariate model		Multivariate stepwise model	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Continuous variables*				
Age (5 years)	0.94 (0.83, 1.07)	0.34	0.85 (0.73, 0.99)	0.041
Duration of epilepsy (5 years)	1.22 (1.05, 1.41)	0.0091	1.31 (1.10, 1.56)	0.0025
Monthly seizure frequency (5 seizures)	1.00 (0.97, 1.03)	0.95		
Categorical variables				
Female	0.64 (0.31, 1.29)	0.21		
Current smoker	1.36 (0.62, 3.00)	0.44		
Drinks alcohol	0.12 (0.02, 0.92)	0.042		
Employment:				
Employed/student	Referent	0.21		
Retired	0.98 (0.33, 2.92)			
Unemployed	1.91 (0.89, 4.11)			
Ophthalmology history of:				
Myopia	0.86 (0.18, 4.10)	0.85		
Presbyopia	-	-		
Decreased central visual acuity	0.69 (0.22, 2.12)	0.52		
Medical history of :				
Asthma	0.78 (0.16, 3.66)	0.75		
Diabetes	0.72 (0.08, 6.13)	0.76		
Hypertension	0.60 (0.13, 2.76)	0.51		
Ischaemic heart disease	0.47 (0.06, 3.81)	0.48		
Family history of:				
Epilepsy	1.18 (0.37, 3.77)	0.78		
Glaucoma	0.86 (0.18, 4.10)	0.85		
Other anti-epileptic drugs				
ACETAZOLAMIDE	2.31 (0.66, 8.11)	0.19		
CARBAMAZEPINE	1.44 (0.68, 3.06)	0.34		
CLOBAZAM	2.32 (0.99, 5.43)	0.052		
GABAPENTIN	1.52 (0.65, 3.56)	0.34		
LEVETIRACETAM	0.65 (0.25, 1.67)	0.37		
LAMOTRIGINE	1.11 (0.55, 2.24)	0.78		
OXCARBAZEPINE	1.49 (0.38, 5.77)	0.57		
PHENOBARBITONE	2.70 (1.10, 6.65)	0.030		
PHENYTOIN	1.94 (0.94, 4.02)	0.075		
TIAGABINE	3.61 (1.14, 8.80)	0.028	3.81 (1.25, 11.57)	0.018

TOPIRAMATE	2.33 (1.09, 5.00)	0.029		
VALPROATE	1.86 (0.91, 3.83)	0.091		

Table 10.8.2 Univariate and multivariate logistic regression for predictors of abnormal WF-mf ERG

* Odds ratios (95% CI) represent 5 units increase.

10.9 QOLIE-31 P and VFQ-25 Questionnaire

All available data was used, with n representing the number of patients who completed questionnaires and who had complied with both the field test and the WF-mfERG. For QOLIE-31 P questionnaire means (standard deviations, SD) are reported for each group and the p-value from either two sample t-test or ANOVA (>2 groups). For the VFQ-25 questionnaire, the data could not be considered normally distributed and therefore alternative non-parametric tests were used. Medians (inter-quartile range, IQR) are quoted for each group and p-values from either the Wilcoxon Rank Sum test or the Kruskal-Wallis test (>2 groups).

At visit 1 80% (45/56) of Vigabatrin group, 96% (47/49) of ex-Vigabatrin group, 98% (45/46) of GABA group and 98% (52/53) of non-GABA group completed quality of life questionnaires.

	Vigabatrin (n=45)	Ex-Vigabatrin (n=47)	GABA (n=45)	nonGABA (n=52)	ANOVA p-value
Seizure Worry	59.4 (23.1)	49.7 (30.1)	55.4 (27.4)	60.6 (28.8)	0.21
Overall Quality of Life	62.4 (16.4)	60.7 (18.5)	63.5 (19.2)	68.0 (17.5)	0.20
Emotional Well- being	61.7 (20.2)	63.0 (16.8)	62.2 (20.3)	70.9 (17.1)	0.046
Energy	52.5 (11.5)	51.0 (11.7)	50.0 (12.4)	52.6 (12.1)	0.67
Cognitive	54.4 (24.5)	53.0 (25.0)	57.2 (23.8)	64.5 (25.2)	0.095
Medicine Effects	67.7 (22.3)	57.5 (24.3)	66.4 (23.5)	68.1 (25.6)	0.11
Social Function	62.7 (20.2)	56.5 (21.2)	64.0 (24.8)	72.7 (24.6)	0.0064
QOLIE	58.9 (16.3)	56.0 (16.2)	59.5 (17.9)	66.4 (16.9)	0.018

Table 10.9.1 Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 between groups

Data are presented as mean (SD)

Overall QOLIE-31 P scores are highest in Vigabatrin and other non GABA group. Seizure worry, medicine effects and energy scored highest in these two groups as well. Emotional well being scores were the highest in other non GABA groups and lowest in the ex-Vigabatrin group.

Table 10.9.2 shows the scores in patients with visual field defects and without visual field defects. Overall quality of life is lower in the group with visual field defects in all categories except medicine effects.

	Visual field defects (n= 70)	No visual field defects (n=107)	T-test p-value
Seizure Worry	52.8 (28.3)	59.8 (26.9)	0.10
Overall QOL	60.7 (17.6)	67.1 (17.3)	0.018
Emotional Well- being	59.3 (18.8)	68.7 (17.9)	0.0010
Energy	50.1 (11.6)	53.0 (12.0)	0.11
Cognitive	55.1 (24.9)	61.0 (24.4)	0.12
Med Effects	65.6 (21.8)	65.4 (25.1)	0.94
Social Function	58.5 (22.2)	69.6 (23.0)	0.0017
QOLIE	56.8 (16.9)	64.1 (16.3)	0.0047

Table 10.9.2: All patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral visual field defects

Data are presented as mean (SD).

	Abnormal mf ERG (n= 32)	No abnormal mf ERG (n=156)	T-test p-value
Seizure Worry	60.1 (23.1)	55.6 (28.7)	0.40
Overall QOL	62.3 (17.2)	64.0 (18.2)	0.63
Emotional Well- being	61.4 (19.3)	65.3 (18.8)	0.28
Energy	53.4 (11.6)	51.2 (12.0)	0.35
Cognitive	55.1 (25.6)	58.0 (24.9)	0.55
Med Effects	66.8 (21.7)	64.7 (24.8)	0.66
Social Function	59.9 (20.6)	65.0 (24.0)	0.26
QOLIE	58.6 (16.4)	60.7 (17.4)	0.53

Table 10.9.3: All patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral abnormal mf ERG

Data are presented as mean (SD).

Table 10.9.3 shows the scores in patients with abnormal WF-mfERG and with normal WF-mfERG. Scores are higher in patients with abnormal WF-mfERG in the categories of seizure worry, energy and medicine effects.

In the Vigabatrin group all patients had lower scores for QOLIE-31 P in all categories with the exception of medicine effects if they had visual field defects. See Table 10.9.4.

	Visual field defects (n= 27)	No visual field defects (n=13)	T-test p-value
Seizure Worry	59.1 (25.1)	58.3 (20.8)	0.92
Overall QOL	62.8 (16.7)	63.5 (14.3)	0.91
Emotional Well- being	61.2 (19.4)	60.8 (22.2)	0.95
Energy	53.0 (12.7)	50.8 (11.1)	0.59
Cognitive	59.3 (25.9)	47.0 (20.1)	0.14
Med Effects	67.4 (22.5)	65.2 (23.8)	0.78
Social Function	62.4 (21.7)	64.2 (19.7)	0.81

QOLIE	60.2 (16.9)	56.9 (15.6)	0.55

Table 10.9.4 Vigabatrin patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral visual field defects
Data are presented as mean (SD).

In Vigabatrin group with QOLIE-31 P, all patients had lower scores in all categories if they had bilateral abnormal WF-mfERG. See Table 10.9.5.

	Abnormal WF-mfERG (n= 23)	No abnormal WF-mfERG (n=22)	T-test p-value
Seizure Worry	61.4 (21.9)	57.3 (25.2)	0.56
Overall QOL	64.1 (18.3)	60.6 (14.3)	0.48
Emotional Well- being	62.3 (20.2)	61.1 (20.6)	0.84
Energy	53.9 (12.8)	51.1 (10.0)	0.42
Cognitive	57.0 (27.2)	51.7 (21.6)	0.48
Med Effects	69.8 (20.4)	65.6 (24.4)	0.53
Social Function	62.8 (21.2)	62.6 (19.4)	0.98
QOLIE	60.4 (17.2)	57.4 (15.5)	0.55

Table 10.9.5 Vigabatrin patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral abnormal WF-mfERG
Data are presented as mean (SD).

In ex-Vigabatrin patients with QOLIE-31 P, medicine effects were scored higher in patients with visual field defects than patients without visual field defects as were seizure worry. All other parameters were scored higher in the group without visual field defects. See Table 10.9.6.

	Visual field defects (n= 19)	No visual field defects (n=25)	T-test p-value
Seizure Worry	52.2 (29.5)	49.0 (31.2)	0.73
Overall QOL	57.9 (14.7)	65.2 (20.2)	0.19
Emotional Well- being	59.5 (17.5)	67.1 (15.8)	0.14
Energy	49.9 (10.2)	53.1 (12.1)	0.35
Cognitive	53.7 (24.6)	54.7 (25.3)	0.90

Med Effects	61.5 (24.5)	55.5 (25.3)	0.43
Social Function	56.0 (19.3)	59.4 (22.3)	0.60
QOLIE	55.3 (15.8)	58.4 (16.0)	0.53

Table 10.9.6 Ex-Vigabatrin patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral visual field defects

Data are presented as mean (SD)

	Abnormal WF-mfERG (n= 9)	No abnormal WF-mfERG (n=38)	T-test p-value
Seizure Worry	57.0 (27.0)	48.0 (30.9)	0.42
Overall QOL	57.5 (13.9)	61.4 (19.5)	0.57
Emotional Well- being	58.9 (17.4)	64.0 (16.8)	0.42
Energy	52.0 (8.2)	50.7 (12.4)	0.77
Cognitive	50.4 (21.6)	53.7 (25.9)	0.73
Med Effects	59.1 (24.3)	57.1 (25.6)	0.83
Social Function	52.7 (18.1)	57.4 (22.0)	0.55
QOLIE	54.1 (13.8)	56.4 (16.9)	0.71

Table 10.9.7 Ex-vigabatrin Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral abnormal WF- mfERG

Data are presented as mean (SD).

In GABA patients with QOLIE-31 P, patients scored lower in all categories if they had visual field defects compared to not having visual field defects. See Table 10.9.8

	Visual field defects (n= 13)	No visual field defects (n=29)	T-test p-value
Seizure Worry	42.0 (31.3)	63.3 (23.2)	0.018
Overall QOL	56.4 (23.0)	66.4 (17.3)	0.12
Emotional Well- being	51.3 (22.1)	66.6 (18.7)	0.026
Energy	45.5 (12.7)	52.6 (12.3)	0.10
Cognitive	46.8 (25.4)	63.4 (22.1)	0.038
Med Effects	64.4 (21.0)	68.8 (22.6)	0.56

Social Function	51.4 (27.4)	70.5 (22.2)	0.22
QOLIE	49.8 (20.2)	64.6 (15.6)	0.013

Table 10.9.8 Other GABA patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral visual field defects

Data are presented as mean (SD)

In other non-GABA patients with QOLIE-31 P, patients scored lower in all categories if they had visual field defects compared to not having visual field defects. See Table 10.9.9

.	Visual field defects (n= 11)	No visual field defects (n=40)	T-test p-value
Seizure Worry	51.3 (29.6)	64.6 (27.2)	0.17
Overall QOL	65.2 (17.8)	69.9 (16.4)	0.42
Emotional Well- being	63.6 (14.3)	73.9 (16.3)	0.063
Energy	48.7 (9.3)	54.1 (12.4)	0.19
Cognitive	57.3 (22.7)	67.8 (24.7)	0.21
Med Effects	69.8 (17.4)	69.1 (26.3)	0.93
Social Function	61.7 (22.0)	77.2 (22.7)	0.050
QOLIE	59.2 (13.3)	69.7 (15.7)	0.048

Table 10.9.9 Non-GABAergic patients: Comparison of Quality of Life in Epilepsy questionnaire (QOLIE-31 P) at visit 1 for bilateral visual field defects

Data are presented as mean (SD).

Overall VFQ-25 scores are similar among all the groups tested. See Table 10.9.10

	Vigabatrin (n=45)	Ex-Vigabatrin (n=47)	GABA (n=45)	non-GABA (n=52)	Kruskal-Wallis p-value
General Health	50 (50-75)	50 (25-50)	50 (50-75)	50 (50-75)	0.13
General Vision	80 (60-80)	80 (60-80)	80 (60-80)	80 (70-80)	0.59
Ocular Pain	100 (88-100)	100 (75-100)	100 (75-100)	100 (75-100)	0.98

Near Activities	100 (83-100)	92 (83-100)	92(83-100)	100 (83-100)	0.70
Distance Activities	100 (92-100)	100 (83-100)	92 (83-100)	100 (92-100)	0.090
Social Functioning	100 (88-100)	100(100-100)	100 (88-100)	100 (100-100)	0.086
Mental Health	94 (88-100)	94 (88-100)	100 (88-100)	94 (94-100)	0.63
Role Difficulties	100 (88-100)	100 (88-100)	100 (88-100)	100 (100-100)	0.52
Dependency	100 (90-100)	100 (80-100)	100 (70-100)	100 (90-100)	0.61
Driving	100 (75-100)	100 (80-100)	100 (90-100)	100 (90-100)	0.012
Colour Vision	100 (100-100)	100 (80-100)	100 (100-100)	100 (90-100)	0.46
Peripheral Vision	100 (75-100)	100 (75-100)	100 (75-100)	100 (100-100)	0.014
Visual Function	95 (86-100)	94 (87-100)	95 (84-98)	95 (90-100)	0.62

Table 10.9.10 Comparison of VFQ-25 questionnaire at visit 1 between groups

Data are presented as median (Interquartile Range).

Scores are lower in patients with visual field defects in the categories of ocular pain, near activities, distance activities and mental health. Scores are lower in patients with visual field defects for peripheral vision and this result was clinically significant. Overall patients with visual field defects have a lower overall visual function score. See Table 10.9.11

	Visual field defects (n=70)	No visual field defects (n=107)	Wilcoxon p-value
General Health	50 (25-75)	50 (50-75)	0.27
General Vision	80 (60-80)	80 (60-80)	0.063

Ocular Pain	88 (75-100)	100 (88-100)	0.018
Near Activities	92 (75-100)	100 (88-100)	0.011
Distance Activities	92 (83-100)	100 (92-100)	0.016
Social Functioning	100 (88-100)	100 (100-100)	0.0058
Mental Health	94 (81-100)	100 (94-100)	0.0028
Role Difficulties	100 (75-100)	100 (100-100)	0.042
Dependency	100 (92-100)	100 (100-100)	0.013
Driving	100 (100-100)	100 (80-100)	0.26
Colour Vision	100 (100-100)	100 (90-100)	0.37
Peripheral Vision	75 (75-100)	100 (100-100)	<0.0001
Visual Function	93 (85-98)	97 (92-100)	0.0042

Table 10.9.11 All patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral visual field defects

Data are presented as median (Interquartile Range).

Scores are lower in patients on Vigabatrin with visual field defects in the categories of ocular pain, mental health. Overall visual function in patients on Vigabatrin with visual field defects was lower than patients with no visual field defects though this result was not significant. See Table 10.9.12

	Visual field defects (n= 33)	No visual field defects (n=18)	Wilcoxon p-value
General Health	50 (25-75)	50 (50-50)	0.95

General Vision	80 (60-80)	80 (80-80)	0.31
Ocular Pain	88 (88-100)	100 (100-100)	0.082
Near Activities	100 (83-100)	100 (83-100)	0.54
Distance Activities	100 (92-100)	100 (92-100)	0.91
Social Functioning	100 (100-100)	100 (100-100)	0.67
Mental Health	94 (88-100)	100 (94-100)	0.28
Role Difficulties	100 (88-100)	100 (88-100)	0.80
Dependency	100 (90-100)	100 (100-100)	0.79
Driving	100 (80-100)	100 (100-100)	0.62
Colour Vision	100 (90-100)	100 (100-100)	0.53
Peripheral Vision	100 (75-100)	100 (75-100)	0.95
Visual Function	95 (90-100)	97 (88-100)	0.90

Table 10.9.12 Vigabatrin patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral visual field defects

Data are presented as median (Interquartile Range).

Scores are lower in patients in ex- Vigabatrin group with visual field defects in the categories of near activities, mental health. Overall visual function in patients that were on Vigabatrin with visual field defects was lower than patients with no visual field defects though this result was not significant. See Table 10.9.13.

	Visual field defects (n= 21)	No visual field defects (n=25)	Wilcoxon p-value
General Health	50 (25-75)	50 (25-50)	0.77
General Vision	80 (60-80)	80 (60-80)	0.51
Ocular Pain	100 (75-100)	100 (75-100)	0.67
Near Activities	92 (75-100)	100 (83-100)	0.28
Distance Activities	100 (75-100)	100 (92-100)	0.35
Social Functioning	100 (100-100)	100 (80-100)	0.75
Mental Health	88 (69-100)	100 (94-100)	0.079
Role Difficulties	100 (88-100)	100 (88-100)	0.70
Dependency	100 (92-100)	100 (100-100)	0.52
Driving	100 (100-100)	100 (90-100)	0.23
Colour Vision	100 (100-100)	100 (80-100)	0.20
Peripheral Vision	100 (75-100)	100 (75-100)	0.27
Visual Function	93 (85-99)	96 (92-100)	0.19

Table 10.9.13 Ex-Vigabatrin patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral visual field defects

Data are presented as median (Interquartile Range).

Scores are lower in all categories in patients in GABA group with visual field defects except dependency, driving and colour vision. Overall visual function scores are lower in GABA group with visual field defects. (See Table 10.9.14)

	Visual field defects (n= 13)	No visual field defects (n=30)	Wilcoxon p-value

General Health	50 (25-50)	75 (50-75)	0.040
General Vision	60 (60-80)	80 (60-80)	0.11
Ocular Pain	88 (75-100)	100 (88-100)	0.10
Near Activities	75 (58-83)	100 (92-100)	0.0009
Distance Activities	75 (67-92)	100 (92-100)	0.0025
Social Functioning	75 (75-100)	100 (100-100)	0.0025
Mental Health	88 (50-100)	100 (94-100)	0.026
Role Difficulties	75 (62-100)	100 (100-100)	0.010
Dependency	100 (83-100)	100 (100-100)	0.065
Driving	100 (100-100)	100 (92-100)	0.99
Colour Vision	100 (75-100)	100 (100-100)	0.061
Peripheral Vision	75 (50-100)	100 (100-100)	0.0002
Visual Function	84 (74-93)	97 (90-98)	0.0041

Table 10.9.14 GABA patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral visual field defects

Data are presented as median (Interquartile Range).

Scores are lower in the categories of ocular pain, near activities and mental health and overall visual function in patients with visual field defects in other non-GABAergic patients. (See Table 10.9.15)

	Visual field defects (n= 11)	No visual field defects (n=41)	Wilcoxon p-value
General Health	50 (50-75)	50 (50-75)	0.86
General Vision	80 (80-80)	80 (70-80)	1.00
Ocular Pain	75 (75-100)	100 (88-100)	0.022
Near Activities	92 (83-100)	100 (92-100)	0.068
Distance Activities	100 (92-100)	100 (92-100)	0.59
Social Functioning	100 (88-100)	100 (100-100)	0.095
Mental Health	94 (88-100)	97 (94-100)	0.70
Role Difficulties	100 (88-100)	100 (90-100)	0.26
Dependency	100 (92-100)	100 (100-100)	0.026
Driving	100 (100-100)	100 (70-100)	0.061
Colour Vision	100 (100-100)	100 (90-100)	0.24
Peripheral Vision	100 (75-100)	100 (100-100)	0.044
Visual Function	90 (88-96)	97 (93-100)	0.022

Table 10.9.15 Non-GABA patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral visual field defects

Data are presented as median (Interquartile Range).

Scores are lower in the categories of ocular pain, near and distance activities, peripheral vision and overall visual function in patients with abnormal bilateral WF-mfERG as compared with normal bilateral WF-mfERG. (See Table 10.9.16)

	Abnormal mf ERG (n=33)	No abnormal mf ERG (n=155)	Wilcoxon p-value
General Health	50 50-75)	50 (25-75)	0.30
General Vision	80 (60-80)	80 (60-80)	0.27
Ocular Pain	88 (88-100)	100 (75-100)	0.32
Near Activities	92 (83-100)	100 (83-100)	0.69
Distance Activities	92 (83-100)	100 (92-100)	0.21
Social Functioning	100 (100-100)	100 (90-100)	0.56
Mental Health	94 (88-100)	94 (88-100)	0.70
Role Difficulties	100 (88-100)	100 (88-100)	0.26
Dependency	100 (100-100)	100 (90-100)	0.92
Driving	100 (70-100)	100 (100-100)	0.073
Colour Vision	100 (80-100)	100 (100-100)	0.33
Peripheral Vision	75 (75-100)	100 (75-100)	0.0036
Visual Function	94 (85-99)	95 (88-99)	0.78

Table 10.9.16 All patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral abnormal WF-mfERG

Data are presented as median (Interquartile Range).

Scores are lower in the categories of ocular pain, distance activities and overall visual function in patients with abnormal bilateral WF-mfERG as compared with normal bilateral WF-mfERG in patients on Vigabatrin. (See Table 10.9.17)

	Abnormal WF-mfERG (n= 23)	No abnormal WF-mfERG (n=22)	Wilcoxon p-value
General Health	50 (50-75)	50 (50-50)	0.13
General Vision	80 (60-80)	80 (60-80)	0.94
Ocular Pain	88 (75-100)	100 (88-100)	0.022
Near Activities	100 (83-100)	100 (75-100)	0.43
Distance Activities	92 (83-100)	100 (92-100)	0.43
Social Functioning	100 (88-100)	100 (88-100)	0.93
Mental Health	94 (88-100)	94 (88-100)	0.97
Role Difficulties	100 (75-100)	100 (100-100)	0.13
Dependency	100 (92100)	100 (100-100)	0.47
Driving	100 (90-100)	100 (100-100)	0.53
Colour Vision	100 (80-100)	100 (100-100)	1.00
Peripheral Vision	75 (50-100)	100 (75-100)	0.28
Visual Function	95 (85-100)	96 (88-100)	0.59

Table 10.9.17 Vigabatrin patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral abnormal mf ERG

Data are presented as median (Inter-quartile Range).

Scores are lower in the categories of general vision, near and distance activities, peripheral vision and overall visual function in patients with abnormal bilateral WF-mfERG as compared with normal bilateral WF-mfERG in ex-Vigabatrin patients (See Table 10.9.18).

	Abnormal WF-mfERG (n= 10)	No abnormal WF-mfERG (n=37)	Wilcoxon p-value
General Health	50 (25-75)	50 (25-50)	0.37
General Vision	60 (60-80)	80 (60-80)	0.27
Ocular Pain	100 (88-100)	100 (75-100)	0.52
Near Activities	92 (83-100)	100 (83-100)	0.58
Distance Activities	92 (75-100)	100 (92-100)	0.26
Social Functioning	100 (90-100)	100 (100-100)	0.098
Mental Health	94 (88-100)	94 (88-100)	0.99
Role Difficulties	100 (88-100)	100 (88-100)	0.68
Dependency	100 (80-100)	100 (100-100)	0.29
Driving	100 (90-100)	100 (100-100)	0.48
Colour Vision	100 (100-100)	100 (90-100)	0.72
Peripheral Vision	88 (75-100)	100 (75-100)	0.59
Visual Function	93 (88-99)	95 (87-100)	0.86

Table 10.9.17 Ex-Vigabatrin patients: Comparison of VFQ-25 questionnaire at visit 1 for bilateral abnormal WF-mfERG
Data are presented as median (Interquartile Range).

10.10 Monthly seizures and ptosis

Clinically, patients seemed to have a greater degree of ptosis if they were well controlled by their anti-epileptic medication and had fewer seizures per month. Table 10.10.1 shows that there is a relationship.

Eye	N	Spearman rank correlation coeffiecient	P-value
Left	80	-0.033	0.77
Right	82	0.106	0.35

Table 10.10.1: Association between number of monthly seizures and degree of Ptosis

10.11 Conclusion

There were no significant differences in basic demographic data (age, gender, duration of epilepsy, median monthly seizure frequency) between individual study groups. There was no evident selection bias on the basis of medical, environmental, and social variables, including family history of epilepsy and/or glaucoma, personal history of other chronic disease (asthma, diabetes, hypertension, ischemic heart disease), cigarette smoking, alcohol use, or levels of employment (data not shown). There were similarly no significant differences among study groups in terms of routine ophthalmological examination, visual acuity, or colour vision.

Bilateral visual field constriction, as determined by static perimetry, was observed in all 4 study groups the prevalence of which ranged between 59% in Group 1 patients who were being treated with VGB at the time of assessment and 21% in Group 4 patients who had never been exposed to any GABAergic AED. In contrast, WF-mfERG abnormalities were observed only in those patients who had been exposed to VGB, with a prevalence of 48% in current VGB patients and 22% in participants with previous exposure to the drug. A total of 21 VGB exposed patients (current and previous) demonstrated visual field defects (as determined by static perimetry) with no associated retinal dysfunction (as determined by WF-mfERG), whereas only 3 VGB exposed patients had demonstrable retinal dysfunction in the absence of apparent visual field constriction.

Investigation of conventional ERG variables revealed bilateral reductions in the amplitude of rod, oscillatory potential, cone A, cone B, and flicker responses in subjects with visual field defects, compared to those without. These reductions were variously observed in patient Groups 1 to 3, but not in Group 4. Only those reductions in oscillatory potential and cone B amplitudes were common to all affected groups and in all cases statistical significance was lost when the data were corrected for multiple comparisons. In contrast, there was a selective association between the bilateral reduction in cone B amplitude and the presence of WF-mfERG abnormalities, which was exclusive to Group 1 patients (current VGB) and which was maintained in the face of correction for multiple testing.

An estimate of total VGB drug load was attempted for all participants in study Groups 1 and 2, although only 15 of 49 patients in Group 2 (previous VGB exposure) had sufficiently detailed clinical records for a reliable figure to be calculated. There was no clear relationship between accumulated ingestion of VGB and the incidence of visual field constriction determined by static perimetry. However, patients with abnormal WF-mfERG findings had a significantly higher median VGB exposure than those with normal WF-mfERG.

Analysis of quality of life questionnaires completed at visit 1 revealed no significant differences in baseline visual health status (VFQ-25) or epilepsy-related quality of life (QOLIE-31) between individual study groups (data not shown). Participants with visual field constriction identified by static perimetry at visit 1 (irrespective of study group) reported a significantly lower peripheral vision score on VFQ-25 than those without visual field defects ($p<0.05$; data not shown). They also reported reduced emotional well-being ($p<0.01$), social functioning ($p<0.05$), and total QOLIE score ($p<0.05$) on QOLIE-31 analysis (data not shown). These observations were made prior to initial ophthalmological testing and were independent of any confirmed visual field constriction or retinal dysfunction. No such associations were observed when visit 1 quality of life measures were compared on the basis of initial WF-mfERG findings (Tables 5 and 6).

A total of 94 participants (29 in Group 1, 23 in Group 2, 18 in Group 3, 24 in Group 4) returned for repeat assessment (Table 7), with no significant or confounding changes to AED treatment regimen (other than modest dosage adjustments) in the intervening period. The median duration between visit 1 and visit 2 was 673 days [range 158 to 2066 days]. There were no differences in basic clinical demographics, routine ophthalmological examination, or the time since last study visit between study groups at repeat assessment (data not shown). Three patients with VGB exposure (2 in Group 1, 1 in Group 2) had *de novo* visual field constriction at visit 2, which had not been apparent at initial assessment. In contrast, six patients (1 in Group 2, 5 in Group 4), who had demonstrated bilateral field defects at visit 1, were subsequently reported as "normal" upon repeat investigation. Only one patient (Group 1) with a normal WF-mfERG at visit 1 had abnormalities on repeat testing 18 months later and none showed any apparent between-visits improvement (Table 7).

Participants who returned for repeat assessment completed further quality of life questionnaires with awareness of the outcome of initial ophthalmological investigation.

These were analysed as both group data and individual paired data on the basis of outcome. Subjects with apparent visual field constriction at visit 1 (irrespective of study group) reported a significantly lower mean distance activities score on visit 2 VFQ-25 ($p<0.05$) and a significant reduction in mean emotional well-being on visit 2 QOLIE-31 ($p<0.05$) compared to those with normal perimetry (data not shown). There were no associations between quality of life measures recorded at study visit 2 and prior knowledge of retinal dysfunction identified by WF-mfERG at visit 1 (Tables 5 and 6). When analysed on an individual patient basis, there were no significant between-visit changes in VFQ-25 or QOLIE-31 measures that could be attributed to awareness of either visual field constriction or retinal dysfunction (data not shown).

In the study it was thought that eyelid position correlated with seizure control i.e. the greater the ptosis then patients tended to have fewer seizures, though the relationship was not found to be statistically significant. Anti-epileptic drugs are designed to dampen neuronal activity and may reduce the neuronal input to the upper lid. Therefore, eyelid ptosis may be a useful clinical sign in compliance and efficacy of these drugs.

Chapter 11

Final discussion

11.1 Demographic data: controls

Since Eke et al described 3 cases of severe visual field constriction in patients on Vigabatrin(11), a number of studies since linked visual dysfunction with Vigabatrin use, often visual field defects. The prevalence remains poorly defined with reports of visual field defects ranging from 0.3%(122) to 75% in patients treated with Vigabatrin.(120-122) This wide range is unlikely to be due to the varied effect of Vigabatrin effect on the retina but may reflect poor sampling in previous studies. Most papers describe at least a 50% prevalence of visual field defects.

Why is the range so variable in different studies? This can be due to a number of problems with study design or sample selection.

There have been few large scale studies to date to document the true prevalence of visual field defects in patients with different types of epilepsy such as reported by Wild and Martinez.(126;162) Cases have been reported of visual field defects associated with other anticonvulsant drugs. These have included constricted fields with phenytoin(141), diazepam(142) and progabide.(104) These defects may be a relatively common side effect of anticonvulsant treatment or even a feature of the natural history of epilepsy.

It has been reported that other factors such as smoking "magnify" the peripheral retinal dysfunction seen with Vigabatrin (139). Many other "factors" have been reported in the literature to be important including cumulative drug dose.(127)

In the study presented in this thesis, patients were divided into 4 groups. These fours groups consisted of: patients on Vigabatrin for at least 2 years; patients on Vigabatrin for at least 1 year and off Vigabatrin for at least 2 years; patients on other GABA-ergic drugs; and patients on no GABA-ergic drugs as illustrated in Table 10.1.1. The patients in this study were matched closely for age, sex, AED and seizure control between four groups. Other factors thought to be important in developing visual field defects such as cumulative drug load could therefore be examined in detail with controls. One of the criticisms of

some of the previous studies is a lack of adequate controls, though it was not known what factors are important in the development of toxicity.

There are several important questions about Vigabatrin toxicity that have been answered by this study and the raw data has been summarized in the conclusions, Chapter 10.

1. Do visual field defects occur in other groups with epilepsy other than patients on Vigabatrin?
2. Do electrophysiological defects occur in all groups and if so which?
3. Can the WF-mfERG be used to diagnose and monitor progression of disease?
4. Is GABA or any other agents important in the development of retinal toxicity?
5. Do visual field defects worsen when continuing on Vigabatrin and are they reversible on stopping Vigabatrin?
6. What factors are important in the development and progression of disease of the visual system associated with Vigabatrin use?
7. Do patients accept Vigabatrin associated visual field defects?

11.2 Do visual field defects occur in other groups with epilepsy other than patients on Vigabatrin?

Table 10.2.1 summarsied the results in patients with and without bilateral visual field defects (visual field defects) in all groups.

In the Vigabatrin group, 33 patients (64.7%) had visual field defects assessed by Humphrey 120 degree static perimetry which was the highest percentage of any of the groups (24 patients with predominantly bilateral nasal loss, 9 patients with symmetrical visual field loss). Prevalence of visual field defects using static Humphrey perimetry in patients with epilepsy on Vigabatrin have varied from 33%(133) to 68%(134) but most studies show about 50% of patients have field defects. 64.7% was therefore within the range of previously reported studies.

Bilateral visual field defects were present in all four groups. The prevalence was highest in the Vigabatrin group (64.7%) followed by the ex-Vigabatrin group (45.6%). The percentage in the groups not exposed to Vigabatrin i.e. GABA-ergic and nonGABA groups were much higher than expected (GABA group, 30.2%, non GABA groups Group 4,

21.2%). The field loss tended to be symmetrical in the GABA and non GABA group as opposed to predominantly bi-nassal which occurred with patients on Vigabatrin. However 8 patients had predominantly bi-nasal defects in the ex-Vigabatrin group and 4 in the Non-GABA group.This result was statistically significant. These patients had all had brain scans and full ophthalmic examination and were not included if there could have been a cause of visual field defects such as glaucoma. Therefore, visual field defects in all four groups can be divided into patients with a 'real' visual field defect (possibly due to their epilepsy) and patients with a 'false positive' visual field defect which was difficult to determine in this study.

Visual field defects can occur in all groups with epilepsy irrespective of Vigabatrin exposure. This has been shown in other reports of other visual field defects with phenytoin(141), diazepam(142) and progabide.(104) There are probably different causes of visual field abnormalities in patients with epilepsy that are not related to Vigabatrin use. Two possible reasons are that antiepileptic drugs generally act to dampen physiological responses in the brain and in the retina therefore they are likely to decrease neuronal transmission in the retina and could cause transient visual field abnormalities causing a real field defect. Also patients with epilepsy have poor attention and concentration making it difficult for them to perform the subjective visual field test causing a false positive field defect.

Undoubtedly being exposed to Vigabatrin increases the percentage of visual field defects in patients with epilepsy. It can be surmised in the group of patients exposed to Vigabatrin (Vigabatrin and ex-Vigabatrin) there there is a subset of patients with visual field defects due to retinal toxicity and a subset of patients who have visual field defects as a result of their epilepsy. These two groups may overlap. Hence, perimetry alone appears not to detect Vigabatrin associated retinal toxicity.

11.3 Do electrophysiological defects occur in all groups and if so which?

We know that visual field defects occur in all groups with epilepsy. One reason could be the poor response of patients with epilepsy leading to false positives in the field test. The ERG is an objective global measure of retinal function. Is the ERG specific to those patients with visual dysfunction due to Vigabatrin? Comparison was made of ERG variables and patients with and without visual field defects and now is summarized in Table 10.4.1 analyzing right and left eyes separately. Significant positive correlation

occurred between visual field defects and oscillatory potential amplitude, cone amplitude and flicker amplitude when all patients with visual field defects were examined.

The four tables in section 10.4 (Table 10.4.2, 10.4.3, 10.4.4 and 10.4.5) showed correlation between ERG parameters and visual field defects in the different groups. Oscillatory potential amplitude, oscillatory potential latency and cone b-wave latency correlated with visual field defects in the Vigabatrin group. Maximal a-wave latency, Maximal b-wave amplitude, oscillatory potential amplitude, cone a-wave amplitude and flicker amplitude correlated with visual field defects in ex-Vigabatrin groups. Maximal b-wave amplitude, oscillatory potential amplitude and cone b-wave amplitude correlated with visual field defects in GABA group. Bilateral flicker amplitude correlated with visual field defects non GABA groups.

Reduced oscillatory potential (OP) amplitudes have been described (in up to 92% of patients (115;151) on Vigabatrin) in several studies although one study has reported no change in oscillatory potential amplitudes(133). In this study there was a positive correlation between visual field defects and OP amplitude in the Vigabtrin, ex-Vigabatrin and GABA groups suggesting a link with GABA not specific to Vigabatrin group only.

The single flash cone and flicker reponses have been reported to be affected more than the rod single flash(44). In this thesis study there was no correlation between rod parameters and bilateral visual field defects in any of the groups studied.

The incidence of decreased cone b-wave amplitude has been reported to vary between 30% and 62%(115;151) In this thesis study there is a positive correlation between visual field defects and cone b-wave amplitude in the GABA group but not in the Vigabatrin and ex-Vigabatrin groups therfore agreeing with previous studies. (115;151)

One study have reported increased cone b-wave latency.(155) However, no significant relationship between cone latency and visual field defects was found in any of the groups in this thesis study.

Studies have reported a decrease in flicker amplitude in up to 92% of patients with a cutoff in amplitude of 70μV in patients on Vigabatrin (158;160). In this study there was a positive correlation between visual field defects and flicker amplitude in the non GABA group.

The conventional ERG responses i.e. OP amplitude, cone b-wave amplitude and flicker amplitude displayed a correlation with visual field abnormalities. The visual field defects in all groups can be corroborated by objective tests suggesting that these defects are true and not false positives. A possible explanation is that these ERG responses and visual field results both represent similar changes occurring in the visual system. One theory is that physiological neurological damping is caused by all anti-epileptic drugs and in some patients this is enough to have visual field defects and abnormal ERG.

11.4 Can the WF-mfERG be used to diagnose and monitor progression of disease?

An abnormal WF-mfERG in patients with Vigabatrin retinal toxicity is one in which the difference between central and peripheral implicit time is abnormal (greater than 2 milliseconds) in both eyes.(2;3) It is the difference between central and peripheral retinal function that is specific to Vigabatrin. One theory is that only the peripheral retina is affected by Vigabatrin toxicity as suggested in previous studies. (3;95) Another study has suggested that Vigabatrin associated retinal toxicity is thought to be diffuse, inducing subtle central visual dysfunction and more severe peripheral visual defects where the density of the cells are the lowest.(98) Because the WF-mfERG measures discrete areas of retinal function we can objectively compare the periphery to the centre. Therefore if there is a difference in function we can us this test to monitor only those patients with visual field defects secondary to Vigabatrin.

Table 10.2.1 showed the results in patients with abnormal WF-mfERG responses in all groups. Only Groups 1 & 2 had abnormal bilateral WF-mfERG abnormalities on testing. Patients not exposed to Vigabatrin did not have abnormal bilateral WF-mfERG. Table 10.6.1 showed that no patient in the GABA-ergic or the non-GABA group with abnormal WF-mfERG on visit 1 or 2. These results are statistically significant. The WF-mfERG therefore seems to be the most specific test for Vigabatrin associated retinal toxicity.

Visual field defects are not as specific because it seems that visual field defects are common in patients with epilepsy. The ERG is not as specific because it is a global measure of retinal function and Vigabatrin seems to selectively affect the peripheral retina. It is the difference between central and peripheral function that is important.

All the patients with an abnormal WF-mfERG at visit 1 and visit 2 had visual field defects. Visual field defects appear to be the first clinical sign of Vigabatrin retinal toxicity. The WF-mfERG was 100% sensitive and 81% specific in detecting vigabtrin associated visual field defects.

Table 10.5.1 summarized the comparison of ERG and WF-mfERG variables between patients with and without bilateral abnormal WF-mfERG. Right and left eyes were also analysed separately. This was done to identify any other factors that might be significant in identifying retinal toxicity.

Significant parameters of the ERG that correlated with bilateral abnormal WF-mfERG were oscillatory potential amplitude and cone b-wave amplitude. However Tables 10.5.2 and 10.5.3 summarized the comparison of ERG and WF-mfERG variables between groups 1 and 2. There was no statistically significant ERG parameter that correlates with bilateral abnormal WF-mfERG specific to each group.

Significant parameters of the WF-mfERG that correlated with bilateral abnormal WF-mfERG in all groups were peripheral P1 amplitude, peripheral N1 implicit time, peripheral N1/P1 ratio and central N1/P1 ratio. Mostly peripheral parameters were affected in patients with retinal toxicity confirming that the periphery is selectively affected in Vigabatrin associated retinal toxicity.

Interestingly central N1/P1 is also significant for retinal toxicity. This may mean that central visual function is subtly affected by Vigabatrin and can be picked up by the WF-mfERG.

In group 1 patients, peripheral implicit time and peripheral N1/P1 in right eyes correlates with bilateral abnormal WF-mfERG. No other WF-mfERG result correlates with bilateral abnormal WF-mfERG specific to each group.

11.5 Is GABA or any other agents important in the development of retinal toxicity?

The manipulation of GABA, a major inhibitory neurotransmitter in the brain has had success in the management of epilepsy. GABA-ergic agents increase GABA levels globally. Vigabatrin is the GABA-ergic agent that induces the highest percentage rise of GABA in the retina.(21) The side effects of increasing GABA concentrations in the retina

are unknown but it has been suggested to lead to retinal toxicity.(43) It is difficult to separate the action of Vigabatrin and GABA. Is it Vigabatrin, GABA, both or neither is responsible for Vigabatrin associated visual defects? In animal models it is difficult to control for GABA. GABA is broken down before therapeutic or toxic levels are achieved in the brain and retina. In recent acute toxicology studies, in isolated retina slices, GABA was applied directly to the retina. Light and Vigabatrin were found to be more important than GABA(1) in causing retinal photoreceptor damage.

In Figure 11.5.1, in the GABA group and non GABA group, there were no patients with abnormal WF-mfERG. Peripheral retinal dysfunction appears to be confined to the current/ex-Vigabatrin users and GABA does not therefore seem to be implicated in the development of peripheral retinal dysfunction.

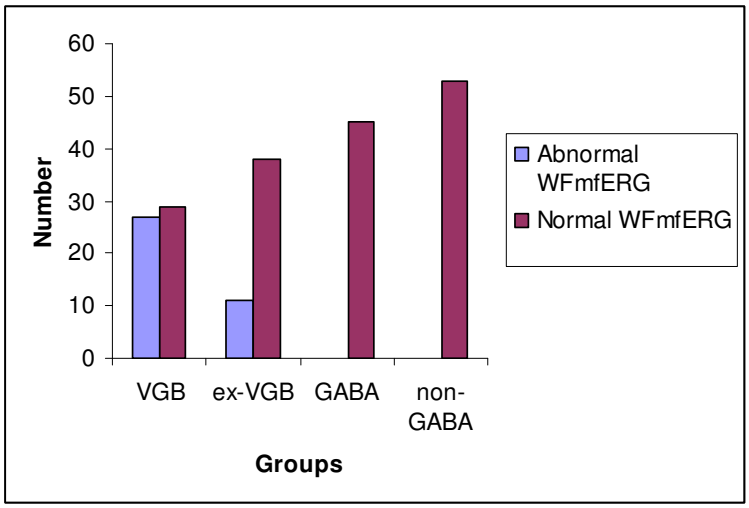


Figure 11.5.1 Normal and Abnormal WF-mfERG in four groups tested

11.6 Do visual field defects worsen when continuing on Vigabatrin and are they reversible on stopping Vigabatrin?

There has been great debate about improvement in visual function following discontinuation of Vigabatrin. Several papers have reported that visual field defects improve(102;102;146;147) on stopping Vigabatrin while other papers have reported that

visual field defects do not improve in the majority of patients on stopping Vigabatrin(138) (148). So the visual field response to stopping Vigabatrin has been reported to be variable. This may be due to visual fields being non-specific in diagnosing Vigabatrin induced visual dysfunction.

Table 10.2.1 showed a smaller percentage of patients with visual field defects in the ex-Vigabatrin group as opposed to the Vigabatrin group (45.6% ex-Vigabatrin versus 64.7% Vigabatrin). This supports the theory that some improvement in visual field defects occurs on stopping Vigabatrin.

However, Table 10.6.1 illustrated the difference in visual field defects between visit 1 and visit 2 for the ex-Vigabatrin group. Most patients had similar findings between the two visits. 8 patients had visual field defects at visit 1 and 2. 9 patients had no visual field defects at visit 1 and visit 2. One patient that had a visual field defect at visit 1 did not have one at visit 2. One patient who had a visual field defects at visit 1 did not have a visual field defects at visit 2. These results suggest that perimetry is largely unchanged in the ex-Vigabatrin group (testing patients at least one year of stopping Vigabatrin and one year apart between visits). Certain patients do not seem to improve on discontinuing Vigabatrin and certain persons do. Although the numbers of patients who chnaged were small (one improved and one worsened). It may be useful following the Vigabatrin and ex-Vigabatrin groups longer term to establish if any of the Vigabatrin group stop taking the drug if their visual fiedl defects improve.

In previous studies on the ERG results with Vigabatrin, some studies have shown that photopic b-wave latency has improved on stopping Vigabatrin(138) without a corresponding reduction in visual field defects. In our data set there is a link between visual field defects and oscillatory potential amplitudes, cone b-wave amplitude and flicker amplitude when all patients with visual field defects are examined (see Table 10.5.1). However there is no statistical significant variation in these parameters between the Vigabatrin group and the ex-Vigabatrin group in our study (see Tables10.5.2 and 10.5.3). Therefore in our data set there is no change in ERG parameters between being on Vigabatrin or off Vigabatrin.

We have already discussed the poor specificity of visual field defects and ERG parameters in monitoring Vigabatrin associated retinal dysfunction. The WF-mfERG is a better tool at monitoring these changes.

In the Vigabatrin group, 13 patients had an abnormal WF-mfERG on visit 1 and 2. One patient who had a normal WF-mfERG on visit 1 had an abnormal WF-mfERG on visit 2. There were no patients with abnormal WF-mfERG on visit 1 who did not have an abnormal WF-mfERG on visit 2. 15 patients did not have an abnormal WF-mfERG on visit 1 or 2. In 1 year, one patient's visual function worsened in our data set. It seems that progression of retinal dysfunction is slow.

In the ex-Vigabatrin group, 4 patients had an abnormal WF-mfERG on visit 1 and 19 patients did not have an abnormal WF-mfERG on visit 1 and 2. No patient improved after at least three years off the drug suggesting that Vigabatrin has a permanent effect on the peripheral retina. These changes are chronic and pathological.

11.7 What factors are important in the development and progression of disease of the visual system associated with Vigabatrin use?

In our data set the influence of baseline patient and clinical characteristics on visual field defects were examined using logistic regression models. Each of the variables were added into the model univariately and then a multivariate stepwise model was constructed retaining only variables significant at $p<0.05$. Odds ratios, 95% confidence intervals and corresponding p-values were reported. Predictors of visual field defects were shown in Table 10.7.1. Predictors of abnormal bilateral WF-mfERG were shown in Table 10.7.2.

Some authors claim that there is no association with age, gender, duration of treatment or cumulative dosage/kg and the severity of visual field defects that could be demonstrated in patients on Vigabatrin.(130); (134;138)

Some studies have found an increased incidence in male patients tested with up to 2:1 relative risk(130)' (126;128;140). One study found a correlation between number of cigarettes smoked and visual field defects.(139)

Authors claim those patients with the largest cumulative dose (>5kg) had a slightly higher incidence of visual field defects.(135) One study showed a correlation with visual field defects once a total ingested dose of at least 1.5kg(139) was achieved. The author theorised that there was a certain minimum load that needed to be achieved before visual field defects occurred. Others have claimed that there is a correlation between the daily dose and

visual field defects.(134) The prevalence of bilateral abnormalities in the WF-mfERG is compared to the drug load of Vigabatrin in Groups 1 & 2 in Table 10.2.7. The results show that in both Group 1 and Group 2 patients who developed bilateral abnormal WF-mfERG had a higher median load of Vigabatrin. Group 1 patients with abnormal WF-mfERG had a median dose of 9416g whereas those patients with normal WF-mfERG had a median dosage was 5201g. Group 2 patients with abnormal WF- mfERG had a median dose of 7690g whereas patients with normal WF-mfERG had a median dosage of 4745g. This result was statistically significant. Group 2 patients with abnormal WF-mfERG had a median dose of 7690g whereas patients with normal WF-mfERG had a median dosage of 4745g.

Vigabatrin cumulative dose is compared to dose duration for normal and abnormal WF-mfERG in Vigabatrin group in Figure 11.7.1.

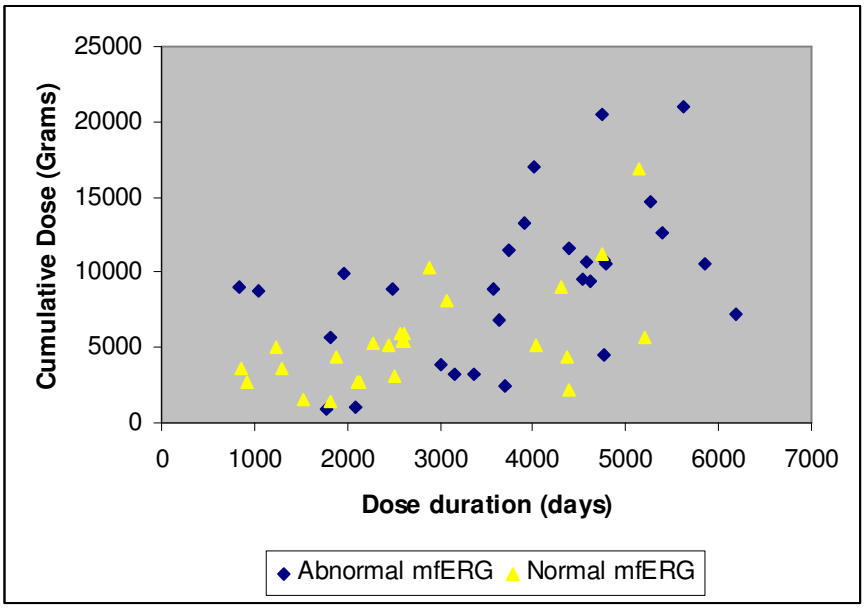


Figure 11.7.1 Vigabatrin cumulative dose versus dose duration for normal and abnormal WF-mfERG.

The data from Figure 11.7.1 was used for Receiver Operator Characteristic Curve analysis (ROC) and this data is presented in Figure 11.7.2.

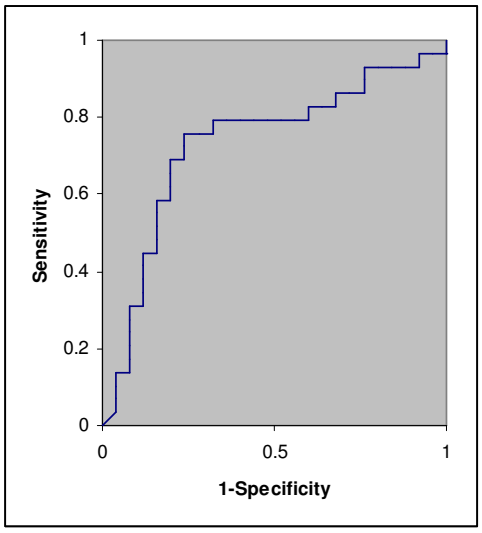


Figure 11.7.2 ROC Curve showing the effect of accumulated dose on peripheral retinal function.

The sensitivity is the fraction of abnormal WF-mfERG results above a threshold accumulated dose and the x-axis shows (1-specificity) values or the fraction of normal WF-mfERG results below a threshold of accumulated dose. Assuming equal importance for sensitivity and specificity, the ROC curve shows an optimum sensitivity of 79.3% and a specificity of 68% and this correspond to an accumulated dose of 5,580 Grams.

Therfore cumulative dose seems to be an important factor in the development of retinal toxicity

11.8 Do patients accept Vigabatrin associated visual field defects?

In summary, all groups have visual field defects and ERG abnormalities. These abnormalities are worse in patients who have been exposed to Vigabatrin. The peripheral retina seems to be selectively affected in patients exposed to Vigabatrin. WF-mfERG is the

most sensitive and specific test to determine those patients with Vigabatrin specific pathology that is chronic. Those patients with a higher cumulative load of Vigabatrin seem to have higher incidence of visual dysfunction. Defects are slowly progressive and permanent.

Two questionnaires were given to patients: QOLIE-31 P and VFQ-25. The Quality of Life in Epilepsy Inventory (QOLIE-31 P) contains seven multi-item scales that tap the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. A QOLIE-31 P overall score was obtained using a weighted average of the multi-item scale scores. A high score confers good qulaity of life. The Visual Function Questionnaire (VFQ-25) generates the following vision-targeted sub-scales: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and color vision, and ocular pain. Additionally, the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in population-based studies.

Table 10.8.1 showed overall QOLIE-31 P and energy scores are highest in Vigabatrin and the non GABA groups suggesting that these patients are happier with their quality of life than the other groups. Surprisingly, seizure worry and medicine effects scored highest in these two groups as well. These scores suggest that even though patients are aware of the side effects of Vigabatrin they have a better quality of life on Vigabatrin than off. Supporting this theory emotional well being scores were the highest in the non GABA group and lowest in the ex-Vigabatrin group.

Table 10.8.3 shows the scores in patients with abnormal WF-mfERG and with normal WF-mfERG. Scores were higher in patients with abnormal WF-mfERG in the categories of seizure worry, energy and medicine effects. These patients would mainly be in the Vigabatrin and ex-Vigabatrin groups.

In Vigabatrin group all patients had higher QOLIE-31 P scores in all categories if they had bilateral abnormal WF-mfERG. See Table 10.8.5. These patients therefore on average thought that their lives were better even though they had visual dysfunction.

In ex-Vigabatrin patients, QOLIE-31 P showed medicine effects and seizure worry were scored higher in patients with abnormal bilateral WF-mfERG than patients without. All other parameters were scored higher in the group without visual field defects. See Table 10.8.6.

The ex-Vigabatrin group is made up of patients who tend to have less control of their epilepsy (see Table 1). These patients had a worse opinion on their quality of life as compared to patients on Vigabatrin.

Interestingly in the GABA-ergic and non GABA-ergic groups all QOLIE-31 P categories were scored lower if there were visual field defects. No patients in GABA and non-GABA groups had abnormal WF-mfERG. Visual field defects may be just one more manifestation of poor epilepsy control or increased numbers of anti-epileptic drugs.

Overall VFQ-25 scores were similar between all groups (see Table 10.8.9). This is surprising because we know visual dysfunction is higher in groups 1 and 2, secondary to Vigabatrin. Patients, on average in each group, may have similar VFQ scores because peripheral retinal dysfunction (leading to peripheral visual field defects) can often be symptomatic until very severe.

A different picture emerges on examining scores group by group. Scores were lower in patients that were on Vigabatrin with visual field defects in the categories of near activities and mental health. Overall visual function in patients that were on Vigabatrin with visual field defects was lower than patients on Vigabatrin with no visual field defects though this result was not significant (see Table 10.8.12). Scores were lower in the categories of ocular pain, near and distance activities, peripheral vision and overall visual function in patients with abnormal bilateral WF-mfERG as compared with normal bilateral WF-mfERG (see Table 10.8.15). Peripheral vision was not scored lower in the Vigabatrin group with abnormal visual field defects but was scored lower in those patients with abnormal WF-mfERG. This may be confirmation that the WF-mfERG is more specific to Vigabatrin associated peripheral retinal toxicity than visual field defects.

Patients on Vigabatrin with abnormal WF-mfERG noticed poor peripheral vision. However the QOLIE-31 P and VFQ-25 suggest the majority were happy on Vigabatrin and as their seizures are controlled. This was also the clinical impression. It therefoer seems

that patients were happy to stay on vigabatrin despite their visula problemsd they have better seizure control and a better overall quality of life.

11.9 Clinical features

11.9.1 Colour vision

Some studies have reported colour defects ranging from 33% to 66% of people using various colour vision tests such as Isihara 38, Farnsworth D15-2 and Hardy Rand Rittler (161) (165) (129) while others have reported no change in colour vision on Vigabatrin with visual field defects(130).

Using Hardy Rand Rittler colour vision test there were no patients with acquired colour vision defects.

11.9.2 Clinical features

Studies have found up to 71% of subjects on Vigabatrin with abnormal findings including retinal artery narrowing, epiretinal membrane, abnormal sheen or pigmentation in the macula, optic atrophy and a decrease in peripapillary nerve fiber layer(44;126;165). Other studies have reported that there has not been any ophthalmological abnormality that could explain visual field loss(135).

There were 2 patients in our data set with attenuated vessels and one patient with white dots in the periphery with visual field defetcs and abnormal bilateral WF-mfERG..

11.9.3 Optic atrophy

Several papers have reported incidences of optic atrophy with Vigabatrin use(11;44). Indeed one of the few pathological reports available has documented loss of ganglion cells and optic atrophy(95). However it is not clear if loss of ganglion cells is a primary phenomenon or secondary one to other retinal pathology. Other studies have found no significant observable changes. No patient had optic atrophy in our data set.

11.10 Conclusion

Visual field defects occur in patients with epilepsy irrespective of Vigabatrin exposure. The pattern of visual field loss in groups other than those on Vigabatrin (pattern of visual field loss is mainly bi-nasal) is generally concentric. There are abnormal ERG results in all groups with positive correlation with visual field defects and abnormal WF-mfERG. The WF- mfERG is a sensitive (100%) and specific (81%) tool we have to monitor Vigabatrin associated neuro-retinal toxicity. It is also much easier for patients to perform than visual field tests. It is objective and therefore attractive to monitor patients with epilepsy who may have difficulty with concentration and attention. The WF-mfERG has shown that Vigabatrin drug load is significant in the development of retinal toxicity.

Chapter12

The Future

12.1 Introduction

This completed two year prospective study examined patients for a maximum of two visits.

12.2 Repeat Wide Field Multi-focal ERG (WF-mfERG)

An ongoing prospective study is being carried out by the Electrodiagnostic Imaging Unit, Glasgow and Epilepsy Unit, Glasgow. Investigations include ophthalmic history and examination, Humphrey visual field examination, ISCEV standard ERG and WF-mfERG. The aim is to test 50 patients in the Vigabatrin and ex-Vigabatrin groups on at least two further occasions.

It is hoped that repeat examinations in patients on Vigabatrin will give a better idea of disease progression hence improving management of patients.

12.3 Optical Coherence Tomography (OCT)

There has been a recent publication on OCT changes in the retinal nerve fiber layer in patients on Vigabatrin.(97) OCT is a relatively new imaging technique that permits in-vivo cross sectional imaging of biological tissue and is very useful in imaging the retina.

The authors concluded that OCT of the retinal nerve fiber layer can identify Vigabatrin-induced damage. OCT measurement of optic nerve is difficult. There is wide variation in sizes of optic nerves and therefore an accurate normal range has not been fully elucidated. A prospective study is being carried out by the Electro-diagnostic Imaging Unit and Epilepsy Unit, Glasgow. OCT will be performed of the optic nerve head in 50 patients on Vigabatrin on at least two visits. There are initial results in 23 patients on Vigabatrin (13 patients on Vigabatrin with visual field defects, 10 patients on Vigabatrin without visual field defects). The thickness of the retinal nerve fiber layer in patients on Vigabatrin compared to controls is statistically significant ($p=0.0019$) in determining patients with visual field defects. However, there is no statistically significantly difference in patients on Vigabatrin with and without visual field defects ($p=0.0953$).

There does not seem to be a role for OCT in monitoring patients with visual field defects to monitor retinal toxicity. Due to attention deficits there may be a role in testing compliance.

12.4 Acute toxicity

A recent study has been done to identify factors contributing to acute Vigabatrin neuro-retinal toxicity. Sprague-Dawley (albino) rats were used for in vivo and ex vivo experiments in light and dark environments. Retinas incubated with Vigabatrin under light had degeneration of photoreceptor outer segments, loss of photoreceptors and structural disruption of outer limiting membrane and damage to Muller cells in all areas of the outer retina (i.e. not only in the periphery) and seemed to be time and dose dependent. Retinas incubated with no light with Vigabatrin and retinas incubated in the light or dark with GABA showed no change. This is a surprising result suggesting that photo-toxicity may be the main underlying pathological mechanism for Vigabatrin associated visual field defects and is unrelated to GABA. Wearing dark glasses may protect patients from the photo-toxic effects and needs to be further investigated.

12.5 Vigabatrin in the treatment of drug addiction

Vigabatrin is being used in increasing frequency in the treatment of drug addiction(229) because of its effect on the reward circuitry of the brain. There may be an expanding role of the WF-mfERG of these patients. At the moment approval for Vigabatrin is being fast tracked through the U.S. Food and Drug Administration (FDA).

Chapter 13

Summary

One of the problems of previous studies was comparing the results of visual testing against appropriate controls. The patients in this study were matched closely for age, sex, AED and seizure control as far as possible. Although visual field abnormalities were found to be higher in the Vigabatrin (59%) and the ex-Vigabatrin group (46%), there were significant visual field abnormalities in non-Vigabatrin groups (25%). On the assessment of spatial retinal function alone however the results were different. Abnormal bilateral WF-mfERG responses were found in the Vigabatrin group (48%) and the ex-Vigabatrin group (22%) but no bilateral WF-mfERG abnormalities were found in any other groups investigated. The study suggests that there are probably different causes of visual field abnormalities in these patients. As anti epileptic drugs generally act to dampen the physiological response in the brain and in the retina, they are likely to cause transient visual field abnormalities. However as the WF-mfERG abnormalities are present in only those patients who have been exposed to Vigabatrin including those no longer on the treatment it would indicate a pathologic (toxic) effect on the retina that remains beyond usage of the drug.

The study indicates that the WF-mfERG is the key investigation to identify retinal toxicity associated with the drug Vigabatrin. A comprehensive analysis of the main demographic factors identified duration of epilepsy/treatment and accumulated load of

Vigabatrin seems to be the only significant risk factor for developing retinal toxicity. The results of the Quality of Life in Epilepsy (QOLIE-31 P) and Visual Function Questionnaires (VFQ-25) in the various groups indicated that people in the Vigabatrin group are more concerned with effective seizure control than with retinal toxicity associated with the drug. Surprisingly the patient group that was most concerned with visual field abnormalities was the non GABA-ergic group.

The study results indicate that visual field defects in patients with epilepsy may have different underlying causes. Some visual field defects are probably related to physiological dampening caused by the drug action. However, there is clear evidence of retinal toxicity

in those patients exposed to Vigabatrin. Therefore, the existing recommended method for assessing visual field or using conventional electrophysiology as an assessment of toxicity is unlikely to be sufficiently specific to identify Vigabatrin associated retinal toxicity. Additionally, the results show that visual field assessment tends to be poorly repeatable in patients with epilepsy (table 5). The benefit of the WF-mfERG is that it is objective and appears only to be influenced by pathologic damage rather than synaptic dampening. An additional benefit is that pre-existing neurological abnormalities that would produce a field defect in patients with epilepsy will not influence the WF-mfERG responses. Thus it is more likely to give the true extent of retinal toxicity and less likely to produce false positives. This is important for assessing patients on Vigabatrin and for the management of the drug in general.

The study results make it clear that only patients exposed to Vigabatrin appear to be at risk of developing bilateral retinal defects and these defects may be slowly progressive with continued Vigabatrin treatment in some patients although this study has limited longitudinal data.

Acknowledgements

Stuart Parks: for his invaluable contribution to this project and his continuing advice

David Keating: for his guidance

Martin Brodie: for his supervision of the patients with epilepsy, his advice on medical management and his supervison

Kevin Kelly: for tirelessly recruiting patients from the Epilepsy Unit, Glasgow

Graeme Sills and John Paul Leach for advice and help with presentations

Angela McCall and Ann McQuiston: who did the electrophysiology tests on most of the patients

Sinead Dudgeon: who helped with presentations and data analysis

Gordon Dutton: for his advice and review.

Alison Foulis: who has taken on the longitudinal project and is re-testing patients on Vigabatrin

Elizabeth McClure and the staff of the Optometry Department: for the provision of visual fields as well as clerical and nursing staff of Tennent Institute who helped with tests

Iain Bryce, William Wykes, Peter Kyle and Charles Diaper: for teaching me Ophthalmology

I would also like to thank the following organizations for their help in funding this project and attendance at meetings.
The Chief Scientist Office, Scottish Office
Vision Science Research, Glasgow University
Singapore Eye Research Institute
Scottish Ophthalmological Club
International Society for Clinical Electrophysiology of Vision (ISCEV)
The Faculty of Medicine, University of Glasgow
Robertson Centre Statistics, University of Glasgow

I am indebted to the patients who participated in this study and without whom this project would not have been possible. These patients were all recruited from the Epilepsy Unit at the Western Infirmary, Glasgow, UK.

I am grateful for all the support my family (Shelisa, Elsie, Rita, Agnes, Arthur, Joshua, Elizabeth and Gill) has provided.

Appendix 1 – Ethical application, patient recruitment and patient information sheet

WEST GLASGOW HOSPITALS UNIVERSITY NHS TRUST

THE WEST ETHICAL COMMITTEE
APPLICATION TO THE ETHICAL COMMITTEE FOR APPROVAL OF A CLINICAL RESEARCH PROJECT

Please read these guidelines before completing the proforma. You are also advised to refer to the document "Working with your Ethics Committee". *

1. One typed copy of this application must be submitted to Secretary, West Ethics Committee, Western Infirmary, **no later than 4pm on the Monday two weeks preceding the meeting of the Committee: the Committee meets on the first and third Tuesday of each month.** Late arriving protocols will not be considered until the next meeting.

2. All of the numbered headings must be addressed. Protocols must be presented in a concise manner with additional pages only being used if absolutely essential. Protocols presented in any other format or which deviate substantially from our guidelines in Working with your Ethics Committee will not be considered.

3. All investigators must sign the supporting Declaration Section 10). Copies of the complete Declaration of Helsinki are available from the Secretary West Ethics Committee. The principal investigator must complete Section 11 if the research project involves participation of healthy volunteers. Copies of the Report "Research on Healthy Volunteers", Royal College of Physicians of London, are available from the Administrator's office.

4 A patient/volunteer consent form must accompany all protocols and must pay heed to the advice given by the Committee on the inclusion of certain standard phrases.

5. The investigators must not recruit medical and nursing students to participate as research volunteers.

6. Protocols will fall from the agenda if information is not forthcoming within 3 months of requests being made by the Committee.

7. **Grants/Charges:** **See Attached Sheet**

Company ? **Charity ? Yes** **Non-funded ?**

8. Is this Project Multi-centred i.e. taking place in 5 or more UK centres **? No**

1. Brief Title of Project:

Assessing retinal toxicity of vigabatrin and other GABA-ergic drugs in patients with refractory epilepsy.

2. Name, Grade and Personal Qualifications of Investigators.

Dr Elaine A. Wilson, Associate Specialist, MBChB, MRCGP
Dr S Parks, Principal Clinical Scientist, BSc, PhD, MInstP, CPhys, SRCS
Dr D Keating, Consultant Electrophysiologist, PhD, FinstP, Fipemb, CEng, CPhys, SRCS
Professor Martin J Brodie, Consultant Clinical Pharmacologist, MD, FRCP
Professor Gordon Dutton, Consultatn Ophthalmologist, MD, FRCS, FRCOphth
Dr Roderick Duncan, Consultant Neurologist, MD, FRCP

Approved by: (If none of the investigators is a Consultant in the appropriate department)

Signature of approving Consultant

** Copies should be available in your department and the hospital libraries. Further copies can be obtained from the West Ethics Committee Secretary*

E
Cor

3. Purpose of Study: (Please outline the background of the work, what information you hope to obtain and what you believe will be benefit to the patient and/or to medical science)

Vigabatrin is an antiepileptic drug (AED), which was licensed in the UK in 1989. The drug is indicated for the treatment of partial seizures with or without secondary generalisation[1] and for infantile spasms[2-5]. It increases the level of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain and retina[6]. The effectiveness of vigabatrin as treatment for otherwise intractable seizures is well-documented and around 8,000 prescriptions are dispensed annually in Scotland.

In 1997 Eke and colleagues described three patients with severe peripheral bilateral visual field defects associated with the use of vigabatrin[7]. Although a number of studies have confirmed this initial report, the prevalence of visual field abnormalities in patients on treatment remains poorly defined (0.14% - 80%)[8-12]. There is also contradictory evidence on whether other GABA-ergic AEDs give rise to similar defects[13-14].

The discrepancies in study results are generally considered to be due to limitations in evaluation techniques. The two principal techniques currently used to assess visual function in these patients comprise perimetry (a subjective technique with poor reproducibility in this patient group) and the electroretinogram (ERG) (an objective technique which lacks spatial resolution and which is affected by the transient physiological effects of the antiepileptic agents themselves). Thus visual field assessment can be unreliable or even unobtainable and electroretinographic abnormalities alone are insufficient to assume a vigabatrin related retinal pathology in this group.

Management is further complicated as many of those with visual field defects are asymptomatic[15-17], and there appears to be no correlation of these abnormalities with accumulated dose[18]. Withdrawal of treatment in seizure-free individuals is not a preferred option as complications arise from failure to adequately manage these patients on alternative AEDs. Epilepsy control is important because uncontrolled seizures increase the risk of sudden unexpected death in epilepsy (SUDEP)[19]. Recently a fatality has been reported as a consequence of withdrawal from vigabatrin[20].

However, with over 200,000 patients worldwide currently receiving vigabatrin therapy and since GABA-ergic antiepileptic drugs are currently used in a variety of indications including manic depression, pain syndromes and the treatment of drug addiction[21-24], information for the effective management of vulnerable patients taking these agents needs to be identified as a matter of urgency.

The Electro-Diagnostic Imaging Unit at Gartnavel General Hospital is one of three groups in the world to have developed a non-invasive investigation, with superior repeatability/reproducibility[25-26], called the Multi-focal Electroretinogram (mfERG). mfERG provides direct topographical information on retinal health using a non-invasive technique performed in less than 8 minutes. The group in Glasgow is unique in that it has developed the technique to assess peripheral retinal function[27], whereas other groups have concentrated on central retinal function. A small pilot study performed in Glasgow demonstrated that eight out of

eleven patients taking vigabatrin had significant visual field defects. A further pilot study matched patients taking vigabatrin with a control group (matched for age, sex, seizure type and epilepsy duration), with no history of vigabatrin exposure, produced the following results: 65 patients were enrolled, 12 of whom could not complete visual field testing or were lost to follow-up. Nineteen patients (59%) taking vigabatrin, but none of the control group were found to have significant peripheral retinal dysfunction consistent with field defects. The results indicated that Wide Field-mfERG is the most sensitive objective technique at identifying visual field abnormalities (100% sensitivity, 89% specificity)[28].

The aim of this study is to provide essential data to improve the management of patients taking vigabatrin. This will include accurately quantifying the extent of retinal defects in patients, assessing visual and epilepsy-related quality of life and identifying possible factors that may increase an individual's risk of developing retinal defects (i.e. polytherapy, status epilepticus, site of epileptiform activity, smoking, alcohol etc.). The study also seeks to establish whether other GABA-ergic AEDs are implicated in the causation of retinal toxicity[29].

E
Cor
us

5. <u>Facilities and Personnel to support the work</u>: Indicate here how the facilities and personnel you have available will enable the project to be adequately executed).

The ElectroDiagnostic Imaging Unit at Gartnavel General Hospital is staffed by three medical physicists, three research assistants, one optometrist and one ophthalmologist. The multi-focal ERG is now performed on several hundred patients per annum.

An experienced ophthalmologist (funded for 2 years by the CSO grant) will be responsible for performing the following investigations: ophthalmic assessment (fundoscopy, visual acuity etc), automated static perimetry, WF-mfERG, conventional electrophysiology and digital fundus photography.

A research nurse (also funded for two years by the CSO grant) will identify and contact suitable patients from the Western Infirmary Epilepsy Unit database and from the Epilepsy Service at the Institute of Neurological Sciences. He/she will document clinical details of the patient's epilepsy and compile investigative and management details for each patient. In addition, he or she will collect information from two health related quality of life questionnaires.

E
Cor
us

6. <u>Patient/Volunteers</u>: (Please indicate how patients and/or volunteers are chosen giving the numbers chosen and justification for these numbers with power calculations where appropriate. Entry and exclusion criteria should be clearly stated.
Particular regard should be paid to the status of women of childbearing age.

Three hundred patients, aged 16 years or over, with partial-onset seizures attending either the Epilepsy Unit (Western Infirmary) or the Institute of Neurological Sciences (Southern General Hospital) will be invited to participate in the study. Each will be taking, or will have previously taken, vigabatrin, an alternative GABA-ergic or non-GABA based AEDs for at least one year.

The following groups will be excluded from participation in this study:

- Patients with photosensitive epilepsy.
- Patients who have significant retinal and/or optic disc abnormalities not associated with vigabatrin therapy.
- Patients with glaucoma.
- Patients at risk of developing angle closure glaucoma.
- Patients with a previous temporal lobectomy.
- Patients who are pregnant.

Based on our previous pilot study, we can expect a drop-out rate of 20% from patients who have agreed to participate (either due to unreliable visual field test results or failure to attend). This would reduce the vigabatrin-based patient group to 120 and our estimate on those with retinal abnormalities to 70 (59%). Following previous comparative studies undertaken by our group, statistical methods will include Bland & Altman techniques[30]. The proportion of patients with toxicity will be tabulated in various sub-groups of interest. This will be repeated for each of the treatment groups separately. The probability of having an event will be modelled by logistical regression, both univariably and multi-variably. The current study has been designed to provide sufficient power to address the main questions of the study (i.e. prevalence of vigabatrin toxicity and possible GABA-ergic toxicity). Sufficient power will only be available for the main demographic factors (e.g. sex, smoking, polytherapy, status epilepticus). Interactions between other demographic parameters (alcohol, genetics etc.) will also be of interest, however, given the limited population base, may only be quantified as an odds ratio. Full analysis will be performed by the Robertson Centre for Biostatistics, where staff have extensive experience of major international multi-centre clinical trials for both the pharmaceutical industry and academic clinical research groups. Results will be presented in the form of odds-ratios, 95% confidence intervals and p-values.

E
Cor
us

7. **<u>Drugs, dosages and non-standard products</u> (Please include all drugs. If a new drug is to be used a copy of the Clinical Trials Certificate or Clinical Trials Exemption Certification from the Committee on Safety of Medicines must be attached).**

Eye drops used for ophthalmic examination and standard electroretinogram will be:

Tropicamide 1% – mydriatic

E
Cor
us

8. **<u>Safety</u>: (Please state briefly the known pharmacology of the drugs used indicating side effects and toxicity, together with hazards of any invasive procedure performed). The minimum information would be that contained in the British Formulary**

Tropicamide 1% is a short acting, relatively week mydriatic, which facilitates examination of the fundus of the eye. It may be associated with a mild stinging sensation of the eye for a few seconds after application and a rise in intra-ocular pressure. It will not be used in any patient found to be at significant risk of developing angle closure glaucoma during clinical assessment. Tropicamide may cause short-lived mild impairment of accommodation and irritation with bright lights.

In a small number of cases, the scleral electrode can cause some minor irritation. This is only a short lasting effect, similar to having a speck of dust in the eye.

		E Cor us
9.	**<u>Radioactive Substances</u>: (If radioisotopes are to used, details of premises clearance by Radiation Protection Officer should be given and certificate of registration with the DHSS must be attached. The approximate dose of radioactivity administration should be stated).** Not applicable	

E
Cor
us

10. <u>Grant or Financial Support</u> (<u>ALL</u> sources of support for the work should be stated including details of all payments to be made to investigators, patients and healthy volunteers.

The project is being funded by a Chief Scientist Office grant.

The total amount of the grant is £152,422.00: £73,575 will be paid in year 1 and £78,847 in year 2,
which will cover staffing costs, indirect costs and consumables.

No payments will be made to the investigators or to patient participants.

11. <u>Supporting Declaration</u> (<u>ALL</u> named investigators must sign).

"I certify that I have considered the declaration of Helsinki and this protocol adheres to the principles contained therein".

12. <u>Research on Healthy Volunteers</u> (Must be signed by the principal investigator/s).

"I certify that I have considered the report of the Royal College of Physicians and this protocol adheres to the principles contained in that report. I confirm that healthily volunteers will have their legal position fully explained to them, particularly in respect of the ability to claim for damages should anything untoward occur to them as a result of their participation in research trails".

Signature.....

Designation.....

Date.....

Approved by the Ethical Committee

Date.....

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE
INFORMATION SHEET FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project
Assessing retinal toxicity of vigabatrin and other GABA-ergic drugs in patients with refractory epilepsy.

Patient's Summary (Purpose of study, nature of procedure, discomfort and possible risks in terms which the
patient or volunteer can understand).

We would like to invite you to take part in a study looking at vigabatrin (Sabril®) and visual fields. It has been suggested that some people taking vigabatrin for their epilepsy may have problems with their visual fields (how wide you can see). It is not known, however, how many people this affects

WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project:

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

Of.....

give my consent to the research procedures above, the nature, purpose and possible consequences
of which have been described to me

by.....

Patient's signature.....Date.....

Doctor's signature.....

GREATER GLASGOW HEALTH BOARD

THE WEST ETHICAL COMMITTEE

PATIENT'S SUMMARY - GUIDELINES FOR INVESTIGATORS

A) The following information must be included in the Patients' Summary unless obviously inappropriate: -

It should be noted that your participation in this study may not be of direct benefit to you, but could help in the development of treatment for the benefit of future patients.

If you do not wish to participate in this study, or wish to withdraw at any time after commencing the trial, your care will in no way be affected.

If you wish to take part in this study, your General Practitioner will be advised of your participation and the clinical management that you will undergo.

If you are, or are likely to become, pregnant you should not participate in the trial.

B) Written informed consent must always be obtained from patients/healthy volunteers.

C) Investigators must not recruit medical and nursing students to participate as research volunteers

West Research Office
Ground Floor, Room 9,
Admin Building
Western Infirmary
Glasgow, G11 6NT

Tel. 0141 211 6281

North Glasgow University Hospitals NHS Trust

West Glasgow Sites

West Project Registration Form

R&D PROJECT I.D. NO:
(office use only)

THIS FORM MUST BE TYPED.

SECTION I: PROJECT DETAILS

I. Project Title

Assessing retinal toxicity of vigabatrin and other GABA-ergic drugs in patients with refractory epilepsy.

I. Name, Relevant Grade and Qualifications of Investigators

Name	**Grade**	**Department**	**Employ Org Trust/Uni/ Other**	**Do you have an Honorary NHS Contract?**	**Telephone No. / Email**
Prof M J Brodie **(Principal Investigator)**	Consultant	Epilepsy Unit	Trust	No	0141 211 2572
Dr Elaine A. Wilson	Associate Specialist	Epilepsy Unit	Trust (Grant funded)	Yes	0141 211 1925 EWILSONEU @aol.com
Dr Stuart Parks	Principal Clinical Scientist	Dept of Ophthalmology	Trust	No	0141 211 0091 s.w.parks@clinmed.gla.ac.uk

Dr D Keating	Consultant Electrophysiologist	Dept of Ophthalmology	Trust	No	0141 211 2758 d.keating@clinmed.gla.ac.uk
Prof. G Dutton	Consultant	Dept of Ophthalmology	Trust	No	0141 211 2090
Dr Roderick Duncan	Consultant	Institute of Neurological Sciences	South Glasgow Trust	No	r.duncan@clinmed.gla.ac.uk

I. Consultant, Head of Department or equivalent person within NGT giving authorisation to this study.

Name	Job Title	Department	Employed by	Tel. No. / email
Prof. M J Brodie	**Professor of Clinical Pharmacology**	**Epilepsy Unit**	**North Glasgow Trust**	**0141 211 2572 Martin.J.Brodie@clinmed.gla.ac.uk**

I. **Please name all NGT sites in which this study will take place – Western Infirmary and Gartnavel General Hospitals**

I. Is the study being conducted with a sponsor? No

If 'yes', state name and details below:

(a)

Name of the Sponsor:	Contact details of the person you are dealing with:
	Name: **Address:** **Tel:** **Fax:** **E-mail:**

(b) Does the Sponsor accept liability?

Yes/No

Contact Commercial/Non-Commercial Research Co-ordinator who will arrange for a Form of Indemnity, if required.

(c) Is the Principal Investigator conducting the study as part of a course requirement of an undergraduate or postgraduate course, other than MD or PhD?

No

If 'yes', state course name:……..

I. Principal Research Question

The aim of this study is to accurately quantify the extent of retinal defects in epilepsy patients exposed to vigabatrin, and therefore provide essential data to improve the management of these patients.

I. **Proposed Start Date** (day/month/year) …1st May 2003…….

Proposed End Date (day/month/year) …1st May 2005…….

II. Methodology

Study type (you may tick more than one)

Re-analysis of original data		Randomised controlled trial	
Laboratory study		Controlled trial without randomisation	
Case note review		Before-after study	
Dose-finding study		Case-control	✓
Questionnaires / interviews		Cohort observation	
Economic evaluation		Cross-sectional study	
Other (please specify)			

I. Outcome Measure Description

Quantification of the extent of retinal defects in patients and assessment of visual and epilepsy-related quality of life.

10. Sample Group

(a) Number of subjects being recruited locally

SITE	GRI	STOBHILL	WESTERN	GARTNAVEL	DENTAL	OTHER (Please Specify)	TOTAL
NUMBER			150			150- Institute of Neurological Sciences – South Glasgow Trust	300

(b) Subject inclusion criteria

- Aged 16 years of age and over

- Male and female
- Currently taking vigabatrin or previously taken vigabatrin for more than one year, or taking an alternative GABA-ergic drug and never exposed to vigabatrin or taking a non-GABA-ergic drug and never exposed to vigabatrin

(c) Subject exclusion criteria

- Patients with photosensitive epilepsy
- Patients with significant retinal and/or optic disc abnormalities not associated with vigabatrin therapy
- Patients with glaucoma
- Patients at risk of developing acute angle closure glaucoma
- Patients with previous temporal lobectomy
- Patients who are pregnant or intending to become pregnant during the study

(d) Source of sample group

Patients who are registered with either the Epilepsy Clinics at the Western Infirmary or the Institute of Neurological Sciences.

11. Does the research go beyond the subjects' standard treatment?

Yes

12. Has statistical advice has been sought on the size, power and design of the project?

Yes

If 'Yes', from whom? Give justification for numbers.
The current study has been designed to provide sufficient power to address the main questions of the study (i.e. prevalence of vigabatrin toxicity and possible GABA-ergic toxicity). Sufficient power will only be available for the main demographic factors, (e.g. sex, smoking, polytherapy, status epilepticus). Full analysis will be performed by the Robertson Centre for Biostatistics. Results will be presented in the form of odds-ratios, 95% confidence intervals and p-values.

13. Provide details of the literature search carried out.

See Key References attached to LREC submission.

14. Activity Areas (please tick more than one if appropriate)

Cancer	
Vascular (includes Respiratory; Diabetes; Stroke)	
Ageing and Neurology (includes Geriatric Medicine; Mental Health; Clinical Neurological Science; Anaesthetics; Epilepsy)	
Maternal, Neonatal & Developmental (includes Paediatric; Genetic Disease; Obstetrics & Gynaecology)	
Renal & Urology	
Dental (includes Oral Surgery)	
Infection & Inflammation (includes Laboratories; Bacteriology; Immunology)	
Gastroenterology, ENT & Ophthalmology	
Orthopaedics, Muscle & Trauma (includes Accident & Emergency; General Surgery; Rheumatology)	
Healthcare & Diet (includes Nutrition; Nursing; PAMs; General Practice; Primary Care; Health Economics)	
Skin (includes Dermatology; Burns; Plastic Surgery)	
Therapeutics & Devices (includes Pharmacology)	

15. NHS Priority Areas (please tick)

Cancer	
CVD/Stroke	
Mental Health	
Public Health	

SECTION 2a: USE OF HUMAN BIOLOGICAL MATERIAL

I. Will the research involve the analysis of existing stored samples of human biological materials? No

If 'yes', please complete this section and also Section 3b.

II. Will the research involve the collection and/or analysis of new samples of human biological materials obtained during the course of this study?

No

If' 'Yes' give details What samples will be collected and/or analysed, and by whom will they be collected? Are samples taken solely for research purposes (or are they a by-product of those taken primarily for clinical purposes i.e. surplus to clinical requirements)?

3. How will the samples be identified?

Indicate if samples can be considered to be identified, coded, de-identified, anonymised or anonymous, and at what stage identifiers are removed. (see guidance notes for definitions.)

4. (a) How long will the sample(s) be stored for during the course of the study?

Months Years Give details.

4. (b) Will samples be stored after the study has ended?

N/A

If ‘Yes’, for how long?

Months Years

Give details.

5. Will the research participant retain any rights to the sample(s)?
N/A

If ‘Yes’, give details.

6. Is it known how the samples will be used in the future?
N/A

Give details and indicate if consent has been obtained for the future use of the samples (broad categories of future use may be acceptable in some cases), and how this will be safeguarded.

7. Does the research involve the analysis or use of genetic material from human biological materials? No

8. Is it possible and/or intended to link the results of any genetic analysis back to individuals? N/A

If ‘No’, explain what safeguards are in place to ensure that this will not happen.

If ‘Yes’, give details.

SECTION 2b: USE OF EXISTING STORED SAMPLES

Complete Section 3b only if the study involves the use of stored or existing samples of human bodily materials (including those held in tissue banks).

1. What samples will be included in the study?

2. What tests/techniques will be carried out on the samples?

3. How will the samples be identified?

Indicate if the samples can be considered to be identified, coded, de-identified, anonymised or anonymous, and at what stage identifiers are removed (see guidance notes for definitions).

4. Has specific consent been obtained previously to use stored samples for this purpose?
Yes / No

If 'Yes', give details.

If 'No', please justify.

5. Does the research involve the analysis or use of genetic material?
Yes / No

If 'Yes', will it be possible to link the results of any genetic analysis back to individuals?

If 'No', please explain why not.

SECTION 3: PHARMACY and FINANCE

PHARMACY (Non-commercial projects only. For commercial projects, the company will form an agreement with Pharmacy)

I. Pharmaceutical aspects and the dispensing of drugs must be discussed with your local Pharmacy representative,

at least 6 weeks before commencing the study.

Site Pharmacists who may approve a clinical trial	Site		Contact No.
Eileen Conkie	Western Infirmary	Clinical Trials Pharmacist	Ext. 52756
Jonathon Allan	Gartnavel General Hospital	Dispensary Pharmacist	Ext. 53316
Carla Forte	Beatson Oncology Centre	Oncology Pharmacist	Ext. 52740
Graham Conkie	Western Infirmary	Production Pharmacist	Ext. 52882
Linda Johnstone	Glasgow Royal Infirmary	Dispensary/Clinical Trials	Ext. 21188 / 24081
Linda Johnstone	Dental Hospital and School	Dispensary/C Trials	Ext. 21188 / 24081
Steven Leadbetter	Glasgow Royal Infirmary	Aseptic Services	Ext 24265
Sally McKendrick	Glasgow Royal Infirmary	Oncology Pharmacist	Ext 24265
Lesley Brown	Stobhill Hospital	Dispensary Pharmacist	Ext 13579

For further information, please contact Mrs F McMillan Clinical Governance Development Pharmacist: WIG Ext. 52706

2. All medicinal products to be administered as part of study:

	Drug 1	Drug 2	Drug 3	Drug 4
Generic Name	**Tropicamide 1%**			
Proprietary name	**Minims®Tropicamide or Mydriacyl**			
Dosage form	**Drops**			
Strength	**1%**			
Route	**Intra-ocular**			
Dosage & frequency	**1 drop each eye**			
Treatment Duration	**1 stat dose**			
Standard Drug or Trial Drug (please indicate)	**Standard drug**			
Total (Standard + Trial) Drug Cost	**Total trial 400 minims £107.60**			

3. Authorised and signed on behalf of Pharmacy Department by:
(Please note that only staff detailed above may sign this section.)

	West Site	East Site
Name		
Job Title		
Signature		
Date		

FINANCE

Is this project COMMERCIAL ☐ **NON-COMMERCIAL** ✓

(Please tick appropriate box)

Definitions

Commercial: Where the study is sponsored by a Pharmaceutical Company

Non-Commercial : Where the study is funded by charities, research councils or Trust Endowment Funds etc.

Commercial Projects

If you have identified your project as Commercial you do not have to complete the Pharmacy and Finance Section. Instead, **please contact Dr Gillian Martin, Commercial Research Co-ordinator, on Tel. No. 0141 211 1813**, to provide details of the Clinical Research Associate.

Non-Commercial Projects

- ***Please contact Elizabeth Stirling / Brenda Dougan in the Finance Department, Trust Headquarters, if you have any queries (Tel No : 201 9748 / 9705).***
- *No part of this form should be left blank - where no costs are incurred please state that there are no costs.*
- *This section **must** be signed by Head of Department/Clinical Director and any other heads of support department as required.*

1. Is this project being submitted for any internal or external funding?
Awarded

2. If yes, is the funding:

Research Council		**Charity**	
University		**Department of Health / NHS**	✓
Endowment fund		**Endowment fellowship**	

Other *(please state)*

3. Funding details

Source of external funding		**COSTS COVERED**	**Please indicate value**
Name of Funder / Funding Body	**CSO**	Staffing	**£107,462**
Funding – awarded/pending	**Awarded**	Facilities	**£**
Grant Ref. No.		Laboratory	**£**
Duration	**26 months**	Radiology	**£**
Proposed Start Date	**1/5/03**	PAMS	**£**
Proposed End Date	**30/6/05**	Drugs	**£**
Value	**£156,576**	Pharmacy Sundries	**£3,000**
		Other (statistical consultancy)	**£3,129**
		Other (indirects)	**£42,985**
		TOTAL	**£156,576**
Administered By			
North Glasgow University Hospitals NHS Trust			
Endowment (Greater Glasgow Health Board)			
University	**Glasgow University**		
Other (Please State)			

4.Please provide details of any drugs, equipment etc being provided free for use in this study, including details of the donor.

5. Costs summary

Staffing

Please detail all staff involved in project regardless of employer / funder and indicate if new staff are required. Please indicate grade of staff if name of individual not yet known.

Name	**Site**	**Employed by**	**Funded by**	**Estimated hours on project *per patient***
Dr Elaine A. Wilson				
Dr S Parks	**GGH**	**Trust**		**0.5**
Dr D Keating	**GGH**	**Trust**		**0.2**
Professor Martin J Brodie				
Professor Gordon Dutton	**GGH**	**Trust**		**0.1**
Dr Roderick Duncan				

Note: Estimated hours per patient includes set up and hours involved on project. Set up time should include "thinking time" along with preparation time for Ethics & Grant submissions.

NHS Service support costs:

All NHS tests / samples taken beyond routine patient care should be listed below.

Laboratories	**Name of test**	**Volume** ***per patient***	**Authorised and signed by head of support department**
Biochemistry			
Haematology			
Pathology/Cytology			
Microbiology			
Virology			
Other			

Radiology / Cardiology	**Description**	**Volume** ***per patient***	**Authorised and signed by head of support department**
CT			
MRI			
X RAY			
Ultrasound			
ECG			
EEG			
Endoscopy			
Other			
Theatre	**Description of procedure**	**Volume** ***per patient***	**Authorised and signed by head of support department**
In Patient Procedure			
Day Case Procedure			
Out Patient Procedure			
Other			

PAMs / other support	**Description**	**Total mins.** ***per patient***	**Authorised and signed by head of support department**
Dietetics			
Occupational Th			
Physiotherapy			
Speech Therapy			
Medical Records			
Library			
Other			

Additional patient stays / visits

Type of Stay	Clinic/Ward/Department Used	Length of Additional Stay/Attendance *per patient*
Inpatient		
Day case		
Outpatient		
Follow-up visits		

Note: Use of accommodation to facilitate a trial, e.g. use of an outpatient clinic to screen patients, should be included above.

Additional pharmacy costs

Please make clear how the drugs / sundries are being funded

Description	Dosage *per patient*	Unit cost	Total cost *per patient*

Please state any other financial implications, e.g. will patients be prescribed drugs from the Trust when they would normally receive them from their G.P. or another hospital? Will there be any drug costs at end of study?

~~Yes~~ / No

Will the project patient population be recruited from other Health Board Areas ?

No

If yes, please provide details.

Supplies and equipment

Please include purchase cost and running cost

Department	Item	Volume	Unit cost	Total cost

Additional costs not covered above

Department	Item	Volume	Unit cost	Total cost
Stationary				
Postage				
Patient Travel				
Patient Meals				
Other				

6. Implications on patient care service and costs

(a) Will the project impact on waiting lists?
~~Yes~~ / No
If yes, state how

(b) Are there any other implications on service costs as a result of this project?
~~Yes~~ / No If yes, please provide details

Note: Include here any savings that may result. If the project has implications on future service developments please describe the impact on treatment and costs / savings.

7.Project authorisation by Clinical Director or Head of Department

I confirm that the above accurately represents the resources required for this project and that the project has my authorisation.

Name	
Job title	
Department	
Signature	
Date	

Appendix 2 – Quality of life in epilepsy questionnaire (QOLIE-31P)

⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ D M Y	**Visit Number:** ⌊_⌋⌊_⌋
Patient's Name (Patient's Initials): _____	**Sex:** ☐ Male ☐ Female
Patient's ID Number: _____	**Date of birth:** ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ D M Y

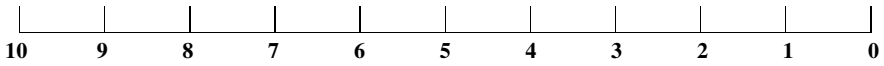
NOTE: ***If you experienced a simple or complex partial seizure within the previous four hours, or a generalized tonic-clonic seizure within the previous 24 hours, please delay completing this questionnaire***

INSTRUCTIONS:

This questionnaire asks about your health and daily activities. **Answer each question** by circling the appropriate number (1, 2, 3…).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin. Please feel free to ask someone to help you if you have difficulty reading or completing the form.

1. Overall, how would you rate your quality of life?
(Circle one number only on the scale below)



Part A.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
2. Did you feel full of life?	1	2	3	4	5	6
3. Did you have a lot of energy?	1	2	3	4	5	6
4. Did you feel worn out?	1	2	3	4	5	6
5. Did you feel tired?	1	2	3	4	5	6

*Reviewing only questions in **Part A**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
6. How much do the above problems and worries about energy **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part B.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
7. Have you been a very nervous person?	**1**	**2**	**3**	**4**	**5**	**6**
8. Have you felt so down in the dumps that nothing could cheer you up?	**1**	**2**	**3**	**4**	**5**	**6**
9. Have you felt calm and peaceful?	**1**	**2**	**3**	**4**	**5**	**6**
10. Have you felt downhearted and low?	**1**	**2**	**3**	**4**	**5**	**6**
11. Have you been a happy person?	**1**	**2**	**3**	**4**	**5**	**6**

*Reviewing only questions in **Part B**, consider the overall impact of these issues on your life **in the past 4 weeks.***

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
12. How much do the above problems and worries about emotions **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part C.

The following questions are about how you FEEL and about problems you may have with daily ACTIVITIES during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

The following question asks about how you FEEL and how things have been going for you.

How much of the time during the past 4 weeks…

(Circle one number)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
13. Has your health limited your social activities (such as visiting friends or close relatives)?	**1**	**2**	**3**	**4**	**5**	**6**

The following questions ask about problems you may have with certain ACTIVITIES.

How much of the time during the past 4 weeks your epilepsy or antiepileptic drugs have caused trouble with…

(Circle one number on each line)

	A great deal	A lot	Somewhat	Only a little	Not at all
14. Leisure time (such as hobbies, going out)	**1**	**2**	**3**	**4**	**5**
15. Driving (or other transport)	**1**	**2**	**3**	**4**	**5**

	Not at all bothersome				Extremely bothersome
16. How much do your work limitations bother you?	**1**	**2**	**3**	**4**	**5**
17. How much do your social limitations bother you?	**1**	**2**	**3**	**4**	**5**

*Reviewing only questions in **Part C**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
18. How much do the above problems and worries about daily activities **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part D.

These questions are about thinking, reading, concentrating and memory problems you may have had during the past 4

weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
19. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	**1**	**2**	**3**	**4**	**5**	**6**

	Yes, a lot	Yes, somewhat	Only A little	No, not at all
20. During the past 4 weeks, have you had any trouble with your memory?	**1**	**2**	**3**	**4**

During the past 4 weeks, how often have you had…

(Circle one number on each line)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
21. Trouble remembering things people told you?	**1**	**2**	**3**	**4**	**5**	**6**
22. Trouble concentrating on reading?	**1**	**2**	**3**	**4**	**5**	**6**
23. Trouble concentrating on one thing at a time?	**1**	**2**	**3**	**4**	**5**	**6**

	Not at all bothersome				Extremely bothersome
24. How much do your memory difficulties bother you?	**1**	**2**	**3**	**4**	**5**

*Reviewing only questions in **Part D**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
25. How much do the above problems and worries about psychological functioning **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part E.

These questions are about problems you may have related to your epilepsy or antiepileptic drugs.

During the past 4 weeks…

(Circle one number on each line)

	Not at all bothersome				Extremely bothersome
26. How much do physical effects of antiepileptic drugs bother you?	**1**	**2**	**3**	**4**	**5**
27. How much do psychological effects of antiepileptic drugs bother you?	**1**	**2**	**3**	**4**	**5**

	Very worried	Somewhat worried	Not very worried	Not worried at all
28. How worried are you that the drugs you are taking may be bad for you if you have to take them for a long time?	**1**	**2**	**3**	**4**

*Reviewing only questions in **Part E**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
29. How much do the above problems and worries about the <u>effects of drugs</u> **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part F.

These questions are about how you FEEL about your fits during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
30. Have you worried about having another fit?	**1**	**2**	**3**	**4**	**5**	**6**

	Very afraid	Somewhat afraid	Not very afraid	Not afraid at all
31. How afraid are you of having a fit during the next 4 weeks?	**1**	**2**	**3**	**4**

	Worry a lot	Worry a little	Don't worry at all
32. Do you worry about hurting yourself during a fit?	**1**	**2**	**3**

	Very worried	Somewhat worried	Not very worried	Not worried at all
33. How worried are you about embarrassment or other social problems due to a fit during the next 4 weeks?	**1**	**2**	**3**	**4**

	Not at all bothersome				Extremely bothersome
34. How much do your fits bother you?	**1**	**2**	**3**	**4**	**5**

*Reviewing only questions in **Part F**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

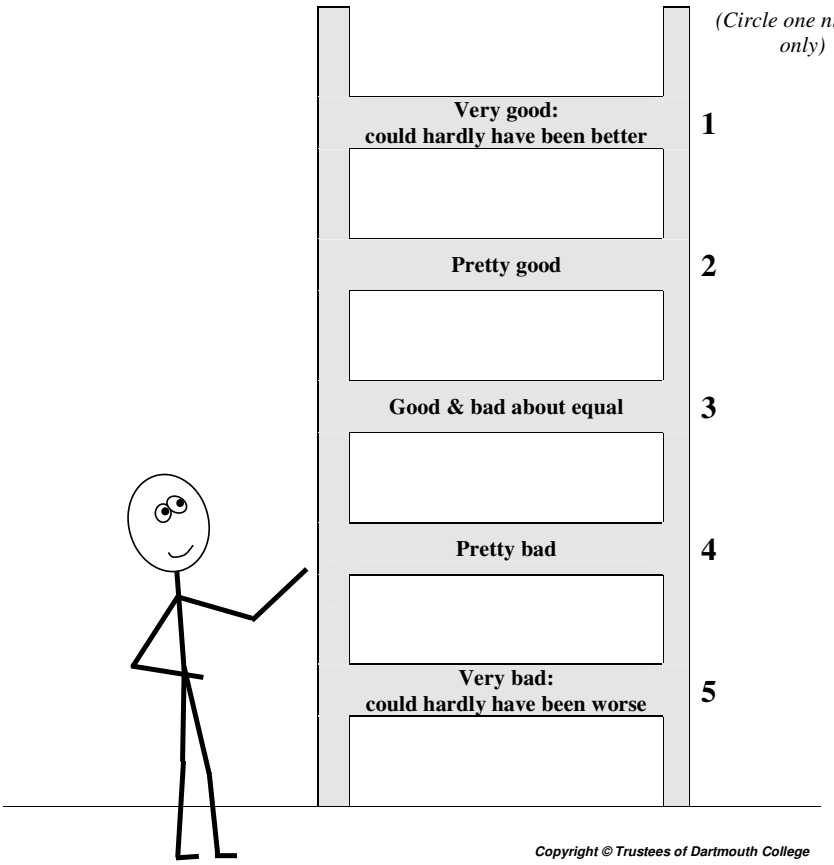
(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
35. How much do the above problems and worries about fits **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part G.

The following question asks about how you FEEL about your overall quality of life. Please give the one answer that comes closest to the way you have been feeling.

36. How has your **QUALITY OF LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?



*Reviewing only questions 1 and 36 in **Part G** (on page 1 and this page), consider the overall impact of your quality of life **in the past 4 weeks**.*

(Circle one number)

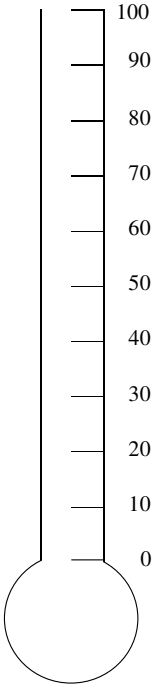
	Not at all	Somewhat	Moderately	A lot	Very much
37. How much does the state of your quality of life **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part H.

38. How good or bad do you think your HEALTH is?
On the thermometer scale below, the best state of health imaginable is 100 and the worst state imaginable is 0. Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as being part of your overall health when you answer this question.**

___

Best Health State Imaginable


100
=
90
80
70
60
50
40
30
20
10
0
= Worst Health State Imaginable

Part I.

*Considering **ALL** the questions you have answered, please **indicate the areas** related to your epilepsy that are most **IMPORTANT** to you **NOW.***

39. ***Number the following topics from '1' to '7' with '1' corresponding to the most important topic and '7' to the least important one. Please use each number only once.***

⌊__⌋ **A.** Energy (tiredness)

⌊__⌋ **B.** Emotions (mood)

⌊__⌋ **C.** Daily activities (work, driving, social)

⌊__⌋ **D.** Mental activity (thinking, concentrating, memory)

⌊__⌋ **E.** Medication effects (physical, mental)

⌊__⌋ **F.** Worry about fits (impact of fits)

⌊__⌋ **G.** Overall quality of life

Please check to be sure you have answered every question on every page.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE ABOUT LIVING WITH EPILEPSY.

SCORING MANUAL FOR THE QUALITY OF LIFE IN EPILEPSY INVENTORY-31 (QOLIE-31)

CONTENT OF THE QOLIE-31

The Quality of Life in Epilepsy Inventory (QOLIE-31) contains seven multi-item scales that tap the following health concepts: emotional well-being, social functioning,

energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. A QOLIE-31 overall score is obtained using a weighted average of the multi-item scale scores. The QOLIE-31 also includes a single item that assesses overall health.

SCORING RULES

Precoded numeric values for responses on some QOLIE-31 items are in the direction such that a higher number reflects a more favorable health state. For example, a circled response of '10' for item 1 corresponds to "Best Possible Quality of Life", while a circled response of '0' corresponds to "Worst Possible Quality of Life." However, precoded numeric values for some other items on the uOLIE-31 are in the direction such that a *lower* number reflects a more favorable health state. For example, a circled response of '1' for item 14 corresponds to more favorable quality of life, while a value of '5' on this item corresponds to less favorable quality of life. As these examples also demonstrate, different items in the QOLIE-31 have different ranges of precoded numeric values. Higher scores always reflect better quality of life (Table 2). To perform this step, write in the converted score for each item in the column labeled "Subtotal" in Table 2. Next, sum the subtotal scores for each scale and write in these values in the places marked "Total." Finally, divide each "Total" by the from 0 to 100 points. Higher scores reflect better quality of life; lower ones, worse quality of life. Note that Table 1 shows the divisors to be used only in situations where *every* item within a given scale has been answered. For example, if item 11 in the Seizure Worry scale was left blank and the other four items in the scale were answered, then the "Total" score for Seizure Worry would be divided by '4' (instead of '5') to obtain the "Final Score:'

<u>OVERALL SCORE</u>

A QOLIE-31 overall score can be derived by weighting and summing QOLIE-31 scale scores (Table 4). QOLIE-31 scale weights were derived from a regression analysis that used a summary score from the OOLIE-89. The QOLIE-31 overall score is calculated by summing the product of each scale score times its weight and summing over all scales (Table4).

Following are Scoring Tables 2 and 4.

Scale/Item Numbers	Response 1	2	3	4	5	6	Subtotal	Final Score, 0-100 point scale
Seizure Worry								
11.	0	20	40	60	80	100	____	
21.	0	33.3	66.7	100	—	—	____	
22.	0	50	100	—	—	—	____	
23.	0	33.3	66.7	100	—	—	____	
25.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 5 = ____
Overall Quality of Life								
1.	(multiply response by 10)						____	
14.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 2 = ____
Emotional Well-Being								
3.	0	20	40	60	80	100	____	
4.	0	20	40	60	80	100	____	
5.	100	80	60	40	20	0	____	
7.	0	20	40	60	80	100	____	
9.	100	80	60	40	20	0	____	
						TOTAL:	____	÷ 5 = ____
Energy/Fatigue								
2.	100	80	60	40	20	0	____	
6.	100	80	60	40	20	0	____	
8.	0	20	40	60	80	100	____	
10.	0	20	40	60	80	100	____	
						TOTAL:	____	÷ 4 = ____
Cognitive								
12.	0	20	40	60	80	100	____	
15.	0	33.3	66.7	100	—	—	____	
16.	0	20	40	60	80	100	____	
17.	0	20	40	60	80	100	____	
18.	0	20	40	60	80	100	____	
26.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 6 = ____
Medication Effects								
24.	0	33.3	66.7	100	—	—	____	
29.	100	75	50	25	0	—	____	
30.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 3 = ____
Social Function								
13.	0	20	40	60	80	100	____	
19.	0	25	50	75	100	—	____	
20.	0	25	50	75	100	—	____	
27.	100	75	50	25	0	—	____	
28.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 5 = ____

QOLIE-31 Scale	Final Scale Score		Weight		Subtotal
Seizure worry	____	×	.08	=	____ (a)
Overall quality of life	____	×	.14	=	____ (b)
Emotional well-being	____	×	.15	=	____ (c)
Energy/fatigue	____	×	.12	=	____ (d)
Cognitive functioning	____	×	.27	=	____ (e)
Medication effects	____	×	.03	=	____ (f)
Social functioning	____	×	.21	=	____ (g)

OVERALL SCORE: Sum subtotals (a) through (g) = ____

Appendix 3 – Visual Functioning Questionnaire - 25

National Eye Institute

Visual Functioning Questionnaire - 25 (VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. **In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.**

2. **Please answer every question (unless you are asked to skip questions because they don't apply to you).**

3. **Answer the questions by circling the appropriate number.**

4. **If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.**

5. **Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.**

6. **If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.**

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

3. How much of the time do you worry about your eyesight?

	(Circle One)
None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

	(Circle One)
None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 ***Skip To Q 15c***

No..... 2

15a. IF NO: Have you never driven a car or have you given up driving?
(Circle One)

Never drove..... 1 ***Skip To Part 3, Q 17***

Gave up 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 ***Skip To Part 3, Q 17***

Mainly other reasons..... 2 ***Skip To Part 3, Q 17***

Both eyesight and other reasons..... 3 ***Skip To Part 3, Q 17***

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me.	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?.....	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

Version 2000

The National Eye Institute 25-Item

Visual Function Questionnaire (VFQ-25)

Version 2000

This final version of the VFQ-25 differs from the previous version in that it includes an extra driving item from the appendix of supplementary questions as part of the base set of items. Also, the revised scoring algorithm excludes the single-item general health rating question from the calculation of the vision-targeted composite score. Because of these 2 changes, the base set of items actually includes 26 questions, however, only 25 are vision-targeted and included in the composite score. Please see the "Frequently Asked Questions" or FAQ section for additional clarifications of these changes.

Background

The National Eye Institute (NEI) sponsored the development of the VFQ-25 with the goal of creating a survey that would measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases. Because of this goal, the survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. Questions included in the VFQ-25 represent the content identified during a series of condition-specific focus groups with patients who had age-related cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, or CMV retinitis. [1]

The VFQ-25 is the product of an item-reduction analysis of the longer field test version of the survey called the 51-item National Eye Institute Vision Function Questionnaire (NEI-VFQ).[2] The longer version contains 51 questions which represent 13 different sub-scales. The NEI-VFQ Field Test Study collected the data needed to examine the reliability and validity of the survey across all of the above-mentioned ocular diseases. Also, reliability and validity was assessed in a heterogeneous group of patients with low vision from any cause and a group of age-matched persons with normal vision. A published report describes the psychometric properties of the longer field test version of the survey. [3] Additional a number of clinical studies have used either the 51 or the 25-item version of the NEI-VFQ across a number of chronic ocular conditions. [4-8] Despite the success of the longer field test version and its continued use, to enhance feasibility a short-form version was planned since the earliest developmental phase.

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 also includes an appendix of additional items from the 51-item version that researchers can use to expand the scales up to 39 total items. All items in the VFQ-25 are from the 51-item field test version; no new items were developed for use in the VFQ-25. Unless otherwise specified, the remainder of this document will use the term VFQ-25 to refer to the base set of items.

The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. There is also a self-administered version of the survey, however, psychometric testing of the self-administered version has not been done. The VFQ-25 generates the following vision-targeted sub-scales: global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2). Additionally, the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in population-based studies. Please see the FAQ section for more information about the general health rating question.

Development of the NEI VFQ-25

The guiding principles for the selection of the short-form items included: 1) low item-level missing data rates; 2) normal distribution of response choices; and 3) retention of items that explained the greatest proportion of variance in the 51-item sub-scales. The items retained in the VFQ-25 and the optional items (provided in the appendix to the survey) are listed on Table 1. A report describing the performance of the VFQ-25 relative to the Field Test version is currently under review. [2] The reliability and validity of the

VFQ-25 is similar to that observed for the 51-item version of the survey. On average, each VFQ-25 sub-scale predicts 92% of the variance in the corresponding 51-item sub-scale score.

Optional Items

Appendix 1 consists of additional questions that users may add to a specific sub-scale. Inclusion of these may be helpful if a particular sub-scale represents the primary domain of vision-targeted HRQOL that is felt to be most important for the condition under study. For example, if a user is testing a new treatment for macular degeneration, by adding near vision questions A3, A4, and A5 to VFQ-25 questions 5, 6, and 7, the investigator would have a six-item near vision scale rather than a three-item scale. The addition of these items would enhance the reliability of the near vision sub-scale and is likely to improve the responsiveness of the sub-scale to the intervention over time (Table 6). If items from the appendix are used, the VFQ-25 developers would encourage users to incorporate all optional items for a given sub-scale. This strategy will enhance the comparability of results across studies.

Scoring

Scoring VFQ-25 with or without optional items is a two-step process:

- First, original numeric values from the survey are re-coded following the scoring rules outlined in Table 2. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

- In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. Table 3 indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the sub-scale that the respondent answered.

Composite Score Calculation

To calculate an overall composite score for the VFQ-25, simply average the vision-targeted sub-scale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

Table 1. Item Number Translation from the 51-Item Field Test Version to the VFQ 25

S = retained in the VFQ-25, A = retained in the appendix should be used for the VFQ-39,
--- = deleted from the VFQ-25 & VFQ-39

Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Ques. #	Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Ques. #
1	general health	S	**1**	**29**	social fx	---	---
2	general health	A	**A1**	**30**	social fx	A	**A9**
3	general vision	S	**2**	**31**	social fx	S	**13**
4	expectations	---	---	**32**	distance vision	A	**A8**
5	well-being/ distress	S	**3**	**33**	distance vision	A	**A7**
6	well-being/ distress	---	---	**34**	distance vision	S	**14**
7	ocular pain	S	**19**	**35**	driving (filter item)	S	**15**
8	expectations	---	---	**35a**	driving (filter item)	S	**15a**
9	expectations	---	---	**35b**	driving (filter item)	S	**15b**
10	expectations	---	---	**35c**	driving	S	**15c**
11	well-being/ distress	S	**25**	**36**	driving	---	---
12	ocular pain	S	**4**	**37**	driving	S	**16**
13	well-being/ distress	---	---	**38**	driving	S	**16a ***
14	general vision	A	**A2**	**39a**	role limitations	S	**17**
15	near vision	S	**5**	**39b**	role limitations	A	**A11a**
16	near vision	A	**A3**	**39c**	well-being/ distress	---	---
17	near vision	S	**6**	**39d**	role limitations	---	---
18	near vision	---	---	**39e**	role limitations	A	**A11b**
19	near vision	S	**7**	**39f**	role limitations	S	**18**
20	distance vision	S	**8**	**40**	well-being/ distress	A	**A12**
21	distance vision	---	---	**41**	dependency	S	**20**
22	distance vision	S	**9**	**42**	well-being/ distress	S	**21**
23	peripheral vision	S	**10**	**43**	well-being/ distress	S	**22**
24	distance vision	A	**A6**	**44**	dependency	---	---

Comment [DS1]:

25	social fx	S	**11**	**45**	dependency	A	**A13**
26	near vision	A	**A4**	**46**	dependency	S	**23**
27	color vision	S	**12**	**47**	dependency	S	**24**
28	near vision	A	**A5**				

* VFQ-25 item 16a was listed in previous versions as part of the appendix of supplemental items (#A10).

Table 2. Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1,3,4,15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a	1	100
A3,A4,A5,A6,A7,A8,A9[c]	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25,	1	0
A11a,A11b,A12,A13	2	25
	3	50
	4	75
	5	100
A1,A2	0	0
	to	to
	10	100

[a] Precoded response choices as printed in the questionnaire.

[b] Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

[c] "A" before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given sub-scale. This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 3. Step 2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Table 4. Step 2: Averaging of Items to Generate VFQ-39 Sub-Scales (VFQ-25 + Optional Items)

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision Specific:		
Social Functioning	3	11, 13, A9
Mental Health	5	3, 21, 22, 25, A12
Role Difficulties	4	17, 18, A11a, A11b
Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Figure 1. Example of VFQ-25 Scoring Algorithm for Near Activities Sub-Scale

5. How much difficulty do you have <u>reading ordinary print in newspapers</u>? Would you say you have:

No difficulty at all..... 1
A little difficulty 2
Moderate difficulty..... 3
Extreme difficulty**.....(4)**
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not
interested in doing this..... 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing . . . ? Would you say you have:

No difficulty at all**.....(1)**
A little difficulty 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not
interested in doing this..... 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf? Would you say you have:

No difficulty at all..... 1
A little difficulty 2
Moderate difficulty..... 3
Extreme difficulty**.....(4)**
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not
interested in doing this..... 6

Scoring example - Figure 1

Items 5, 6, and 7 are used to generate the near activities sub-scale score (Table 3). Each of the items has 6 response choices. Response choice 6 indicates that the respondent does not perform the activity because of reasons that are unrelated to vision. If a respondent selects this choice, the answer is treated as missing and an average of the remaining items is calculated. Response choice 5 indicates that an activity is so difficult that the participant no longer performs the activity. This extremely poor near vision response choice is recoded to "0" points before taking an average of all three items. To score all items in the same direction, Table 2 shows that responses 1 through 5 for items 5, 6, and 7 should be recoded to values of 100, 75, 50, 25, and 0 respectively. If the respondent is missing one of the items, the person's score will be equal to the average of the two non-missing items.

Formula:

$$\text{Mean} = \frac{\text{(Score for each item with a non-missing answer)}}{\text{Total number of items with non-missing answers}}$$

Example:

$$\text{With responses converted: } = \frac{(25 + 100 + 25)}{3} = 50$$

Note: 100 = Best, 0 = Worst possible score.

Psychometric properties of

VFQ-25 sub-scales

Psychometric data for VFQ-25 reported in the earlier pre-publication version of the scoring manual have been updated and submitted for peer-reviewed publication.[2] The values reported in this document are identical to those reported in the future publication and should be used when citing the performance characteristics of the VFQ-25.

Statistical Power Calculations

Tables 8, 9, and 10 are provided to estimate statistical power when using the VFQ-25 and VFQ-39. These tables estimate the number of subjects needed per group to attain 80% power (alpha = 0.05, two-tailed) depending on the anticipated difference in scores between groups. Table 8 contains power calculations for changes over time between two experimental (i.e. randomized) groups using a repeated-measures design. For example, if one were interested in being able to detect a 5-point difference for the VFQ-25 General Vision sub-scale, one would need 271 subjects per group. Table 9 shows power calculations for two experimental groups using a single, post-intervention measurement design. Such a design is not as precise as a design that uses a baseline and post-intervention measurement points (i.e., more subjects are needed per group to detect the same difference). Table 10 provides corresponding sample size information for a non-experimental (i.e. non-randomized) repeated-measures design where subjects self-select into the two groups. One sees that the number of subjects needed per group is more than that needed for a randomized experiment (Table 8) and less than the number needed for a randomized, post-intervention-only measurement design (Table 9).

Table 8. Sample sizes needed per group to detect differences in *change over time* between two experimental groups for the VFQ-25, repeated measures design

Scale Name	SD	Number of Points Difference 2	5	10	20
VFQ-25:					
General Health	26.00	1696	271	68	17
General Vision	21.00	1106	177	44	11
Ocular Pain	17.00	725	116	29	7
Near Activities	29.00	2110	338	84	21
Distance Activities	29.00	2110	338	84	21
Social Functioning	27.00	1829	293	73	18
Mental Health	27.00	1829	293	73	18
Role Difficulties	29.00	2110	338	84	21
Dependency	28.00	1967	315	79	20
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-25 Composite	20.00	1004	161	40	10
VFQ-39:					
General Health	21.00	1106	177	44	11
General Vision	19.00	906	145	36	9
Ocular Pain	17.00	725	116	29	7
Near Activities	28.00	1967	315	79	20
Distance Activities	26.00	1696	271	68	17
Social Functioning	25.00	1568	251	63	16
Mental Health	26.00	1696	271	68	17
Role Difficulties	28.00	1967	315	79	20
Dependency	27.00	1829	293	73	18
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-39 Composite	21.00	1106	177	44	11

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

Table 9. Sample sizes needed per group to detect differences between two experimental groups for the VFQ-25, *post-intervention measures only*.

Scale Name	SD	Number of Points Difference 2	5	10	20
VFQ-25:					
General Health	26.00	2650	424	106	26
General Vision	21.00	1729	277	69	17
Ocular Pain	17.00	1133	181	45	11
Near Activities	29.00	3297	527	132	33
Distance Activities	29.00	3297	527	132	33
Social Functioning	27.00	2858	457	114	29
Mental Health	27.00	2858	457	114	29
Role Difficulties	29.00	3297	527	132	33
Dependency	28.00	3073	492	123	31
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21
Peripheral Vision	27.00	2858	457	114	29
VFQ-25 Composite	20.00	1568	251	63	16
VFQ-39:					
General Health	21.00	1729	277	69	17
General Vision	19.00	1415	226	57	14
Ocular Pain	17.00	1133	181	45	11
Near Activities	28.00	3073	492	123	31
Distance Activities	26.00	2650	424	106	26
Social Functioning	25.00	2450	392	98	25
Mental Health	26.00	2650	424	106	26
Role Difficulties	28.00	3073	492	123	31
Dependency	27.00	2858	457	114	29
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21
Peripheral Vision	27.00	2858	457	114	29
VFQ-39 Composite	21.00	1729	277	69	17

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, and power = 80%.

Table 10. Sample sizes needed per group to detect differences between two *self-selected groups* for the VFQ-25, repeated measures design

Scale Name	SD	Number of Points Difference 2	5	10	20
VFQ-25:					
General Health	26.00	2120	339	85	21
General Vision	21.00	1383	221	55	14
Ocular Pain	17.00	906	145	36	9
Near Activities	29.00	2637	422	105	26
Distance Activities	29.00	2637	422	105	26
Social Functioning	27.00	2286	366	91	23
Mental Health	27.00	2286	366	91	23
Role Difficulties	29.00	2637	422	105	26
Dependency	28.00	2459	393	98	25
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral Vision	27.00	2286	366	91	23
VFQ-25 Composite	20.00	1254	201	50	13
VFQ-39:					
General Health	21.00	1383	221	55	14
General Vision	19.00	1132	181	45	11
Ocular Pain	17.00	906	145	36	9
Near Activities	28.00	2459	393	98	25
Distance Activities	26.00	2120	339	85	21
Social Functioning	25.00	1960	314	78	20
Mental Health	26.00	2120	339	85	21
Role Difficulties	28.00	2459	393	98	25
Dependency	27.00	2286	366	91	23
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral	27.00	2286	366	91	23
VFQ-39 Composite	21.00	1383	221	55	14

Note: Scales are all scored on 0-100 possible range.Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

Frequently Asked Questions (FAQ)

Q. *What kind of permissions are required to use the VFQ-25 in a research study?*

The VFQ-25 is a public document available without charge for all researchers to use provided they identify the measure as such in all publications and cite the appropriate developmental papers. Users do not need to notify the developers or the NEI that they intend to use the measure. However, there are some specific permissions for using the VFQ-25 that are detailed on the cover page of the questionnaire itself. These include acknowledging in all publications that the VFQ-25 was developed by RAND and funded by the NEI, and that any changes made to the measure for your particular study will be identified as such.

Q. *Can I change the format of the VFQ-25 to suit my study?*

Any change to the wording or order of the items would constitute a change to the measure and should be specified as such in any published papers. Other than this, it is expected that researchers may need to change the format or appearance of items to suit their purposes.

As of August 2000, to our knowledge no studies have reported on the effect of item order on responses to VFQ-25 or other similar vision-targeted surveys. That is, whether responses change depending where particular items appear in the questionnaire. However, to ensure the comparability of scores across studies, it is our position that the order of items should not be changed.

Q. Has the VFQ-25 been translated into any other languages?

As of August 2000, the developers are aware of translation into approximately 9 languages. For the cost of distribution, a Spanish language version for Mexican-American populations is available from the UCLA and RAND based developers. The developers will provide researchers with the names of other persons to contact for other language translations. Should researchers wish to translate the VFQ-25, the same permissions apply, with the additional requirement that all publications specify responsibility for the translation along with instructions for obtaining a copy of the translated version.

Q. Do you have any additional normative information for specific populations?

The developers currently are not conducting studies for the express purpose of further investigating the psychometric properties of the VFQ-25 or producing normative data. However, many researchers are currently using the VFQ-25 as an endpoint or outcome in a number of health services and clinical studies. It is likely that as these studies are completed, results that are relevant to better understanding the performance of the VFQ-25 will accompany the main results of each study. The developers and staff at the NEI are aware of other researchers who are collecting condition-specific normative data on population-based samples with the VFQ-25 and when possible will provide contact information for these investigators to new users.

Q. How relevant is the normative data provided in the scoring manual to my sample?

The means, standard deviations, and statistical power values shown in this document were estimated using cross-sectional data from the Field Test Study. Participants recruited for the Field Test were not randomly sampled, but rather were identified for enrollment based on clinical criteria biased towards persons with moderate to severe forms of each target disease. Further, because it was our desire to enroll a broad spectrum of patients based on disease severity, we did not take into consideration treatment status. Please see references #3 for a full description of the NEI-VFQ field test study sample.

Q. Why is a single-item general health item included in the VFQ-25?

During the developmental phase of the NEI-VFQ, vision-targeted health-related quality of life (HRQOL) was a relatively new concept. For this reason, we included this question to insure that researchers had a minimal amount of information about a person's general health status to use as a benchmark against other published samples or cohorts.

This general health rating question has been widely used in studies and is a robust predictor of future health and mortality. However, to fully measure generic HRQOL, many quality of life measurement experts recommend including a separate generic measure of HRQOL such as the SF-36 or SF-12.[9] In such a situation the single-item VFQ-25 general health rating question is not needed because the identical question is asked as part of these surveys.[10, 11]

Q. Should we be looking at the sub-scales or the composite score?

The VFQ-25 sub-scales are grouped by theme or domain. So, for example, items having to do with near vision are differentiated from items having to do with other vision activities like distance vision or ocular pain. This does not mean that the items are not highly correlated or that they are psychometrically distinct. What it does mean is that researchers should beforehand carefully consider which vision-specific domains are most likely to be influenced by a particular disease and/or treatment and then focus on the results from those sub-scales to support their findings.

The composite score is best used in situations where an overall measure of vision-targeted health related quality of life is desired. For example, in studies where it is not clear what the specific impact of ocular disease or a new treatment might be. Also, in situations where differences can be hypothesized between groups beforehand across multiple sub-scales but the overall sample size of the study is relatively small, because it is likely that the error term for the composite score is likely to be smaller than for any given sub-scale, it may be more efficient to represent these differences as a single score.

Q. What benefit is there to using the VFQ-25 over a measure more specific to a particular disease, like the Activity of Daily Vision Scale (ADVS)[10] for persons with age-related cataracts?

The VFQ-25 contains items that are very similar to items found in other vision-targeted measure like the ADVS that are more task oriented. However, whereas the ADVS was designed specifically to assess a set of activities most relevant to patients undergoing cataract surgery, the VFQ-25 expands the range of activities to measure the impact of ocular disease on broader domains of health such as social and emotional well-being. Serious ocular diseases that lead to irreversible loss of vision are likely to impact dimensions of a person's life beyond simple tasks such as driving or reading the newspaper, and similarly, by preserving vision, many successful interventions also will impact persons' lives at this more global level. Especially in these situations, use of the VFQ-25 should be considered.

Q. Why does the response to item 15b, "stopped driving due to vision <u>and</u> other reasons", generate a missing score for the subsequent driving items?

Driving items 15, 15a, and 15b are filter questions designed to specify whether a person has ever driven a car, and if so, whether they are currently driving or if they have stopped. If people have never driven a car, then, of course, their answers should be set to missing for all driving items. Similarly, this also applies to people who have stopped driving for other reasons not due to vision. However, in the course of pilot testing the field test participants wanted this additional mixed response option. It was our decision that although persons did indeed report not driving due to vision, it was not clear how much of a role the "other" reason also played in this decision. Therefore, we set the scoring criteria for this response to be missing for all subsequent driving items to be absolutely sure that all driving responses reflected only problems with vision. Should researchers wish to change this response option to allow persons to answer subsequent driving

items (currently there is a skip to item #17), this change should be noted in subsequent publications.

References

1. Mangione CM, Berry S, Lee PP, et al. Identifying the content area for the National Eye Institute Vision Function Questionnaire (NEI-VFQ): Results from focus groups with visually impaired persons. *Arch Ophthalmol.* 1998;116:227-238.

2. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25). *Arch Ophthalmol*. 2001;119:1050-1058.

3. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire, the NEI-VFQ. *Arch Ophthalmol*. 1998;116:1496-1504

4. Gutierrez P, Wilson MR, Johnson C, Gordon M, Cioffi GA, Ritch R; Sherwood M, Meng K, Mangione CM. Influence of glaucomatous visual field loss on health-related quality of life. *Arch Ophthalmol*. 1997;115:777-84.

5. Parrish RK 2nd, Gedde SJ, Scott IU, Feuer WJ, Schiffman JC, Mangione CM, Montenegro-Piniella A. Visual function and quality of life among patients with glaucoma. *Arch Ophthalmol*. 1997;115:1447-55

6. Quality of life assessment in the collaborative ocular melanoma study: design and methods. COMS-QOLS Report No. 1. COMS Quality of Life Study Group. *Ophthal. Epidemiology*. 1999;6:5-17.

7. Scott IU, Smiddy WE, Schiffman J, Feuer WJ, Pappas CJ. Quality of life of low-vision patients and the impact of low-vision services. *Amer. J. Ophthalmol*. 1999;128:54-62.

8. Cole SR, Beck RW, Moke PS, Gal RL, Long DT. The National Eye Institute Visual Function Questionnaire: experience of the ONTT. Optic Neuritis Treatment Trial. *Invest Ophthalmol Vis Sci* 2000;41:1017-21.

9. Mangione CM, Lee PP, Hays RD. Measurement of visual functioning and health-related quality of life in eye disease and cataract surgery. In B. Spilker (ed.), Quality of Life and Pharmacoeconomics in clinical trials, 2nd edition. New York: Raven Press 1996:1045-1051.

10. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. *Health Econ* 1993;2:217-227.

11. Ware J Jr, Kosinski M, Keller SD 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33A.

Attachments include:

NEI VFQ-25	(IA = Interviewer-Administered format) (SA = Self-Administered format)

Reference List

(1) Izumi Y, Ishikawa M, Benz AM, Izumi M, Zorumski CF, Thio LL. Acute vigabatrin retinotoxicity in albino rats depends on light but not GABA. Epilepsia 2004; 45(9):1043-1048.

(2) McDonagh J, Grierson DJ, Keating D, Parks S. The wide field multifocal ERG reveals a retinal defect caused by vigabatrin toxicity. Br J Ophthalmol 2001; 85(1):119-120.

(3) McDonagh J, Stephen LJ, Dolan FM, Parks S, Dutton GN, Kelly K et al. Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003; 61(12):1690-1694.

(4) Brodie MJ, Schechter PJ. Diagnosis. Fine Print, Oxford UK, 1999: 12.

(5) Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. Epilepsia 1991; 32(4):429-445.

(6) Tallis. Incidence of epilepsy in relation to age. 2005: 442-448.

(7) Brodie JD, Schachter SC. Epilepsy. Oxford: Fine Print, 1999.

(8) Cocito L, Maffini M, Loeb C. Vigabatrin in chronic epilepsy: a 7-year follow-up study of responder patients. Seizure 1993; 2(4):301-307.

(9) Riikonen R. The latest on infantile spasms. Curr Opin Neurol 2005; 18(2):91-95.

(10) Bernal B, Altman NR. Evidence-based medicine: neuroimaging of seizures. Neuroimaging Clin N Am 2003; 13(2):211-224.

(11) Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997; 314(7075):180-181.

(12) Schmidt T, Gram L. CNS drugs. 1995.

(13) AWAPARA J, LANDUA AJ, FUERST R, SEALE B. Free gamma-aminobutyric acid in brain. J Biol Chem 1950; 187(1):35-39.

(14) Ben Menachem E. Vigabatrin. Epilepsia 1995; 36 Suppl 2:S95-104.

(15) Meldrum BS. Excitatory amino acid receptors and their role in epilepsy and cerebral ischemia. Ann N Y Acad Sci 1995; 757:492-505.

(16) CURTIS DR, WATKINS JC. The excitation and depression of spinal neurones by structurally related amino acids. J Neurochem 1960; 6:117-141.

(17) Schechter PJ, Tranier Y, Jung MJ, Sjoerdsma A. Antiseizure activity of gamma-acetylenic gamma-aminobutyric acid: a catalytic irreversible inhibitor of gamma-aminobutyric acid transaminase. J Pharmacol Exp Ther 1977; 201(3):606-612.

(18) Weiss F, Koob GF. Drug addiction: functional neurotoxicity of the brain reward systems. Neurotox Res 2001; 3(1):145-156.

(19) Marc RE, Murry RF, Basinger SF. Pattern recognition of amino acid signatures in retinal neurons. J Neurosci 1995; 15(7 Pt 2):5106-5129.

(20) Xu W, Cormier R, Fu T, Covey DF, Isenberg KE, Zorumski CF et al. Slow death of postnatal hippocampal neurons by GABA(A) receptor overactivation. J Neurosci 2000; 20(9):3147-3156.

(21) Sills GJ, Patsalos PN, Butler E, Forrest G, Ratnaraj N, Brodie MJ. Visual field constriction: accumulation of vigabatrin but not tiagabine in the retina. Neurology 2001; 57(2):196-200.

(22) Sills GJ, Butler E, Forrest G, Ratnaraj N, Patsalos PN, Brodie MJ. Vigabatrin, but not gabapentin or topiramate, produces concentration-related effects on enzymes and intermediates of the GABA shunt in rat brain and retina. Epilepsia 2003; 44(7):886-892.

(23) VRBA R, GAITONDE MK, RICHTER D. The conversion of glucose carbon into protein in the brain and other organs of the rat. J Neurochem 1962; 9:465-475.

(24) KILLAM KF, BAIN JA. Convulsant hydrazides. I. In vitro and in vivo inhibition of vitamin B6 enzymes by convulsant hydrazides. J Pharmacol Exp Ther 1957; 119(2):255-262.

(25) Sarhan S, Seiler N. Metabolic inhibitors and subcellular distribution of GABA. J Neurosci Res 1979; 4(5-6):399-421.

(26) Bormann J. Electrophysiology of GABAA and GABAB receptor subtypes. Trends Neurosci 1988; 11(3):112-116.

(27) McKernan RM, Whiting PJ. Which GABAA-receptor subtypes really occur in the brain? Trends Neurosci 1996; 19(4):139-143.

(28) Pham TM, Lacaille JC. Multiple postsynaptic actions of GABA via GABAB receptors on CA1 pyramidal cells of rat hippocampal slices. J Neurophysiol 1996; 76(1):69-80.

(29) Swartzwelder HS, Bragdon AC, Sutch CP, Ault B, Wilson WA. Baclofen suppresses hippocampal epileptiform activity at low concentrations without suppressing synaptic transmission. J Pharmacol Exp Ther 1986; 237(3):881-887.

(30) Mott DD, Bragdon AC, Lewis DV, Wilson WA. Baclofen has a proepileptic effect in the rat dentate gyrus. J Pharmacol Exp Ther 1989; 249(3):721-725.

(31) Olsen RW, Avoli M. GABA and epileptogenesis. Epilepsia 1997; 38(4):399-407.

(32) Enz R, Ross BJ, Cutting GR. Expression of the voltage-gated chloride channel ClC-2 in rod bipolar cells of the rat retina. J Neurosci 1999; 19(22):9841-9847.

(33) Qian H, Dowling JE. Novel GABA responses from rod-driven retinal horizontal cells. Nature 1993; 361(6408):162-164.

(34) Qian H, Dowling JE. GABAA and GABAC receptors on hybrid bass retinal bipolar cells. J Neurophysiol 1995; 74(5):1920-1928.

(35) Johnson EW, de Lanerolle NC, Kim JH, Sundaresan S, Spencer DD, Mattson RH et al. "Central" and "peripheral" benzodiazepine receptors: opposite changes in human epileptogenic tissue. Neurology 1992; 42(4):811-815.

(36) French JA, Mosier M, Walker S, Sommerville K, Sussman N. A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. Vigabatrin Protocol 024 Investigative Cohort. Neurology 1996; 46(1):54-61.

(37) Study RE, Barker JL. Diazepam and (--)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. Proc Natl Acad Sci U S A 1981; 78(11):7180-7184.

(38) Pow DV, Baldridge W, Crook DK. Activity-dependent transport of GABA analogues into specific cell types demonstrated at high resolution using a novel immunocytochemical strategy. Neuroscience 1996; 73(4):1129-1143.

(39) Masland RH. Amacrine cells. Trends Neurosci 1988; 11(9):405-410.

(40) Mustafa BA. Diversity of GABA receptors in the vertebrate outer retina. Trends Neurosci 1995; 18(3):118-120.

(41) Euler T, Wassle H. Different contributions of GABAA and GABAC receptors to rod and cone bipolar cells in a rat retinal slice preparation. J Neurophysiol 1998; 79(3):1384-1395.

(42) Kapousta-Bruneau NV. Opposite effects of GABA(A) and GABA(C) receptor antagonists on the b-wave of ERG recorded from the isolated rat retina. Vision Res 2000; 40(13):1653-1665.

(43) Coupland SG, Zackon DH, Leonard BC, Ross TM. Vigabatrin effect on inner retinal function. Ophthalmology 2001; 108(8):1493-1496.

(44) Miller NR, Johnson MA, Paul SR, Girkin CA, Perry JD, Endres M et al. Visual dysfunction in patients receiving vigabatrin: clinical and electrophysiologic findings. Neurology 1999; 53(9):2082-2087.

(45) Livingston JH, Beaumont D, Arzimanoglou A, Aicardi J. Vigabatrin in the treatment of epilepsy in children. Br J Clin Pharmacol 1989; 27 Suppl 1:109S-112S.

(46) Jung MJ, Lippert B, Metcalf BW, Bohlen P, Schechter PJ. gamma-Vinyl GABA (4-amino-hex-5-enoic acid), a new selective irreversible inhibitor of GABA-T: effects on brain GABA metabolism in mice. J Neurochem 1977; 29(5):797-802.

(47) Butler WH. The neuropathology of vigabatrin. Epilepsia 1989; 30 Suppl 3:S15-S17.

(48) Sills GJ. Pre-clinical studies with the GABAergic compounds vigabatrin and tiagabine. Epileptic Disord 2003; 5(1):51-56.

(49) Leach JP, Sills GJ, Majid A, Butler E, Carswell A, Thompson GG et al. Effects of tiagabine and vigabatrin on GABA uptake into primary cultures of rat cortical astrocytes. Seizure 1996; 5(3):229-234.

(50) Wu Y, Wang W, Richerson GB. Vigabatrin induces tonic inhibition via GABA transporter reversal without increasing vesicular GABA release. J Neurophysiol 2003; 89(4):2021-2034.

(51) Hanaya R, Sasa M, Kiura Y, Serikawa T, Kurisu K. Effects of vigabatrin on epileptiform abnormal discharges in hippocampal CA3 neurons of spontaneously epileptic rats (SER). Epilepsy Res 2002; 50(3):223-231.

(52) Halonen T, Pitkanen A, Saano V, Riekkinen PJ. Effects of vigabatrin (gamma-vinyl GABA) on neurotransmission-related amino acids and on GABA and benzodiazepine receptor binding in rats. Epilepsia 1991; 32(2):242-249.

(53) Larsson OM, Gram L, Schousboe I, Schousboe A. Differential effect of gamma-vinyl GABA and valproate on GABA-transaminase from cultured neurones and astrocytes. Neuropharmacology 1986; 25(6):617-625.

(54) Bernasconi R, Klein M, Martin P, Christen P, Hafner T, Portet C et al. Gamma-vinyl GABA: comparison of neurochemical and anticonvulsant effects in mice. J Neural Transm 1988; 72(3):213-233.

(55) Sills GJ, Butler E, Thompson GG, Brodie MJ. Vigabatrin and tiagabine are pharmacologically different drugs. A pre-clinical study. Seizure 1999; 8(7):404-411.

(56) Schechter PJ, Tranier Y, Jung MJ, Bohlen P. Audiogenic seizure protection by elevated brain GABA concentration in mice: effects of gamma-acetylenic gaba and gamma-vinyl GABA, two irreversible GABA-T inhibitors. Eur J Pharmacol 1977; 45(4):319-328.

(57) Holland KD, McKeon AC, Canney DJ, Covey DF, Ferrendelli JA. Relative anticonvulsant effects of GABAmimetic and GABA modulatory agents. Epilepsia 1992; 33(6):981-986.

(58) Levy RH MRMB. Antiepileptic Drugs. 4th ed. New York: 2004.

(59) Haegele KD, Schoun J, Alken RG, Huebert ND. Determination of the R(-)- and S(+)-enantiomers of gamma-vinyl-gamma-aminobutyric acid in human body fluids by gas chromatography--mass spectrometry. J Chromatogr 1983; 274:103-110.

(60) Haegele KD, Schechter PJ. Kinetics of the enantiomers of vigabatrin after an oral dose of the racemate or the active S-enantiomer. Clin Pharmacol Ther 1986; 40(5):581-586.

(61) Saletu B, Grunberger J, Linzmayer L, Schwartz JJ, Haegele KD, Schechter PJ. Psychophysiological and psychometric studies after manipulating the GABA system by vigabatrin, a GABA-transaminase inhibitor. Int J Psychophysiol 1986; 4(1):63-80.

(62) Ben Menachem E, Persson LI, Schechter PJ, Haegele KD, Huebert N, Hardenberg J et al. The effect of different vigabatrin treatment regimens on CSF biochemistry and seizure control in epileptic patients. Br J Clin Pharmacol 1989; 27 Suppl 1:79S-85S.

(63) Schechter PJ. Clinical pharmacology of vigabatrin. Br J Clin Pharmacol 1989; 27 Suppl 1:19S-22S.

(64) Menachem EB, Persson LI, Schechter PJ, Haegele KD, Huebert N, Hardenberg J et al. Effects of single doses of vigabatrin on CSF concentrations of GABA, homocarnosine, homovanillic acid and 5-hydroxyindoleacetic acid in patients with complex partial epilepsy. Epilepsy Res 1988; 2(2):96-101.

(65) Ben Menachem E, Persson LI, Mumford J, Haegele KD, Huebert N. Effect of long-term vigabatrin therapy on selected neurotransmitter concentrations in cerebrospinal fluid. J Child Neurol 1991; Suppl 2:S11-S16.

(66) Schechter PJ, Hanke NF, Grove J, Huebert N, Sjoerdsma A. Biochemical and clinical effects of gamma-vinyl GABA in patients with epilepsy. Neurology 1984; 34(2):182-186.

(67) Gram L, Lyon BB, Dam M. Gamma-vinyl-GABA: a single-blind trial in patients with epilepsy. Acta Neurol Scand 1983; 68(1):34-39.

(68) Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ et al. Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. Neurology 1987; 37(2):184-189.

(69) Tassinari CA, Michelucci R, Ambrosetto G, Salvi F. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987; 44(9):907-910.

(70) Tartara A, Manni R, Galimberti CA, Hardenberg J, Orwin J, Perucca E. Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study. Epilepsia 1986; 27(6):717-723.

(71) Loiseau P, Hardenberg JP, Pestre M, Guyot M, Schechter PJ, Tell GP. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia 1986; 27(2):115-120.

(72) Rimmer EM, Richens A. Double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. Lancet 1984; 1(8370):189-190.

(73) Mumford JP, Dam M. Meta-analysis of European placebo controlled studies of vigabatrin in drug resistant epilepsy. Br J Clin Pharmacol 1989; 27 Suppl 1:101S-107S.

(74) Ring HA, Heller AJ, Farr IN, Reynolds EH. Vigabatrin: rational treatment for chronic epilepsy. J Neurol Neurosurg Psychiatry 1990; 53(12):1051-1055.

(75) Benry JWBSR. Multicenter dose response study of vigabatrin in adults with focal epilepsy. Epilepsia 1983; 34(supp6)(S67).

(76) Cocito L, Maffini M, Perfumo P, Roncallo F, Loeb C. Vigabatrin in complex partial seizures: a long-term study. Epilepsy Res 1989; 3(2):160-166.

(77) Dam M. Long-term evaluation of vigabatrin (gamma vinyl GABA) in epilepsy. Epilepsia 1989; 30 Suppl 3:S26-S30.

(78) Pedersen SA, Klosterskov P, Gram L, Dam M. Long-term study of gamma-vinyl GABA in the treatment of epilepsy. Acta Neurol Scand 1985; 72(3):295-298.

(79) Remy C, Beaumont D. Efficacy and safety of vigabatrin in the long-term treatment of refractory epilepsy. Br J Clin Pharmacol 1989; 27 Suppl 1:125S-129S.

(80) Grant SM, Heel RC. Vigabatrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 1991; 41(6):889-926.

(81) Kalviainen R, Halonen T, Pitkanen A, Riekkinen PJ. Amino acid levels in the cerebrospinal fluid of newly diagnosed epileptic patients: effect of vigabatrin and carbamazepine monotherapies. J Neurochem 1993; 60(4):1244-1250.

(82) Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; Suppl 2:S52-S59.

(83) Michelucci R, Tassinari CA. Response to vigabatrin in relation to seizure type. Br J Clin Pharmacol 1989; 27 Suppl 1:119S-124S.

(84) Pitkanen A, Ylinen A, Matilainen R, Luukkainen R, Mervaala E, Seppanen R et al. Long-term antiepileptic efficacy of vigabatrin in drug-refractory epilepsy in mentally retarded patients. A 5-year follow-up study. Arch Neurol 1993; 50(1):24-29.

(85) Dulac O, Chiron C, Luna D, Cusmai R, Pajot N, Beaumont D et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; Suppl 2:S30-S37.

(86) Matilainen R, Pitkanen A, Ruutiainen T, Mervaala E, Sarlund H, Riekkinen P. Effect of vigabatrin on epilepsy in mentally retarded patients: a 7-month follow-up study. Neurology 1988; 38(5):743-747.

(87) Kalviainen R, Aikia M, Partanen J, Sivenius J, Mumford J, Saksa M et al. Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: an interim report. J Child Neurol 1991; Suppl 2:S60-S69.

(88) Gibson JP, Yarrington JT, Loudy DE, Gerbig CG, Hurst GH, Newberne JW. Chronic toxicity studies with vigabatrin, a GABA-transaminase inhibitor. Toxicol Pathol 1990; 18(2):225-238.

(89) Butler WH, Ford GP, Newberne JW. A study of the effects of vigabatrin on the central nervous system and retina of Sprague Dawley and Lister-Hooded rats. Toxicol Pathol 1987; 15(2):143-148.

(90) Yarrington JT, Gibson JP, Dillberger JE, Hurst G, Lippert B, Sussman NM et al. Sequential neuropathology of dogs treated with vigabatrin, a GABA-transaminase inhibitor. Toxicol Pathol 1993; 21(5):480-489.

(91) Schroeder CE, Gibson JP, Yarrington J, Heydorn WE, Sussman NM, Arezzo JC. Effects of high-dose gamma-vinyl GABA (vigabatrin) administration on visual and somatosensory evoked potentials in dogs. Epilepsia 1992; 33 Suppl 5:S13-S25.

(92) Arezzo JC, Schroeder CE, Litwak MS, Steward DL. Effects of vigabatrin on evoked potentials in dogs. Br J Clin Pharmacol 1989; 27 Suppl 1:53S-60S.

(93) Neal MJ, Shah MA. Development of tolerance to the effects of vigabatrin (gamma-vinyl-GABA) on GABA release from rat cerebral cortex, spinal cord and retina. Br J Pharmacol 1990; 100(2):324-328.

(94) Cohen JA, Fisher RS, Brigell MG, Peyster RG, Sze G. The potential for vigabatrin-induced intramyelinic edema in humans. Epilepsia 2000; 41(2):148-157.

(95) Ravindran J, Blumbergs P, Crompton J, Pietris G, Waddy H. Visual field loss associated with vigabatrin: pathological correlations. J Neurol Neurosurg Psychiatry 2001; 70(6):787-789.

(96) Buncic JR, Westall CA, Panton CM, Munn JR, MacKeen LD, Logan WJ. Characteristic retinal atrophy with secondary "inverse" optic atrophy identifies vigabatrin toxicity in children. Ophthalmology 2004; 111(10):1935-1942.

(97) Wild JM, Robson CR, Jones AL, Cunliffe IA, Smith PE. Detecting vigabatrin toxicity by imaging of the retinal nerve fiber layer. Invest Ophthalmol Vis Sci 2006; 47(3):917-924.

(98) Jensen H, Sjo O, Uldall P, Gram L. Vigabatrin and retinal changes. Doc Ophthalmol 2002; 104(2):171-180.

(99) Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin. Chronic refractory epilepsy may have role in causing these unusual lesions. BMJ 1997; 314(7095):1693.

(100) Arndt CF, Derambure P, Defoort-Dhellemmes S, Hache JC. Outer retinal dysfunction in patients treated with vigabatrin. Neurology 1999; 52(6):1201-1205.

(101) Wong IC, Mawer GE, Sander JW. Severe persistent visual field constriction associated with vigabatrin. Reaction might be dose dependent. BMJ 1997; 314(7095):1693-1694.

(102) Krakow K, Polizzi G, Riordan-Eva P, Holder G, MacLeod WN, Fish DR. Recovery of visual field constriction following discontinuation of vigabatrin. Seizure 2000; 9(4):287-290.

(103) Beran RG. New antiepileptic medications. Med J Aust 1995; 162(3):118-119.

(104) Baulac M, Nordmann JP, Lanoe Y. Severe visual-field constriction and side-effects of GABA-mimetic antiepileptic agents. Lancet 1998; 352(9127):546.

(105) Kalviainen R, Brodie MJ, Duncan J, Chadwick D, Edwards D, Lyby K. A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. Northern European Tiagabine Study Group. Epilepsy Res 1998; 30(1):31-40.

(106) Sorri I, Herrgard E, Viinikainen K, Paakkonen A, Heinonen S, Kalviainen R. Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. Epilepsy Res 2005; 65(1-2):117-120.

(107) Comaish IF, Gorman C, Brimlow GM, Barber C, Orr GM, Galloway NR. The effects of vigabatrin on electrophysiology and visual fields in epileptics: a controlled study with a discussion of possible mechanisms. Doc Ophthalmol 2002; 104(2):195-212.

(108) Spanaki MV, Siegel H, Kopylev L, Fazilat S, Dean A, Liow K et al. The effect of vigabatrin (gamma-vinyl GABA) on cerebral blood flow and metabolism. Neurology 1999; 53(7):1518-1522.

(109) Edvinsson L, Krause DN. Pharmacological characterization of GABA receptors mediating vasodilation of verebral arteries in vitro. Brain Res 1979; 173(1):89-97.

(110) Kelly PA, McCulloch J. The effects of the GABAergic agonist muscimol upon the relationship between local cerebral blood flow and glucose utilization. Brain Res 1983; 258(2):338-342.

(111) Hilton EJ, Cubbidge RP, Hosking SL, Betts T, Comaish IF. Patients treated with vigabatrin exhibit central visual function loss. Epilepsia 2002; 43(11):1351-1359.

(112) Hosking SL, Hilton EJ. Neurotoxic effects of GABA-transaminase inhibitors in the treatment of epilepsy: ocular perfusion and visual performance. Ophthalmic Physiol Opt 2002; 22(5):440-447.

(113) Crofts K, Brennan R, Kearney P, O'Connor G. Vigabatrin-induced optic neuropathy. J Neurol 1997; 244(10):666-667.

(114) Lawden MC, Eke T, Degg C, Harding GF, Wild JM. Visual field defects associated with vigabatrin therapy. J Neurol Neurosurg Psychiatry 1999; 67(6):716-722.

(115) Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998; 50(3):614-618.

(116) Schmetterer L, Findl O, Strenn K, Graselli U, Kastner J, Eichler HG et al. Role of NO in the O2 and CO2 responsiveness of cerebral and ocular circulation in humans. Am J Physiol 1997; 273(6 Pt 2):R2005-R2012.

(117) Kiss B, Dallinger S, Findl O, Rainer G, Eichler HG, Schmetterer L. Acetazolamide-induced cerebral and ocular vasodilation in humans is independent of nitric oxide. Am J Physiol 1999; 276(6 Pt 2):R1661-R1667.

(118) Rimmer EM, Richens A. Interaction between vigabatrin and phenytoin. Br J Clin Pharmacol 1989; 27 Suppl 1:27S-33S.

(119) Wilton LV, Stephens MD, Mann RD. Visual field defect associated with vigabatrin: observational cohort study. BMJ 1999; 319(7218):1165-1166.

(120) Kalviainen R, Nousiainen I, Mantyjarvi M, Nikoskelainen E, Partanen J, Partanen K et al. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. Neurology 1999; 53(5):922-926.

(121) Malmgren K, Ben Menachem E, Frisen L. Vigabatrin visual toxicity: evolution and dose dependence. Epilepsia 2001; 42(5):609-615.

(122) Vanhatalo S, Nousiainen I, Eriksson K, Rantala H, Vainionpaa L, Mustonen K et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia 2002; 43(7):748-756.

(123) Lawden MC. Vigabatrin, tiagabine, and visual fields. J Neurol Neurosurg Psychiatry 2003; 74(3):286.

(124) Hardus P, Verduin WM, Postma G, Stilma JS, Berendschot TT, van Veelen CW. Concentric contraction of the visual field in patients with temporal lobe epilepsy and its association with the use of vigabatrin medication. Epilepsia 2000; 41(5):581-587.

(125) Pedley TA, Hauser WA. Sudden death in epilepsy: a wake-up call for management. Lancet 2002; 359(9320):1790-1791.

(126) Wild JM, Martinez C, Reinshagen G, Harding GF. Characteristics of a unique visual field defect attributed to vigabatrin. Epilepsia 1999; 40(12):1784-1794.

(127) Visual field constriction on vigabatrin. Prescrire Int 2000; 9(45):210-211.

(128) Schmidt T, Ruther K, Jokiel B, Pfeiffer S, Tiel-Wilck K, Schmitz B. Is visual field constriction in epilepsy patients treated with vigabatrin reversible? J Neurol 2002; 249(8):1066-1071.

(129) Graniewski-Wijnands HS, van der TK. Electro-ophthalmological recovery after withdrawal from vigabatrin. Doc Ophthalmol 2002; 104(2):189-194.

(130) Newman WD, Tocher K, Acheson JF. Vigabatrin associated visual field loss: a clinical audit to study prevalence, drug history and effects of drug withdrawal. Eye 2002; 16(5):567-571.

(131) Hayashi T, Negishi K. Suppression of retinal spike discharge by dipropylacetate (Depakene): a possible involvement of GABA. Brain Res 1979; 175(2):271-278.

(132) Arndt CF, Salle M, Derambure PH, Defoort-Dhellemmes S, Hache JC. The effect on vision of associated treatments in patients taking vigabatrin: carbamazepine versus valproate. Epilepsia 2002; 43(8):812-817.

(133) Daneshvar H, Racette L, Coupland SG, Kertes PJ, Guberman A, Zackon D. Symptomatic and asymptomatic visual loss in patients taking vigabatrin. Ophthalmology 1999; 106(9):1792-1798.

(134) van der TK, Graniewski-Wijnands HS, Polak BC. Visual field and electrophysiological abnormalities due to vigabatrin. Doc Ophthalmol 2002; 104(2):181-188.

(135) Hardus P, Verduin WM, Engelsman M, Edelbroek PM, Segers JP, Berendschot TT et al. Visual field loss associated with vigabatrin: quantification and relation to dosage. Epilepsia 2001; 42(2):262-267.

(136) Fledelius HC. Vigabatrin-associated visual field constriction in a longitudinal series. Reversibility suggested after drug withdrawal. Acta Ophthalmol Scand 2003; 81(1):41-46.

(137) Besch D, Kurtenbach A, Apfelstedt-Sylla E, Sadowski B, Dennig D, Asenbauer C et al. Visual field constriction and electrophysiological changes associated with vigabatrin. Doc Ophthalmol 2002; 104(2):151-170.

(138) Johnson MA, Krauss GL, Miller NR, Medura M, Paul SR. Visual function loss from vigabatrin: effect of stopping the drug. Neurology 2000; 55(1):40-45.

(139) Manuchehri K, Goodman S, Siviter L, Nightingale S. A controlled study of vigabatrin and visual abnormalities. Br J Ophthalmol 2000; 84(5):499-505.

(140) Nicolson A, Leach JP, Chadwick DW, Smith DF. The legacy of vigabatrin in a regional epilepsy clinic. J Neurol Neurosurg Psychiatry 2002; 73(3):327-329.

(141) Lorenz R, Kuck H. [Visual disorders caused by diphenylhydantoin: clinical and electro-ophthalmologic findings]. Klin Monatsbl Augenheilkd 1988; 192(3):244-247.

(142) Elder MJ. Diazepam and its effects on visual fields. Aust N Z J Ophthalmol 1992; 20(3):267-270.

(143) Ludwig BI, Marsan CA. Clinical ictal patterns in epileptic patients with occipital electroencephalographic foci. Neurology 1975; 25(5):463-471.

(144) Kaufman KR, Lepore FE, Keyser BJ. Visual fields and tiagabine: a quandary. Seizure 2001; 10(7):525-529.

(145) Armijo JA, Cuadrado A, Bravo J, Arteaga R. Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. Ther Drug Monit 1997; 19(5):491-498.

(146) Dieterle L, Becker EW, Berg PA, Berkenfeld R, Reinshagen G. [Allergic vasculitis caused by Vigabatrin]. Nervenarzt 1994; 65(2):122-124.

(147) Versino M, Veggiotti P. Reversibility of vigabratin-induced visual-field defect. Lancet 1999; 354(9177):486.

(148) Nousiainen I, Mantyjarvi M, Kalviainen R. No reversion in vigabatrin-associated visual field defects. Neurology 2001; 57(10):1916-1917.

(149) Paul SR, Krauss GL, Miller NR, Medura MT, Miller TA, Johnson MA. Visual function is stable in patients who continue long-term vigabatrin therapy: implications for clinical decision making. Epilepsia 2001; 42(4):525-530.

(150) Hardus P, Verduin WM, Postma G, Stilma JS, Berendschot TT, van Veelen CW. Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. Br J Ophthalmol 2000; 84(7):788-790.

(151) Harding GF, Robertson KA, Edson AS, Barnes P, Wild J. Visual electrophysiological effect of a GABA transaminase blocker. Doc Ophthalmol 1998; 97(2):179-188.

(152) Ludwig BI, Marsan CA. Clinical ictal patterns in epileptic patients with occipital electroencephalographic foci. Neurology 1975; 25(5):463-471.

(153) Kalviainen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. CNS Drugs 2001; 15(3):217-230.

(154) Harding GF, Wild JM, Robertson KA, Lawden MC, Betts TA, Barber C et al. Electro-oculography, electroretinography, visual evoked potentials, and multifocal electroretinography in patients with vigabatrin-attributed visual field constriction. Epilepsia 2000; 41(11):1420-1431.

(155) Harding GF. Severe persistent visual field constriction associated with vigabatrin. Four possible explanations exist. BMJ 1997; 314(7095):1694.

(156) Ruether K, Pung T, Kellner U, Schmitz B, Hartmann C, Seeliger M. Electrophysiologic evaluation of a patient with peripheral visual field contraction associated with vigabatrin. Arch Ophthalmol 1998; 116(6):817-819.

(157) Hardus P, Verduin W, Berendschot T, Postma G, Stilma J, van Veelen C. Vigabatrin: longterm follow-up of electrophysiology and visual field examinations. Acta Ophthalmol Scand 2003; 81(5):459-465.

(158) Harding GF, Wild JM, Robertson KA, Rietbrock S, Martinez C. Separating the retinal electrophysiologic effects of vigabatrin: treatment versus field loss. Neurology 2000; 55(3):347-352.

(159) Hardus P, Verduin WM, Berendschot TT, Kamermans M, Postma G, Stilma JS et al. The value of electrophysiology results in patients with epilepsy and vigabatrin associated visual field loss. Acta Ophthalmol Scand 2001; 79(2):169-174.

(160) Ponjavic V, Andreasson S. Multifocal ERG and full-field ERG in patients on long-term vigabatrin medication. Doc Ophthalmol 2001; 102(1):63-72.

(161) Banin E, Shalev RS, Obolensky A, Neis R, Chowers I, Gross-Tsur V. Retinal function abnormalities in patients treated with vigabatrin. Arch Ophthalmol 2003; 121(6):811-816.

(162) Harding GF, Spencer EL, Wild JM, Conway M, Bohn RL. Field-specific visual-evoked potentials: identifying field defects in vigabatrin-treated children. Neurology 2002; 58(8):1261-1265.

(163) Harding GF. Severe persistent visual field constriction associated with vigabatrin. Benefit: risk ratio must be calculated for individual patients. BMJ 1998; 316(7126):232-233.

(164) Mecarelli O, Rinalduzzi S, Accornero N. Changes in color vision after a single dose of vigabatrin or carbamazepine in healthy volunteers. Clin Neuropharmacol 2001; 24(1):23-26.

(165) Krauss GL, Johnson MA, Sheth S, Miller NR. A controlled study comparing visual function in patients treated with vigabatrin and tiagabine. J Neurol Neurosurg Psychiatry 2003; 74(3):339-343.

(166) Vanhatalo S, Paakkonen L, Nousiainen I. Visual field constriction in children treated with vigabatrin. Neurology 1999; 52(8):1713-1714.

(167) Harding GF, Robertson KA, Holliday I. Field specific visual evoked potentials for assessment of peripheral field defect in a paediatric population. Suppl Clin Neurophysiol 2000; 53:323-330.

(168) Gross-Tsur V, Banin E, Shahar E, Shalev RS, Lahat E. Visual impairment in children with epilepsy treated with vigabatrin. Ann Neurol 2000; 48(1):60-64.

(169) Iannetti P, Spalice A, Perla FM, Conicella E, Raucci U, Bizzarri B. Visual field constriction in children with epilepsy on vigabatrin treatment. Pediatrics 2000; 106(4):838-842.

(170) Luchetti A, Amadi A, Gobbi G. Visual field defects associated with vigabratin monotherapy in children. J Neurol Neurosurg Psychiatry 2000; 69(4):566.

(171) Russell-Eggitt IM, Mackey DA, Taylor DS, Timms C, Walker JW. Vigabatrin-associated visual field defects in children. Eye 2000; 14 (Pt 3A):334-339.

(172) Vanhatalo S, Alen R, Riikonen R, Rantala H, Aine MR, Mustonen K et al. Reversed visual field constrictions in children after vigabatrin withdrawal--true retinal recovery or improved test performance only? Seizure 2001; 10(7):508-511.

(173) Fraunfelder FT. Drug induced ocular side effects and drug interactions. 2 ed. Philadelphia: 1982.

(174) Madreperla SA, Johnson MA, Nakatani K. Electrophysiologic and electroretinographic evidence for photoreceptor dysfunction as a toxic effect of digoxin. Arch Ophthalmol 1994; 112(6):807-812.

(175) Weleber RG, Shults WT. Digoxin retinal toxicity. Clinical and electrophysiological evaluation of a cone dysfunction syndrome. Arch Ophthalmol 1981; 99(9):1568-1572.

(176) Buchanan TA, Lyness RW, Collins AD, Gardiner TA, Archer DB. An experimental study of quinine blindness. Eye 1987; 1 (Pt 4):522-524.

(177) Brinton GS, Norton EW, Zahn JR, Knighton RW. Ocular quinine toxicity. Am J Ophthalmol 1980; 90(3):403-410.

(178) Zahn JR, Brinton GF, Norton E. Ocular quinine toxicity followed by electroretinogram, electro-oculogram, and pattern visually evoked potential. Am J Optom Physiol Opt 1981; 58(6):492-498.

(179) Kaiser-Kupfer MI, Kupfer C, Rodrigues MM. Tamoxifen retinopathy. A clinicopathologic report. Ophthalmology 1981; 88(1):89-93.

(180) Colley SM, Elston JS. Tamoxifen optic neuropathy. Clin Experiment Ophthalmol 2004; 32(1):105-106.

(181) AtLee WE, Jr. Talc and cornstarch emboli in eyes of drug abusers. JAMA 1972; 219(1):49-51.

(182) Thomas EL, Laborde RP. Retinal and choroidal vascular occlusion following intralesional corticosteroid injection of a chalazion. Ophthalmology 1986; 93(3):405-407.

(183) Martidis A, Yung CW, Ciulla TA. Talc embolism: a static retinopathy. Am J Ophthalmol 1997; 124(6):841-843.

(184) Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991; 23(8):292-296.

(185) RUBIN M, Bernstein HN, ZVAIFLER NJ. STUDIES ON THE PHARMACOLOGY OF CHLOROQUINE. RECOMMENDATIONS FOR THE TREATMENT OF CHLOROQUINE RETINOPATHY. Arch Ophthalmol 1963; 70:474-481.

(186) Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol 1985; 12(4):692-694.

(187) Neubauer AS, Samari-Kermani K, Schaller U, Welge-Lubetaen U, Rudolph G, Berninger T. Detecting chloroquine retinopathy: electro-oculogram versus colour vision. Br J Ophthalmol 2003; 87(7):902-908.

(188) ARDEN GB, KOLB H. SCREENING TEST FOR CHLOROQUINE RETINOPATHY. Lancet 1964; 41:41.

(189) Tzekov RT, Serrato A, Marmor MF. ERG findings in patients using hydroxychloroquine. Doc Ophthalmol 2004; 108(1):87-97.

(190) Maturi RK, Yu M, Weleber RG. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users. Arch Ophthalmol 2004; 122(7):973-981.

(191) Penrose PJ, Tzekov RT, Sutter EE, Fu AD, Allen AW, Jr., Fung WE et al. Multifocal electroretinography evaluation for early detection of retinal dysfunction in patients taking hydroxychloroquine. Retina 2003; 23(4):503-512.

(192) Granit R. Sensory mechanisms of the retina (with an appendix on electroretinography). First ed. London: Oxford University Press, 1947.

(193) Sutter EE, Tran D. The field topography of ERG components in man--I. The photopic luminance response. Vision Res 1992; 32(3):433-446.

(194) Sutter EE, Tran D. The field topography of ERG components in man--I. The photopic luminance response. Vision Res 1992; 32(3):433-446.

(195) Keating D, Parks S, Evans A. Technical aspects of multifocal ERG recording. Doc Ophthalmol 2000; 100(2-3):77-98.

(196) Fricker SJ, Sanders JJ. A new method of cone electroretinography: the rapid random flash response. Invest Ophthalmol 1975; 14(2):131-137.

(197) Larkin RM, Klein S, Ogden TE, Fender DH. Nonlinear kernels of the human ERG. Biol Cybern 1979; 35(3):145-160.

(198) Ogden TE, Larkin RM, Fender DF, Cleary PE, Ryan SJ. The use of non-linear analysis of the primate ERG to detect retinal dysfunction. Exp Eye Res 1980; 31(4):381-388.

(199) Fricker SJ, Sanders JJ. Clinical studies of the evoked response to rapid random flash. Electroencephalogr Clin Neurophysiol 1974; 36(5):525-532.

(200) Srebro R, Weldon W. Visually Evoked Potentials to Pseudorandom Binary Sequence Stimulation. Arch Ophthalmol 1980; 98:296-298.

(201) Sutter EE, Tran D. The Field Topography of ERG Components in Man - I. The Photopic Luminance Response. Vision Res 1992; 32(3):433-446.

(202) Dolan FM, Gavin M., Parks S, Keating D. Recovery of visual function in a patient with birdshot chorioretinitis. Br J Ophthalmol 2003; In press.

(203) Dolan FM, Parks S, Hammer H, Keating D. The wide field multifocal electroretinogram reveals retinal dysfunction in early retinitis pigmentosa. Br J Ophthalmol 2002; 86(4):480-481.

(204) Muscat S, Fahad B, Parks S, Keating D. Optical coherence tomography and multifocal electroretinography of X-linked juvenile retinoschisis. Eye 2001; 15(Pt 6):796-799.

(205) Keating D, Parks S, Malloch C, Evans A. A comparison of CRT and digital stimulus delivery methods in the multifocal ERG. Doc Ophthalmol 2001; 102(2):95-114.

(206) McDonagh J, Grierson DJ, Keating D, Parks S. The wide field multifocal ERG reveals a retinal defect caused by vigabatrin toxicity. Br J Ophthalmol 2001; 85(1):119-120.

(207) Chisholm JA, Keating D, Parks S, Evans AL. The impact of fixation on the multifocal electroretinogram. Doc Ophthalmol 2001; 102(2):131-139.

(208) McDonagh J, Stephen LJ, Dolan FM, Parks S, Dutton GN, Kelly K et al. Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003; In press.

(209) Dolan FM, Parks S, Hammer H, Keating D. The wide field multifocal electroretinogram reveals retinal dysfunction in early retinitis pigmentosa. Br J Ophthalmol 2002; 86(4):480-481.

(210) Muscat S, Fahad B, Parks S, Keating D. Optical coherence tomography and multifocal electroretinography of X-linked juvenile retinoschisis. Eye 2001; 15(Pt 6):796-799.

(211) Keating D, Parks S, Malloch C, Evans A. A comparison of CRT and digital stimulus delivery methods in the multifocal ERG. Doc Ophthalmol 2001; 102(2):95-114.

(212) McDonagh J, Grierson DJ, Keating D, Parks S. The wide field multifocal ERG reveals a retinal defect caused by vigabatrin toxicity. Br J Ophthalmol 2001; 85(1):119-120.

(213) Chisholm JA, Keating D, Parks S, Evans AL. The impact of fixation on the multifocal electroretinogram. Doc Ophthalmol 2001; 102(2):131-139.

(214) Marmor MF, Hood DC, Keating D, Kondo M, Seeliger M, Miyake Y. Guidelines for basic multifocal electroretinography (mfERG). Doc Ophthalmol 2003; 106(2):105-115.

(215) Keating D, Parks S, Smith D, Evans A. The multifocal ERG: unmasked by selective cross-correlation. Vision Res 2002; 42(27):2959-2968.

(216) Sutter E. The interpretation of multifocal binary kernels. Doc Ophthalmol 2000; 100(2-3):49-75.

(217) Han Y, Bearse MA, Jr., Schneck ME, Barez S, Jacobsen CH, Adams AJ. Multifocal electroretinogram delays predict sites of subsequent diabetic retinopathy. Invest Ophthalmol Vis Sci 2004; 45(3):948-954.

(218) Ohshima A, Hasegawa S, Takada R, Takagi M, Abe H. Multifocal electroretinograms in patients with branch retinal artery occlusion. Jpn J Ophthalmol 2001; 45(5):516-522.

(219) Dolan FM, Parks S, Keating D, Dutton GN, Evans AL. Multifocal electroretinographic features of central retinal vein occlusion. Invest Ophthalmol Vis Sci 2003; 44(11):4954-4959.

(220) Greenstein VC, Holopigian K, Seiple W, Carr RE, Hood DC. Atypical multifocal ERG responses in patients with diseases affecting the photoreceptors. Vision Res 2004; 44(25):2867-2874.

(221) Jurklies B, Weismann M, Husing J, Sutter EE, Bornfeld N. Monitoring retinal function in neovascular maculopathy using multifocal electroretinography - early and long-term correlation with clinical findings. Graefes Arch Clin Exp Ophthalmol 2002; 240(4):244-264.

(222) Wildberger H, Niemeyer G, Junghardt A. Multifocal electroretinogram (mfERG) in a family with occult macular dystrophy (OMD). Klin Monatsbl Augenheilkd 2003; 220(3):111-115.

(223) Scholl HP, Schuster AM, Vonthein R, Zrenner E. Mapping of retinal function in Best macular dystrophy using multifocal electroretinography. Vision Res 2002; 42(8):1053-1061.

(224) Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. Epilepsia 1997; 38(8):859-880.

(225) Cohen JA, Fisher RS, Brigell MG, Peyster RG, Sze G. The potential for vigabatrin-induced intramyelinic edema in humans. Epilepsia 2000; 41(2):148-157.

(226) Lawrenson JG, Kelly C, Lawrenson AL, Birch J. Acquired colour vision deficiency in patients receiving digoxin maintenance therapy. Br J Ophthalmol 2002; 86(11):1259-1261.

(227) Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 1998; 39(1):81-88.

(228) Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119(7):1050-1058.

(229) Fechtner RD, Khouri AS, Figueroa E, Ramirez M, Federico M, Dewey SL et al. Short-term treatment of cocaine and/or methamphetamine abuse with vigabatrin: ocular safety pilot results. Arch Ophthalmol 2006; 124(9):1257-1262.