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THE EFFECTIVENESS OF LAMOTRIGINE IN THE TREATMENT OF  
PHOTOSENSITIVE EPILEPSY

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Doctor of Philosophy

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The University of Aston in Birmingham

The effectiveness of lamotrigine in the treatment of photosensitive epilepsy

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PhD

2002

Photosensitive epilepsy and associated pattern sensitivity are more prevalent in females and are usually treated with sodium valproate. Sodium valproate has an adverse effect profile, which particularly affects females, including teratogenicity, association with the polycystic ovary syndrome and weight gain. It would be useful therefore if an alternative treatment for photosensitive epilepsy could be found.

The principle aim of this study was to investigate the effectiveness of lamotrigine in the treatment of photosensitive epilepsy in adults and children. Patients were either drug-naïve, commencing lamotrigine therapy or were transferring from other antiepileptic drugs to lamotrigine (primarily sodium valproate) due to lack of response, adverse effects or desired pregnancy.

The photoparoxysmal response in the electroencephalograph was used as the primary measure of photo and pattern sensitivity. In addition the effects of lamotrigine on occipital spikes and normal responses in the EEG to visual stimuli were investigated. Secondary measures also included the resting EEG, seizures, body mass index, menstrual function, mood and cognitive function.

The results suggest that in adult patients lamotrigine is efficacious in the treatment of photosensitive epilepsy, although it appears inferior to sodium valproate. Lamotrigine does however have a more favourable adverse effect profile than valproate. The results indicate that lamotrigine therapy is suitable for photosensitive epilepsy in women of childbearing age or in patients experiencing unacceptable adverse effects with valproate therapy. Patients are more likely to respond to lamotrigine treatment if they present with sensitivity to a limited number of frequencies.

Lamotrigine does not seem to be as efficacious in the treatment of children, although again it may be considered a second line drug if the child does not respond to or will not tolerate sodium valproate.

**KEYWORDS:** Photosensitive Epilepsy, Lamotrigine, Treatment, Pattern Sensitivity

of the patients

and their students

and their students

and their students

**For Nancy and Betty**



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## **Chapter 1 Photosensitive epilepsy**

Epilepsy is the most common serious central nervous system (CNS) disorder with an incidence of 50 in 100,000 (Goodridge and Shorvon, 1983). It was defined by Hughlings Jackson in 1873 as "the tendency for occasional, sudden, extensive, rapid and local discharge of grey matter". This discharge is an abnormal brain reaction, which may involve the brain in its entirety or only part of the brain, and depending on the areas of the brain involved, may also have clinical accompaniment. A more recent definition is that of Leonard who described epilepsy as "a group of disorders that are characterised by sudden and transient episodes (seizures) of motor (convulsions), sensory, autonomous or psychic origin" (Leonard, 1997). This definition illustrates that the generic term "epilepsy" encompasses a wide range of specific disorders, with a variety of causes and clinical manifestations.

Approximately 5% of the population have a lowered convulsive threshold, which can be genetically predetermined or lowered as a result of brain damage, metabolic or physiological changes in function, some drugs or stress leading to the occurrence of seizures (Betts, 1998). On the basis of aetiology there are two broad groups: primary/idiopathic epilepsies and secondary/symptomatic epilepsies. In the primary epilepsies there is no known cause for the disorder although many appear to be genetically predetermined by complex inheritance. Figures suggest that 60% of cases are idiopathic (Betts, 1998).

### **1.1.1 Classification of epilepsy**

Epilepsy can be classified in terms of the type of seizure and in terms of the type of epilepsy/epileptic syndrome. As in all disorders it is difficult to create a complete empirical classification but attempts have been made to provide a framework from which experts can work (Porter, 1982). By classifying seizure types the physician is able to determine a diagnosis and aetiology and therefore more effectively treat the patient.

Fundamentally seizures are divided into two main groups; generalised and partial seizures. In partial seizures there is clinical and/or electroencephalographic evidence of a localised onset. In generalised seizures there is no evidence of localised onset. This may be due to a multifocal origin of the seizure or due to the fact that a localised onset cannot be determined by the current technology used to assess the seizure (Porter, 1982). Table 1.1 details the classification of seizures currently used in medical practice.

*Table 1.1 International classification of epileptic seizures from the Commission on Classification and Terminology of the International League Against Epilepsy 1981*



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Based on the classification of seizures epilepsy is then divided into a similar classification, table 1.2 details this.

*Table 1.2 International classification of epilepsies and epileptic syndromes and related seizure disorders. From Hopkins and Shorvon, 1995*



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### 1.1.1 Mechanisms of partial and generalised epilepsy

In epilepsy neuronal activity can be described as being hypersynchronous, autonomous and increased, coupled with a disorganisation of the normal rhythms of the brain. The initiation of epileptic events commences with a sudden brief depolarisation of the cell membrane, termed the paroxysmal depolarising shift (PDS) (Matsumoto and Marsan, 1964). The neuronal resting potential rises above threshold for 10-50 times the duration of a normal action potential (Bleck and Klawans, 1990). It is thought that the PDS represents a normal postsynaptic response to hyperactivity within excitatory circuits (Connors and Gutnick, 1984). Indeed cells which produce PDSs can also produce normal excitatory postsynaptic potentials (EPSPs) (Schwartzkroin and Wyler, 1980), suggesting that they are not abnormal, but may act in an abnormal manner depending on thresholds.

The PDS is produced by alterations to either the cell's own biophysical properties or by abnormal synaptic input, such as altered ionic conductance (Bleck and Klawans, 1990). The PDS is followed by an afterhyperpolarisation (AHP), due to an influx of calcium ions ( $\text{Ca}^{2+}$ ) which opens the potassium channel (Dichter and Ayala, 1987). This AHP limits the duration of interictal discharges (Mutani et al, 1995). However if there is a failure of  $\text{Ca}^{2+}$  input then the PDS develops into an ictal discharge. The AHP disappears and is replaced by a long sustained depolarisation with burst firing of the neurons (Mutani et al, 1995). Burst firing is the term used for the volley of high-frequency impulses or action potentials (700-1000 per second), also termed "sustained repetitive firing" (SRF) (Ward, 1969). Further neurons may then begin to fire in synchrony through excitatory synaptic mechanisms of sodium ions ( $\text{Na}^+$ ) pouring into the neurone due to the sodium channel opening rapidly after the depolarisation of the neuronal membrane (Schwartzkroin, 1993). This then produces neurotransmitter and receptor changes in both the surrounding area and in areas which receive inputs from these cells.

Lockard suggests that within an epileptic focus there is a collection of what she terms group I cells or epileptogenic cells which are constantly firing in epileptic mode i.e. burstfiring - high frequency action potentials (Lockard, 1980). These cells, sometimes

referred to as pacemaker or bursting cells, are surrounded by group II neurons which either fire in a normal manner or in epileptogenic mode. If these group II cells also engage in the epileptogenic firing seen in the pacemaker cells, then seizure propagation occurs and the epileptogenic activity spreads to normal cells. The primary epileptogenic focus (i.e. the pacemaker cells), from which the depolarisation originated, can induce secondary epileptogenic foci (i.e. group II cells) in other areas via synaptic links, which can eventually lead to propagation over all the cortical and subcortical structures (i.e. generalisation over the entire brain).

The origin of the depolarisation shift which initiates these events is in the hyperexcitability of the original pacemaker cells. There have been various explanations put forward to explain this increased excitability. Raisman and Field suggest that the increased excitability is a result of new synapse formation (Raisman and Field, 1973), also termed sprouting (Chapman and Meldrum, 1991) following damage to existing synaptic connections (such as that resulting from birth assault, head injury, etc). Their theory is based on experimental studies showing the formation of new dendritic spines following severance of hypothalamic-hippocampic connections. They suggested that the new synaptic connections receive neurotransmitters that normally would not be received, resulting in abnormal excitation. These new synaptic connections may also serve to provide an excitatory feedback system (Chapman and Meldrum, 1991) allowing the continuation of excessive excitation.

Post-mortem studies in humans have shown that abnormal sprouting of the mossy fibre system to the hippocampus can be found in some patients with epilepsy (Sutula et al, 1989). Pedley suggests that other alterations to dendrites may be the cause of the increased excitability displayed by neurons in epilepsy (Pedley, 1984). He proposes that changes to dendritic morphology, such as regrowth after damage, may affect the density of ion channels and therefore alter the conductance of excitatory or inhibitory signals, i.e. more/less input to ion channels. Alternatively neuronal shrinkage may result in a facilitation of the carriage of depolarisation to the soma (Pedley, 1984).

Other authors have focused on defective ion channels as the basis of increased neuronal excitability. Gumnit suggested that glial mechanisms may be impaired and are thus unable to deal adequately with excessive potassium leading to increased excitation within the neurons (Gumnit, 1979). However, Glotzner showed that glia in an epileptic focus were actually more effective at potassium removal, which would suggest less excitability (Glotzner, 1973). In vivo epileptic activity can be evoked in normal neurons with an inward current of calcium ions (Llinàs and Jahnsen, 1982) and spikes may be produced in dendrites of hippocampal and neocortical pyramidal cells with an increase of calcium conductance following a strong depolarisation (Schwartzkroin and Wyler 1980). This suggests that defective calcium channels may play a major role in epileptogenesis. Indeed if  $\text{Ca}^{2+}$  input falls, sustained depolarisation occurs which results in burst firing.

Similar theories involving irregularities of sodium ion channels have also been put forward (Schwartzkroin and Prince, 1977) since when sodium ions enter the neurone there is again an increase in burst firing. Indeed recent genetic discoveries (Cooper and Jan, 1999) have pointed towards mutations in ion gates particularly those involving sodium. Seizure activity itself can also cause changes in the neurons involved such as cell death (due to an influx of calcium ions as a result of excessive glutamate release), loss of fibres, disorganisation of synapses, and sprouting of fibres following loss creating secondary changes in neuronal excitability (Meldrum, 1994). These changes may offer an explanation of how seizures may become self-reinforcing with increasing numbers of seizures leading to an increased risk of status epilepticus.

It has also been suggested that increased neuronal excitability is the result of some endogenous epileptogenic compound found in the brain of which individuals with epilepsy have higher levels. Although no such compound has been named candidates such as tetrahydroisoquinolines, beta-carbolines and quinolinic acid have all been suggested due to their convulsant and excitotoxic properties. Unfortunately although this is an interesting theory it is somewhat lacking in evidence in the literature.

Propagation of this abnormal activity can be seen as a result of a failure of inhibition. Inhibitory pathways within the central nervous system (CNS) are based upon two neurophysiological mechanisms: presynaptic inhibition and postsynaptic inhibition. Presynaptic inhibition acts on excitatory fibres and has an indirect effect on neurons (which is most evident in the lower levels of the CNS and in the peripheral nervous system (PNS)). Postsynaptic inhibition acts via the hyperpolarisation of the postsynaptic membrane (evident in higher CNS levels). Propagation of seizure activity is likely, therefore, to be due to a breakdown of these mechanisms. Again it is not known why these mechanisms break down but it is probably due to damage to/alteration of function in the synapses.

Both pre and postsynaptic inhibition are mediated by the inhibitory neurotransmitters: gamma-aminobutyric acid (GABA), glycine and possibly by endogenous benzodiazepines. Therefore any impairment of these substances would lead to a breakdown of normal inhibition and a consequent increase in the tendency of the abnormal bursting behaviour to spread (Andersen and Gjerstad, 1981). Unfortunately this theory is again lacking in evidence. This breakdown of normal inhibition may be due to a genetic predisposition or the presence of some form of epileptogenic lesion, thus lowering the excitatory threshold.

In the partial epilepsies the mechanisms work as described above. The PDS of the resting membrane potential in a group of epileptic neurons triggers a burst of action potentials which become synchronous due to an imbalance in endogenous neurotransmitters which modulate the response (Smith et al, 1998). The neurons in this epileptic focus exhibit this PDS whilst the peripheral neurons only produce hyperpolarisation and therefore prevent the discharge from spreading (Ure and Perassolo, 2000)

In generalised epilepsies models suggest that the mechanisms differ from the partial epilepsies. There is an assumption that a functional anatomical system in the rostral brain stem and diencephalon exerts electrical influence over the entire cerebral cortex (Schmidt and Wilder, 1968). Indeed seizures seem to involve thalamocortical circuits which

alternate between an inhibitory phase and an excitatory phase (Ure and Perassolo, 2000). Glutamate seem to mediate the excitatory phase and GABA<sub>B</sub> the inhibitory phase. Suppression of this inhibition promotes the transition from non-convulsive generalised discharges to convulsive generalised discharges (Mutani et al, 1995). There is some evidence that this is mediated via calcium T channels found abundantly in neurons in the thalamus, although discussion of the precise action is beyond the scope of this chapter.

## **1.2 Reflex epilepsy**

In the reflex epilepsies the seizures experienced are triggered by a specific stimuli. Estimates suggest that 5% of people with epilepsy experience reflex seizures (Servet et al, 1962). The seizures may be simple reflex seizures triggered by relatively simple stimuli such as flashing lights in photosensitive epilepsy or repetitive tones in audiogenic epilepsy. Alternatively the stimuli may be more complex as in reading epilepsy (Christie et al, 1988), eating epilepsy and in the case of seizures induced by thinking (Wilkins et al, 1982). In these more complex reflex seizures the trigger is either the integration of higher cortical function or the actual anticipation/psychological response to the precipitant. This suggests that the seizures may be a conditioned response and in some cases this is indeed true and patients may respond to therapy involving conditioning (Dreifuss, 1998).

Reflex seizures can also be divided into generalised and partial seizures. Table 1.3 lists the reflex seizures in their respective categories. The mechanisms of reflex seizures can be complex and involve distinct areas of the brain associated with the processing of the specific trigger stimuli or, as in complex reflex seizures, areas of the brain associated with integration of the sensory modalities. It is beyond the scope of this chapter to discuss all these mechanisms but the specific mechanisms of visually induced seizures will be discussed later.

Table 1.3: Summary of reflex seizures

	Generalised seizures	Partial seizures
Trigger	<ul style="list-style-type: none"> <li>• Light stimuli</li> <li>• Thinking and decision making</li> </ul>	<ul style="list-style-type: none"> <li>• Startle</li> <li>• Somatosensory stimulation (in the absence of startle)</li> <li>• Proprioception</li> <li>• Music, sound or voice</li> <li>• Hot water immersion</li> <li>• Eating</li> <li>• Reading and other language functions (including primary reading epilepsy)</li> </ul>

### 1.3 Photosensitive epilepsy

Photosensitive epilepsy (PSE) is a form of epilepsy characterised by reflex seizures in response to visual stimulation, the most common environmental triggers being the television, sunlight and fluorescent lighting (Harding and Jeavons, 1994). Estimates of the incidence of PSE within the epileptic population vary between 2 and 5%. (Harding and Jeavons 1994) The incidence of PSE within the normal population is approximately 1 in 10,000 (Harding and Jeavons, 1994). The condition is age and sex dependent with an increased incidence in females, the female to male ratio being quoted at between 1.5-2:1, and the most frequent age of onset is between 12 and 18 years (Harding and Jeavons, 1994). Pattern sensitivity is closely linked to photosensitivity, the majority of patients who are photosensitive are also pattern sensitive (i.e. have reflex seizures in response to particular patterns, generally of geometric form), although some people demonstrate pattern sensitivity and do not have epilepsy nor demonstrate photosensitivity.

Photo and pattern sensitivity are examples of secondary generalised epilepsy. The most common seizure induced by photic or pattern stimulation are tonic-clonic or absence seizures. Often photosensitive and pattern sensitive patients also experience spontaneous seizures. The underlying mechanism of PSE is unknown although it is assumed that it is a manifestation of inhibitory failure in the visual cortex. On the EEG photosensitivity is

characterised by a distinct response to intermittent photic stimulation (IPS), the photoparoxysmal response (PPR), which consists of generalised spike and wave activity or slow wave activity.

### **1.3.1 Definition of terms**

Before discussing photosensitive epilepsy in more detail it is first necessary to define the terms used in the literature, which will be included in this thesis. The term photosensitivity denotes the presence of EEG abnormality (the specific types of which will be discussed later) in response to intermittent photic stimulation. Pattern sensitivity similarly is defined by EEG abnormality to presentation of a patterned stimulus (Jeavons, 1985). In photosensitive epilepsy the patient has seizures induced by visual stimulation (e.g. flashing lights, sunlight flickering through trees), which may also be patterned in nature i.e. patterned sensitive epilepsy, with triggers such as escalator treads.

Pure photo/pattern sensitive epilepsy is diagnosed when the patient only has seizures in response to visual stimuli. Epilepsy with photo/pattern sensitivity is diagnosed when the patient has spontaneous seizures and additionally experiences visually induced seizures and/or demonstrates abnormality on the EEG to IPS or pattern stimulation.

### **1.3.2 Incidence of photosensitive epilepsy**

The prevalence of photosensitivity in patients with epilepsy is about 4-5% (Aziz et al, 1989, Binnie and Jeavons, 1992, Harding, 1994). The prevalence is age dependent with reports of 1 in 10,000 in the general population (Harding, 1980, Jeavons, 1982) rising to 1 in 4,000 in the adolescent population (Harding, 1980, Jeavons, 1982). More conservative reports of incidence have been made with figures of 1.1 in 100,000 in the general population and 5.7 in 100,000 in the age range of 7-9 years (Quirk et al, 1995a). However the criteria for the diagnosis of photosensitivity was stricter in the latter study. Furthermore a diagnosis of pattern sensitivity was not included and the methods of photic stimulation were not standardised throughout the centres involved. The prevalence of



photosensitivity is at its greatest within the ages of 10-25 years (Kasteleijn-Nolst Trenité, 1989).

The mean age of onset has been reported as 8 years (Campanille et al, 1995, Kasteleijn-Nolst Trenité, 1989) and 14 years (Jeavons, 1982, Jeavons, 1985, Harding, 1994). Gerken reports that two thirds of patients display symptoms before the age of 6 years (Gerken, 1969) and other studies suggest that the first seizure occurs before the age of 20 years in 80% (Jeavons, 1982) or 90% (Harding, 1994) of patients. Binnie and Jeavons point out that photosensitivity is often diagnosed around 12-14 years but a clinical history taken from the patient will usually reveal that symptoms have been present from an earlier age (Binnie and Jeavons, 1992).

Photosensitivity tends to remain in untreated patients as they mature with 63% of patients still showing evidence of photosensitivity at 14 years follow up from age of onset (Harding et al, 1997). Although there is some evidence that abnormalities of the EEG may change with age, with a decrease in the evocation of generalised abnormalities to IPS (Waltz et al, 1992), and photosensitivity does disappear by the third decade in 25% of patients (Harding et al, 1997).

The mean age of onset differs with gender, with females presenting earlier at 11.8 years and males at 14.9 years (Aziz et al, 1989). Indeed PSE is more common in females with a ratio of 2:1 being reported by many researchers (Gerken, 1969, Jeavons, 1982, Jeavons, 1985, Kasteleijn-Nolst Trenité, 1989, Binnie and Jeavons, 1992, Harding, 1994 and Quirk et al, 1995a). Females also show a greater sensitivity range (the number of frequencies in IPS which evoke EEG abnormalities in IPS) which is independent of age, suggesting genetic mechanisms which will be discussed in further detail later.

In patients presenting with photosensitivity, pure photosensitive epilepsy (i.e. no spontaneous seizures) occurs in 40% of patients whereas epilepsy with photosensitivity (i.e. visually induced and spontaneous seizures) occurs in 60% of patients (Kasteleijn-Nolst Trenité, 1989).

### **1.3.3 Seizure types**

The seizures occurring in both pure photosensitive epilepsy and epilepsy with photo/pattern sensitivity are predominately generalised (Kasteleijn-Nolst Trenité, 1989). Some partial seizures may occur but are uncommon (Jeavons, 1985) with only 2.8% displaying focal/partial seizures (Harding and Jeavons, 1994) although recent work suggests that photically induced seizures could be regarded as partial seizures with secondary generalisation in some cases (Hennessey and Binnie, 2000). Aziz and colleagues reported that 44.4% of 81 patients displayed primary generalised tonic-clonic seizures and 36.6% displayed secondary generalised seizures (Aziz et al, 1989).

Tonic-clonic seizures are the most common seizure type reported in PSE with absences and myoclonic seizures also occurring (Jeavons, 1985, Kasteleijn-Nolst Trenité, 1989, Harding, 1994). In Quirk and colleagues' multicentered study out of 90% of all newly diagnosed photosensitive patients whose seizures could be classified 68% had generalised seizures, 11% had absence seizures, 8% had myoclonic seizures and 2% had partial seizures (Quirk et al, 1995b).

### **1.3.4 Seizure precipitants**

Seizures can be induced through a variety of environmental visual stimuli. Common seizure triggers reported include sunlight flickering through trees or reflecting off water, fluorescent lighting (particularly if faulty) and strobe lighting (Hess et al, 1974, Jeavons, 1982, Kasteleijn-Nolst Trenité, 1989). Patterned stimuli may also induce seizures in patients who are pattern sensitive, although this occurs in a reduced number of patients with estimates ranging from 11% (Kasteleijn-Nolst Trenité, 1989) to 20% (Binnie and Jeavons, 1992). Patterned stimuli are more likely to evoke seizures if they are high contrast and precipitants include escalator steps, window blinds and striped materials/wallpaper (Jeavons, 1982, Kasteleijn-Nolst Trenité, 1989).

The most common environmental visual precipitant is the television (Zifkin and Kasteleijn-Nolst Trenité, 2000). Reports suggest the TV elicits seizures in 60% (Kasteleijn-Nolst Trenité, 1989, Harding, 1994) to 87% (Brinciotti et al, 1994) of patients, particularly if the patient is watching it at a close distance (less than 1 metre). It appears that the way in which the picture is made up on the screen accounts for the large proportion of patients displaying sensitivity to the TV. The television has a screen flicker of 50Hz in Europe (60Hz in other countries) which is created as the picture is being scanned. At close viewing distances a flicker of half this frequency (25Hz) can be resolved. As will be discussed later this temporal frequency is highly epileptogenic. 100Hz televisions do not pose as great a risk and 92% of patients who displayed abnormalities on the EEG to a 50Hz TV showed a reduction or abolition of their sensitivity when viewing the same material on a 100Hz TV (Fylan and Harding, 1997).

Associated with the television are video games, which also induce seizures with a combination of the facts that they are played through the television and that they often display high contrast patterned material (Harding et al, 1994, Quirk et al, 1995b, Badinand-Hubert et al, 1998). These games are often played for an extended period of time, introducing another provoking factor; fatigue, which increases the likelihood of a seizure being provoked (Aziz et al, 1989).

#### **1.4 Pattern sensitivity**

Pattern sensitivity is closely linked to photosensitivity with about half of photosensitive patients also showing EEG abnormalities to high contrast patterns (Jeavons, 1982), usually stripes (Zifkin and Kasteleijn-Nolst Trenité, 2000). Some patients only display pattern sensitivity but this is rare and the disorders are probably a continuum (Harding, 1994). Brinciotti and colleagues studied 67 patients presenting with visually induced seizures; 67.2% in total were sensitive to patterned stimuli (Brinciotti et al, 1994). Fifty one percent were sensitive to both photic and pattern stimulation, 33.3% were only sensitive to photic stimulation and 16% were only sensitive to pattern stimulation. In the 16% that were only sensitive to pattern stimulation focal abnormalities were more

common. For all patients the TV was the most common seizure precipitant (Brinciotti et al, 1994). Kasteleijn-Nolst Trenité found 19% of patients with visually induced seizures were sensitive to pattern stimulation only and patterned stimuli evoked abnormalities in 54% of those patients displaying photosensitivity (Kasteleijn-Nolst Trenité, 1989). This lower figure quoted in comparison to the Brinciotti study is probably due to differences in pattern stimulation with the Brinciotti study using a more provocative reversing patterned stimulus. Interestingly there was no difference in the sensitivity ranges in the pattern sensitive and non-pattern sensitive patients (Kasteleijn-Nolst Trenité, 1989). However Brinciotti et al found that the patients who were not sensitive to pattern had a lower sensitivity range than those who were (Brinciotti et al, 1994). This suggests that patients who display pattern sensitivity have a more excitable visual cortex than those who do not.

### **1.5 Mechanisms of photo and pattern sensitivity**

Photosensitive epilepsy appears to be purely biological as opposed to being a psychological or acquired disorder, with evidence of genetic predetermination, although inheritance appears complex (Doose and Gerken, 1973). There are close links between photosensitivity and occipital spikes, a phenomenon that represents inhibitory failure in the visual cortex. It has been suggested that dopamine and GABA may play a fundamental role in photosensitivity. Structurally single-photon-emission-computed-tomography (SPECT) scans have suggested abnormal cerebral perfusion in frontal and parietal regions of PSE patients (Kapucu et al, 1996), whereas functional magnetic resonance imaging (fMRI) studies have suggested increased vascular reactivity in the occipital cortex (Hill et al, 1999). Both studies suggest increased excitability in these areas.

#### **1.5.1 Genetics**

There appears to be a strong genetic component to photosensitive epilepsy with differences in the prevalence depending on race. In India the prevalence has been reported at 0.6% (Saleem et al, 1994) and in Africa 1.6% (Danesi and Oni, 1983). It was

originally suggested that these differences in the prevalence compared to the Western population may be due to the amount of sunlight in these countries and that the occurrence of photoparoxysmal responses may be diminished due to increased sunlight. However a study in Zimbabwe investigated the relationship between PPRs, sunlight and race and found that there was no variation in PPRs with the mean monthly sunshine duration but the prevalence of PPRs did vary with race. In whites it was 1.5%, 1.18% in Asians and 0.36% in coloured and 0.09% in blacks (Adamolekun et al, 1998). A similar study in Namibia also found a more extensive difference in the prevalence of PPRs with race, the prevalence being 0.4% in blacks, 4.2% in mixed race and 5.2% in whites, clearly indicating genetic rather than environmental factors are involved (De Graaf, 1992).

It is clear from talking to photosensitive patients that many have a family history of epilepsy with reports varying in the literature from 8% (Jeavons, 1982), 10% (Harding, 1994) 14% (Aziz et al, 1989) 21% (Kasteleijn-Nolst Trenité, 1989), 43% (Campanille et al, 1995) 45% (Brinciotti et al, 1994) to 51% (Harding et al, 1997). Obviously there is a large range reported as family history relies on patient reports which may be inaccurate. Also a family member may grow out of their epilepsy but careful questioning may reveal a dislike of lights when they were young which could suggest photosensitivity being present at an earlier age (Jeavons, 1982).

Generally first degree relatives are at the greatest risk of also having photosensitivity, this risk diminishing with genetic distance (Kasteleijn-Nolst Trenité, 1989). Baier and Doose found EEG abnormalities in 23% of siblings of photosensitives with siblings of photosensitive parents being at higher risk (Baier and Doose, 1987). In a study of 135 patients and 371 relatives Waltz and colleagues found a 39% incidence of abnormalities to visual stimuli in first degree relatives if they had epilepsy and 44% incidence if they did not. The incidence of abnormalities to visual stimuli was 15% in the parents of those who had epilepsy and 18% in those who did not (Waltz et al, 1992).

It appears inheritance is complex and there may be many types of abnormal response to visual stimuli in one family. Herrick and his colleagues found that in 11 siblings two had seizures in front of the television, all with generalised spike and wave abnormalities on the EEG. A further sibling had generalised spike and wave activity in their EEG but had not experienced any seizures. The mother and 23 other siblings displayed occipital spikes in response to IPS (Herrick et al, 1975). Waltz and Stephani suggest that the major determinant of photoparoxysmal responses in siblings of photosensitive patients is the presence of PPRs in their parents EEGs with 50% of siblings demonstrating photosensitivity if one parent was also photosensitive and only 15% of siblings displaying PPRs if both parents were not photosensitive. They conclude that this suggests autosomal-dominant transmission of photosensitive epilepsy (Waltz and Stephani, 2000).

### **1.5.2 Occipital Spikes**

Occipital spikes (OS) appear to be associated with photosensitive epilepsy, as 65% of photosensitive patients exhibit occipital spikes in their resting EEGs and OS are present in visual evoked potentials from patients who are photosensitive (Harding, 1994). During intermittent photic stimulation occipital spikes are frequently seen as a precursor to a photoparoxysmal response. Both phenomena are genetically predetermined, with 40% of siblings of PSE patients also exhibiting photosensitivity (Doose and Gerken, 1973) and occipital spikes are frequently found in EEGs of relatives of PSE patients (Herrick et al, 1975).

It has been suggested that OS are representative of excitatory potentials resulting from impaired inhibition (Panayiotopoulos et al, 1972). These may act as a primary focus within the visual cortex, which may then develop into a secondary sub-cortical discharge and, with appropriate conditions, a clinical seizure. However occipital spikes are also found in the EEGs of people who do not have epilepsy and do not have relatives who display photosensitivity (Maheshwari and Jeavons, 1975). This could be explained by viewing OS purely as evidence of a hyperexcitable visual cortex. Under certain

circumstances (i.e. IPS), the visual cortex is stimulated enough to produce an inappropriate response (i.e. increased excitation), in those predisposed. Occipital spikes are the electrophysiological result of this lowered inhibition. Those with further decreased inhibition may then go on to develop PPRs and eventually clinical seizures.

Treatment with valproate however suggests a slightly different mechanism underlying occipital spikes than that underlying photoparoxysmal responses. Sodium valproate may abolish clinical seizures and PPRs but treatment does not abolish occipital spikes suggesting that occipital spikes and convulsive threshold are independent (Harding and Jeavons, 1994).

Experiments to determine the most provocative stimulus parameters to evoke OS and PPRs suggest that each phenomenon may be generated in a different division of the visual system. Harding and Fylan suggest that PPRs are generated by the parvocellular system and occipital spikes are generated by the magnocellular visual system (Harding and Fylan, 1999). This idea will be discussed in greater detail later in this chapter. They conclude that the fact that occipital spikes are often seen preceding a PPR is simply fortuitous. Occipital spikes may not be a focal abnormality and PPRs the result of secondary generalisation, but the two phenomena may be independent of each other and OS only appear before PPRs due to the faster processing speed of the magnocellular pathway (Harding and Fylan, 1999)

### **1.5.3 Dopamine**

Dopamine (Da) has been implicated in the genesis of photosensitivity (Quesney et al 1981). The evidence for its involvement is derived mainly from studies with apomorphine (a dopamine agonist). Apomorphine blocks photosensitivity (Quesney et al 1981) in both humans and the photosensitive baboon *PapioPapio*. From this finding Quesney and colleagues have proposed that an impairment of dopaminergic inhibition is pivotal in PSE. It is suggested that photic stimulation induces thalamocortical volleys, which then reduce the cortical release of dopamine and hence reduce cortical inhibition.

In individuals with lowered existing inhibition seizures may then result due to hyperexcitability in the cortex. In order to determine if this is the case, studies are required to determine whether in fact doperminergic inhibition is reduced by IPS in people without epilepsy. Doperminergic inhibition may then be further reduced in patients with photosensitivity. It may be that some other inhibitory mechanism has failed in photosensitivity and the further reduction in doperminergic mediated inhibition resulting from photic stimulation simply allows the expression of photoparoxysmal responses and clinical seizures. Evidence of a reduction of doperminergic terminals and receptors in patients who are photosensitive is so far lacking. Also the response to IPS in Papiopapio is a photomyoclonic response and although study of the animal has been useful in developing models of photosensitivity there are obvious differences with the mechanism generating the photoparoxysmal response in humans (Quesney et al, 1981).

#### **1.5.4 GABA**

GABA transmission has been demonstrated to be of significance in epilepsy and appears also to be involved in photosensitivity. In animals convulsants which are antagonists of GABA increase the likelihood of eliciting a photoparoxysmal response or clinical seizure in response to photic stimulation (Meldrum, 1979). These block the postsynaptic depolarising action of GABA. Unfortunately there have been no equivalent studies carried out with human photosensitivity. However seizures induced by photic stimulation and photoparoxysmal responses are seen with withdrawal from alcohol, barbiturates and benzodiazepines (Meldrum and Wilkins 1984). A relative impairment of GABA mediated inhibition is also associated with withdrawal from these substance (Meldrum and Wilkins 1984). Drugs which enhance inhibition mediated by GABA have been shown to prevent PPRs and seizures e.g. benzodiazepines, barbiturates, and GABA-transaminase inhibitors e.g. VinylGABA and sodium valproate, (Meldrum and Wilkins 1984) again implying that photosensitive epilepsy may be due to an impairment of GABAergic inhibition.



It has therefore been proposed (Meldrum and Wilkins, 1984) that the primary basis of photosensitivity is an impairment of the GABAergic inhibitory mechanism. Meldrum and Wilkins suggest that this may be more prominent in the occipital or frontorolandic cortex, thereby accounting for EEG manifestations of frontal dominance in PPRs and occipital spikes, or that it may be diffusely spread over the entire cortex. This impairment could, they state, be the result of either a biochemical abnormality (enzymes, receptors or membranes) or originate from a pathological pattern of interconnections between synapses. With this system failure photosensitivity can then be seen as a further failure of the inhibitory network under the condition of "overload". There is no evidence that excitation is abnormal or enhanced in PSE and the response may simply be due to the failure of inhibitory mechanisms (Meldrum and Wilkins, 1984). They suggest a "critical mass" of excitation at which the PPR will occur. Due to the critical mass of excitation and the lack of inhibition neurons may fire in the burst-firing manner seen in epileptic foci. If the number of these bursting neurons increases to the point where they mutually excite each other, synchronous firing is achieved, resulting in the subsequent discharge or PPR (Meldrum and Wilkins, 1984).

Gloor suggests a similar theory to that of the mechanisms behind general epileptogenesis which Meldrum and Wilkins apply to PSE. Gloor views the paroxysmal depolarisation as a normal response to excessive excitation. This coupled with a pathological impairment of inhibition leads to an increased likelihood of further paroxysmal depolarisation depending upon the neural networks firing rate and the input of excitatory stimulation to the network. If the input is large enough and affects a critical amount of neurons epileptic activity is the result. In the case of PSE, visual stimulation provides excessive excitation to the neuronal network involved, namely cells within the visual cortex. A lack of GABAergic inhibition leads to paroxysmal depolarisation further desensitising cells to any remaining inhibition, resulting in a photoparoxysmal response with an accompanying clinical seizure if the excitatory impulse is sufficient to elicit further neuronal structures (Gloor, 1979).

### 1.5.5 The visual cortex

Whatever the underlying mechanisms creating a decrease in inhibition, it is apparent that the visual cortex has a central role in the elicitation of the photoparoxysmal response. Evidence suggests that the trigger mechanism may reside in the visual cortex, more specifically in the striate cortex. Results from various studies investigating the evocative nature of patterned stimuli have suggested that the trigger mechanism involves binocular cells (Wilkins et al, 1975) which are contained in the visual cortex. Further studies (Wilkins et al 1979, Darby et al, 1986) suggest that the trigger mechanism involves complex cells in the striate cortex, as these cells are particularly sensitive to line orientation and other spatial characteristics. These cells also respond maximally to binocular stimulation (Wilkins et al, 1975), which may explain why monocular stimulation is less evocative in producing photoparoxysmal responses. These cells in the primary visual cortex process all visual input and have small receptive fields they are therefore more likely to overload as they are non specific in their response.

However electroretinogram (ERG) studies suggest that the retina may also be involved in photosensitive epilepsy (Medina and Leston, 1990, Broughton et al, 1969). The amplitude of the ERG has been shown to be increased in PSE patients, which indicates increased retinal excitability, causing abnormal synaptic input to an already compromised area in the visual cortex. This is unlikely to be the cause of photosensitivity but increased excitability in the retina may change neocortical excitability through specific afferent pathways to the striate cortex or by non-specific pathways such as the retino-geniculo-thalamic path or the retino-extrageniculate-pretectal-thalamic pathway (Crighel and Matei 1983). Panayiotopoulos and his colleagues suggests that the specific neuronal group involved in the reticulo-cortical group and that an abnormality in these neurons allows these cells to effectively become epileptic pacemakers under appropriate conditions i.e. those provided by provocative visual stimulation (Panayiotopoulos et al, 1972). Epileptiform activity appears to arise within the visual cortex, which may then become generalised due to the aforementioned lack of inhibition.

As mentioned previously a suggestion of a “critical mass” of neurons had been put forward (Meldrum and Wilkins, 1984). Essentially cortical neurons are stimulated by the visual precipitant and if a critical mass of neurons reach a threshold then an epileptiform discharge occurs (Wilkins et al, 1990). Evidence for this is available in pattern sensitivity, a small pattern in the centre of vision may have the same epileptogenic effect as a large pattern in the peripheral vision. Essentially the same neurons are not being stimulated but the same amount of neurons are stimulated (Wilkins et al, 1990). If pattern stimuli is presented to only one visual field i.e. the left or right, focal discharges in the contralateral area of the occipital region can be evoked (Wilkins et al, 1981) implying secondary generalisation. Further evidence that photosensitive epilepsy is a form of secondary generalisation is provided by drug studies. Valproate, effective in the treatment of PSE abolishes PPRs but posterior responses such as occipital spikes remain, suggesting that the drug may well be controlling the generalisation of the activity but not its initiation. It has been suggested that the triggering of epileptiform activity in PSE occurs in the striate or prestriate cortex.

Whatever the trigger mechanism involved it appears that the stimulus itself is particularly synchronous, which may explain why photosensitive epilepsy is the most common form of reflex epilepsy (Wilkins, 1986). For example flashing lights demonstrate temporal synchronicity and repetitive patterns demonstrate spatial synchronicity, this may in turn promote the synchronicity of firing in the neurons. If enough neurons are elicited then, through impaired inhibition, further neurons are recruited via synaptic pathways resulting in a generalised discharge. Indeed if a pattern repeatedly changes direction the neuronal network involved fires in synchrony as neurons are selective to one direction and not the other. If the aforementioned critical mass is then achieved an epileptiform discharge is initiated and corticothalamic relays further increase the degree of neuronal synchrony and perpetuate the spread of the discharge (Wilkins et al, 1990).

### **1.5.6 The magnocellular and parvocellular systems**

The magnocellular and parvocellular systems are divisions of the visual system. In the retina there are two different types of retinal ganglion cell; M-cells and P-cells, corresponding to the two different pathways. This separation continues in the lateral geniculate nucleus (LGN) and is also maintained in the primary visual cortex (V1), where the cells synapse in different layers.

The cells in the two systems differ in their response to visual stimuli. Magnocellular cells respond preferentially to low spatial, high temporal frequency stimuli. They are not chromatically sensitive but are sensitive to luminance contrast, saturating at low contrast. The cells in the parvocellular system respond preferentially to stimuli which are high in spatial frequency and low in temporal frequency. They are less sensitive to those in the magnocellular system to luminance contrast, and show a linear increase in activity as contrast increases. The majority of P-cells demonstrate some chromatic selectivity.

Stimuli that activate the parvocellular system tend to be more epileptogenic (Harding and Fylan, 1999) and it has been suggested that photosensitive epilepsy may be a result of a deficit in the parvocellular system. Harding and Fylan investigated the stimulus parameters required to evoke PPRs and OS. They found that photoparoxysmal responses were activated by stimuli displaying characteristics of P-cells; i.e. high contrast, chromatic, whereas occipital spikes were elicited by stimuli displaying characteristics more like the magnocellular system; i.e. low contrast, moving stimuli (magnocellular cells do not respond to stationary stimuli). They concluded that PPRs, which are deemed as a clinical indicator of PSE, are generated by the parvocellular system. Occipital spikes however are generated by the magnocellular system and should not be regarded as clinically significant (Harding and Fylan, 1999).

However Arnold Wilkins suggests that pattern sensitive epilepsy may be generated via the magnocellular system. As has been discussed previously the cells of the magnocellular system do not code for colour and pattern sensitive patients are not

sensitive to gratings with different coloured strips but are only sensitive to those with a difference in luminance. Conversely Harding and Fylan demonstrated that PPRs could not be elicited by an isochromatic cartoon with variations in luminance. When shown in colour however, abnormalities were evoked (Harding and Fylan, 1999).

Wilkins also suggests that the fact that patients are sensitive to IPS up to 60Hz indicates magnocellular involvement as cells are tuned for higher temporal resolution. He also points out that patterns which fail to fuse binocularly are less epileptogenic (Wilkins et al, 1990), again suggesting that PSE is a deficit of the magnocellular cells which are tuned for binocular disparity. The magnocellular system has lower spatial resolution than the parvocellular system and pattern sensitive patients tend to be sensitive to patterns of fairly low spatial frequencies (Wilkins et al, 1990).

There seems to be some contradictory evidence present for either systems' involvement in PSE. It may well be that photo/pattern sensitivity could involve both visual pathways, with those patients who are purely pattern sensitive having hyperexcitability concentrated in the magnocellular system and those who are sensitive to both light and pattern showing more involvement of the larger parvocellular system and therefore showing a wider range of sensitivity to visual stimuli.

### **1.5.7 Contrast gain control**

There is evidence that patients with photosensitive epilepsy may have a defect in contrast gain control. Porciatti and his colleagues have found that in patients with visually induced seizures cortical activity increases and does not saturate at higher levels of contrast, whereas it does in normal controls (Porciatti et al, 2000).

The amplitude of visual evoked potentials recorded in patients increased with increasing contrast and showed no saturation and phase was not shortened as was seen in controls. This was true for sinusoidal gratings that reversed at frequencies of 4-10Hz. At higher temporal frequencies the patients showed the same saturation as normal controls. The

authors concluded by saying that this could implicate impaired cortical contrast gain control in PSE patients (Porciatti et al, 2000)

These results may also implicate a deficit in the magnocellular system in which the cells normally saturate at low contrasts. However Harding and Fylan's work with stimulus parameters required to evoke PPRs and occipital spikes demonstrated a failure in contrast gain control within the parvocellular system with no saturation evident in PPRs, whereas normal saturation was evident in the magnocellular system with occipital spikes. Again these data appear contradictory, perhaps indicating that contrast gain control may be impaired in one or both visual systems depending on the individual patient's sensitivity.

### **1.6 Epilepsy presenting with photo and pattern sensitivity**

Photo and pattern sensitivity is most commonly found in patients with idiopathic generalised epilepsies (Frucht et al, 2000). Overall as a group 25% of patients with idiopathic generalised epilepsy (IGE) display photosensitivity (Hopkins et al, 1995). Within this group of epilepsies photosensitivity is most commonly reported in juvenile myoclonic epilepsy (JME) with reports of 17.4% (Shiraishi et al, 2001) to 50% (Panayiotopoulos et al, 1994) of patients displaying photosensitivity to IPS. Juvenile myoclonic epilepsy accounts for 5-11% of all cases of epilepsy and the mean age of onset is 10 years (Hopkins et al, 1995). Seizure presentation usually commences with absences developing into myoclonic jerks and then tonic-clonic seizures as the child ages. Flashing lights and video screens are the most common visual seizure precipitants and JME can be effectively treated with sodium valproate (Hopkins et al, 1995).

In childhood absence epilepsy 18% of patients display photosensitivity (Hopkins et al, 1995) and 10-20% of patients with juvenile absence epilepsy show abnormalities on IPS (Hopkins et al, 1995). Both of these syndromes respond to valproate or ethosuximide. Between 7.6% (Shiraishi et al, 2001) and 13% (Wolf, 1992) of patients diagnosed as having epilepsy with generalised tonic-clonic seizures on awakening are photosensitive.

Generally in the partial epilepsies the percentage of patients who are photosensitive is much lower than that of the generalised epilepsies with reports of only 0.7% of patients displaying abnormalities on IPS (Shiraishi et al, 2001). However there is a much higher proportion of photosensitives found in occipital lobe epilepsy (OLE). In occipital lobe epilepsy the resting EEG may be normal or shows spikes or spike and wave activity in occipital regions. Sometimes this epileptic activity is only seen when recording with an additional OZ electrode (Guerrini et al, 1995). Occasionally spontaneous generalised spike and wave activity is also seen in the resting EEG (Guerrini et al, 1995). Often a lesion is present in the occipital lobe but the syndrome is frequently misdiagnosed (Guerrini et al, 1995). Mean age of onset is 12 years (Guerrini et al, 1995).

Seizures are usually generalised tonic-clonic with visual hallucinations (Kaymaz and Forta 2000), blindness and visual agnosia (Yamada et al, 1999) often occurring prior to the seizure depending on where the epileptiform activity originates from in the occipital cortex. Seizures may be spontaneous but are usually visually triggered, with common precipitants being the television, video games, computer screens, flickering sunlight and rapid transition from darkness to light (Guerrini et al, 1995). Abnormalities are seen on IPS (Kaymaz and Forta, 2000) although the frequency of this varies between studies with some reporting that only 6.1% of patients are photosensitive (Shiraishi et al, 2001) whereas others suggest that all patients with occipital lobe epilepsy display photosensitivity (Guerrini et al, 1995). OLE may respond to treatment with sodium valproate or carbamazepine (Guerrini et al, 1995).

## **Chapter 2: The electroencephalograph in photosensitive epilepsy**

### **2.1 The electroencephalograph in epilepsy**

The electroencephalogram (EEG) measures the summation of the brain's electrical activity. The waveforms seen are representations of the electrical activity produced by the postsynaptic and somatic membranes within the cerebral cortex. This activity is the result of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). The EEG seen at the scalp represents a "spatial average" of electrical activity generated from millions of pyramidal cells (Pedley, 1984). If the activity of each neurone was random and independent of the surrounding neurons then the activity from each neurone would cancel out the activity from the surrounding neurons and no potentials would be recorded from the scalp. Therefore to record these potentials a number of neurons must be acting in synchrony.

The dendrites of these pyramidal cells are perpendicular to the cortex and lie parallel to each other (Pedley, 1984). The current resulting from the EPSPs and IPSPs flows across the neuronal membranes of the pyramidal cells, generating large extracellular potential fields, due to the alignment of the neurons. These potential fields can then be measured at the scalp as the EEG. (Lopes da Silva and Storm van Leeuwen, 1977). With cortical or scalp EEG recording epileptiform activity is characterised by spikes or spikes with associated slow waves. This EEG pattern can be regarded as "electrical markers" of the individual's susceptibility to seizures, with interictal EEG abnormalities being highly correlated with epilepsy (Pedley, 1984).

The spikes are representative of excitatory phenomena and are a result of excessive and synchronous neuronal firing. A spike on the EEG is a representation of dendritic depolarisation, the summation of excitatory impulses in the cell (Gloor, 1972). Extracellular microelectrode recordings demonstrate this. A massive slow depolarisation shift is seen followed by a sudden breakdown of membrane potential (hyperpolarisation) which produces bursts of axosomatic spikes (repetitive action potentials). The



summation of these spikes is the single spike seen in the cortical or scalp EEG (Kiloh et al, 1974).

The associated slow wave of the cortical or scalp EEG is the result of inhibitory phenomena and represents the relative electrical silence of somatic hyperpolarisation. The slow wave is generated by inhibitory postsynaptic potentials and appears to prevent the proceeding spike discharge of the depolarising shift from becoming repetitive and self-sustained.

Components of epileptiform EEG phenomena, (i.e. the spike and its associated slow wave) appear of negative polarity on the EEG. The spike is generated from the dendrites of the neurons which are situated towards the outside of the cortex. There is more depolarisation towards the outside of the cortex, the depths of the cortex being more positive in relation and so both phenomena appear negative on the EEG (Speckman et al, 1972).

Further electrophysiological changes are seen in association with epileptic discharges. Direct current (DC) changes appear to initiate epileptic events. Very slow shifts are evident which are negative towards the centre of the epileptogenic focus and more positive towards the outside. This appears to be a sign of depolarisation and consequentially the group of cells involved become more responsive to normal excitatory inputs hence allowing the repetitive action potentials or burst firing (Speckman et al, 1972).

## **2.2 The resting electroencephalograph in photosensitive epilepsy**

The resting EEG in patients with photosensitive epilepsy may be normal with a variety of reports in the literature suggesting that the percentage of patients with a normal EEG varies from 39% (Quirk et al, 1995a) to 60% (Aziz et al, 1989). If abnormalities are seen they may be non-specific, occurring in between 9% (Quirk et al, 1995a) and 18.8% (Aziz et al, 1989) of patients. Non specific abnormalities seen include excessive slow wave

activity and Kasteleijn-Nolst Trenité reports that photosensitives show intermingling of alpha and slow wave activity more often than patients with other types of epilepsy (Kasteleijn-Nolst Trenité, 1989). Alternatively spike and wave complexes can be seen, again the percentage of patients displaying such abnormalities varies considerable between studies. Aziz et al reported spike and wave complexes in only 21% of photosensitive patients (Aziz et al, 1989), whereas Quirk and her colleagues reported such epileptiform activity in 52% of their patients (Quirk et al, 1995a).

These spontaneous abnormalities seen in the resting EEG may be focal or generalised and are strongly associated with seizure type. Patients with focal abnormalities tend to have partial seizures and those displaying generalised abnormalities have tonic-clonic or absence seizures (Gilliam and Chiappa, 1995). Spontaneous epileptiform abnormalities in photosensitives are also significantly related to seizure occurrence. If patients demonstrate photoparoxysmal responses and spontaneous seizures they are more sensitive to monocular photic stimulation and are more likely to experience myoclonic jerks (Jeavons et al, 1966). They are also more likely to have a history of seizures (Gilliam and Chiappa, 1995) in comparison to those patients who only display abnormalities in response to photic stimulation.

### **2.3 Intermittent photic stimulation**

Intermittent photic stimulation (IPS) is a technique whereby patients are exposed to a flashing light of various temporal frequencies under controlled conditions whilst the EEG is being recorded. Generally it is performed after the resting record has been recorded and after hyperventilation has been performed. In some clinical department it is performed as part of the EEG investigation in all patients who have been referred for an EEG. It is necessary to perform IPS in all patients who are referred with a history of seizures or subjective sensations in response to visual stimuli. In some departments pattern stimulation is also carried out with the patient's EEG response being recorded in response to the presentation of pattern, usually black and white stripes. If the patient normally wears spectacles then these should be worn during IPS (Jeavons, 1982).

Stimulation should be binocular (Binnie and Jeavons, 1992) and the effects of monocular stimulation should be investigated if abnormalities are evoked (Jeavons, 1982, Harding, 1994).

### **2.3.1 Flash stimulus parameters**

During stimulation fixation should be central (Jeavons, 1982, Binnie and Jeavons, 1992, Harding, 1994), it is essential that the patient looks at the centre of the lamp as a shift of gaze to the edge will inhibit both normal and abnormal responses (Jeavons et al, 1972). A short flash should be used to avoid injury to the retina (Jeavons, 1969) and in order to evoke epileptiform responses the intensity of the light should be at least 0.4 joules, or 400nit-s per flash (Binnie et al, 1982).

The flash should be varied from 1-60 flashes per second with a separate presentation of each frequency (Harding and Jeavons, 1994). Particular attention should be paid to the frequencies of 25 and 50 flashes per seconds as these are the frequencies associated with the television (Harding and Jeavons, 1994) which is, as has been previously discussed, the most common seizure precipitant in photosensitive epilepsy. Attention should also be paid to the frequencies of 15-20 flashes per second as these are the most provocative frequencies (Binnie and Jeavons, 1992) with 92% of photosensitive patients displaying abnormal responses to the flash rate of 20 flashes per second (Jeavons et al, 1966).

A grid should be placed over the photic lamp to create a high contrast pattern over the area of illumination as this increases the probability of evoking epileptiform discharges (Jeavons, 1982, Binnie and Jeavons, 1992, Harding, 1994). Fylan and her colleagues report that diffuse IPS is a more accurate predictor of seizure control than patterned IPS (Fylan et al, 1999) so diffuse stimulation should also be performed.

Much research has been carried out on the stimulus parameters and as a result a standardised protocol had been suggested for use in clinical departments (Kasteleijn-Nolst Trenité et al, 1999). A Grass photostimulator is preferred and the lamp should be

placed 30cm away from the nasion with the patient fixating at a central point marked on the lamp. Separate trains of flashes should be delivered each being 10 seconds in duration, with the eyes open for the first five seconds and then the patient should be asked to close their eyes for the remaining five seconds. A minimum of seven seconds interval should be allowed between each train of flashes. The flash rates of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 flashes per second should be performed in succession. Then the flash rates of 60, 50, 40, 30 and 25 flashes per second should be delivered (Kasteleijn-Nolst Trenité et al, 1999). If abnormalities are evoked the stimulus should be immediately terminated to prevent a clinical seizure. Intermittent photic stimulation should then continue at the remaining flash rates to determine the patient's sensitivity range (i.e. the frequencies evoking abnormal activity).

### **2.3.2 Pattern stimulus parameters**

For pattern stimulation black and white stripes with equal width and sharp contours i.e., displaying a square wave luminance profile, are the preferred stimulus (Binnie and Wilkins, 1998). The Michelson contrast of the pattern should be more than 0.4 (Binnie and Wilkins, 1998). The spatial frequencies tested should include 1-4cpd, i.e. each stripe must subtend between 7.5 and 30 minutes of the visual arc (Wilkins et al, 1980). The probability of evoking a discharge increasing with increased angular subtense of the stimulus over the range of 2° to 48° (Binnie and Jeavons, 1992).

Luminance should be high and a greater line to width ratio is more provocative (Harding, 1994). Smaller patterns require higher levels of illumination to evoke epileptiform abnormalities than larger patterns (Wilkins et al, 1980). If the pattern is to reverse the temporal modulation of 15-20Hz is the most provocative regardless of the patterns spatial frequency (Harding, 1994). No particular orientation of the pattern is more likely to evoke epileptiform responses when considering all pattern sensitive patients as a group, however individual patients may display marked orientation selectivity (Wilkins et al, 1979).

## 2.4 Classification of responses to intermittent photic stimulation

There are four main responses to intermittent photic stimulation; photic driving occipital spikes, the photomyoclonic response and the photoparoxysmal response. Photic driving and the photomyoclonic response are generally considered as normal responses. There is some debate over the clinical significance of occipital spikes. The photoparoxysmal response is viewed as abnormal and is part of the diagnostic criteria for photosensitive epilepsy.

Two other forms of normal activity (figures 2.1 and 2.2) may also be seen in response to intermittent photic stimulation. These are large VEPs evident in the resting record, seen time locked with the stimulus, over the occipital electrodes and lambda activity, again evident over the occipital electrodes. Both of these types of activity occur with the eyes open.

*Figure 2.1: VEPs seen in the EEG, over the occipital electrodes, in response to diffuse photic stimulation at 1 flash per second*

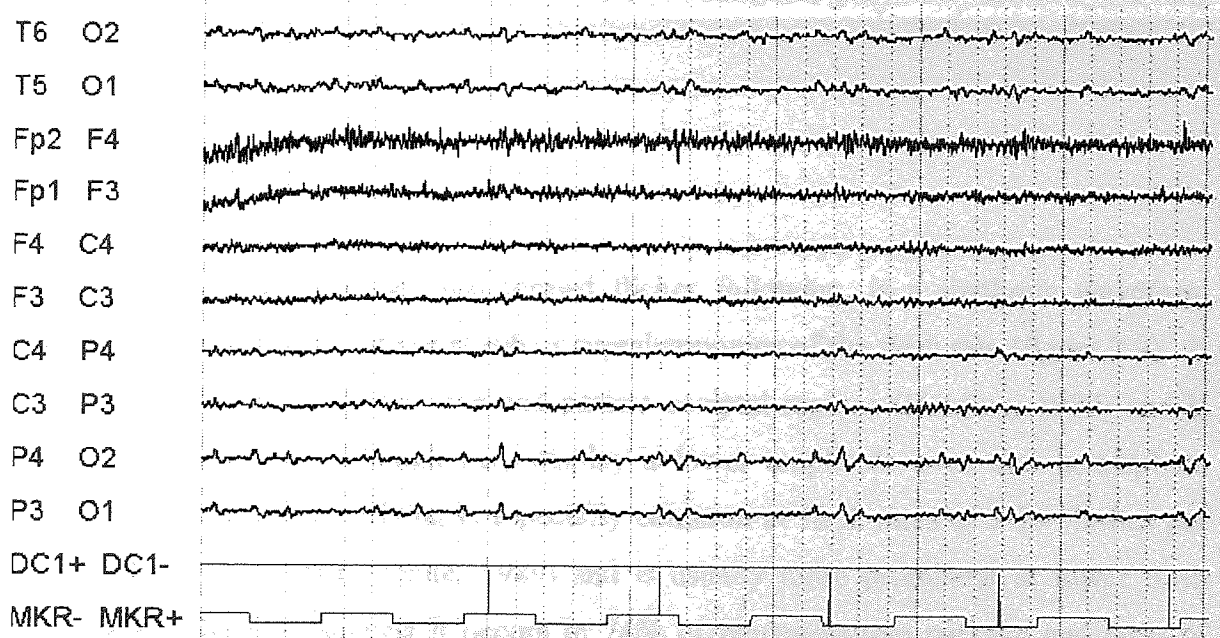
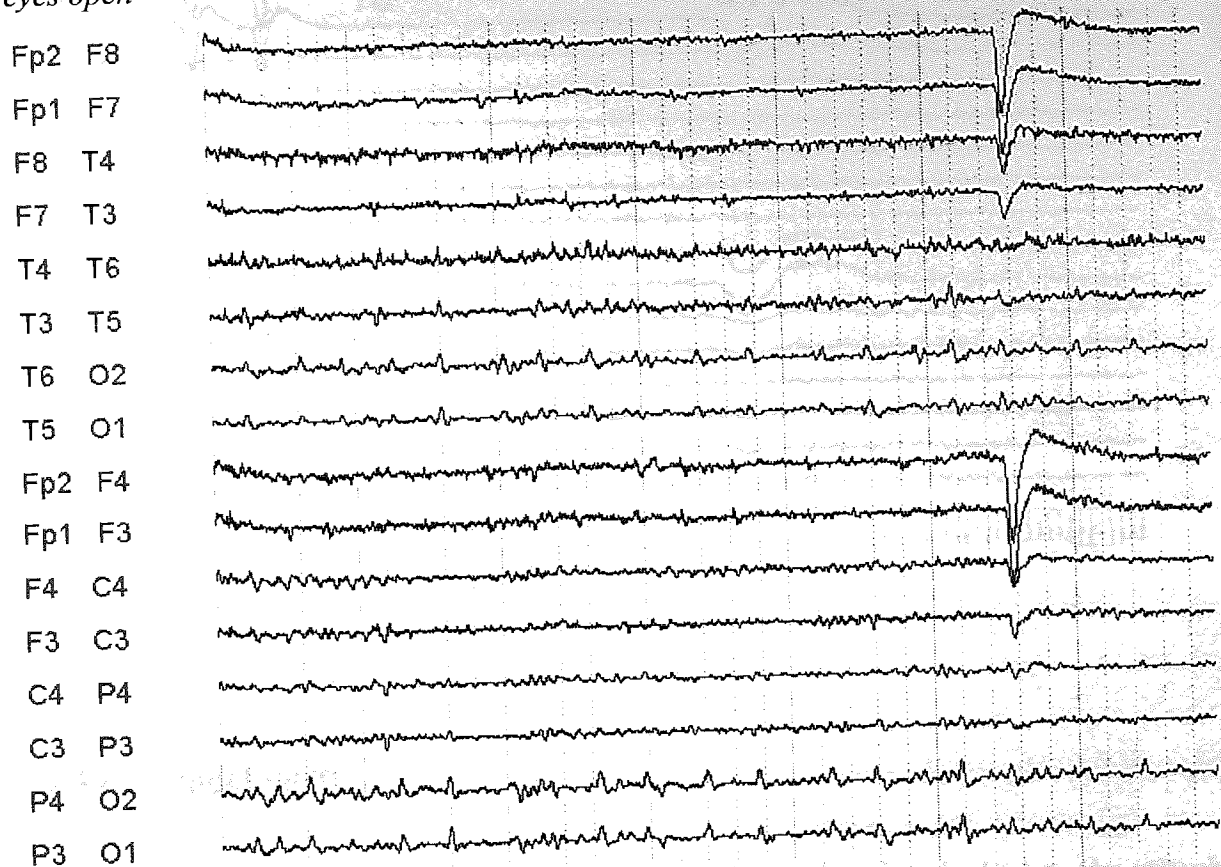




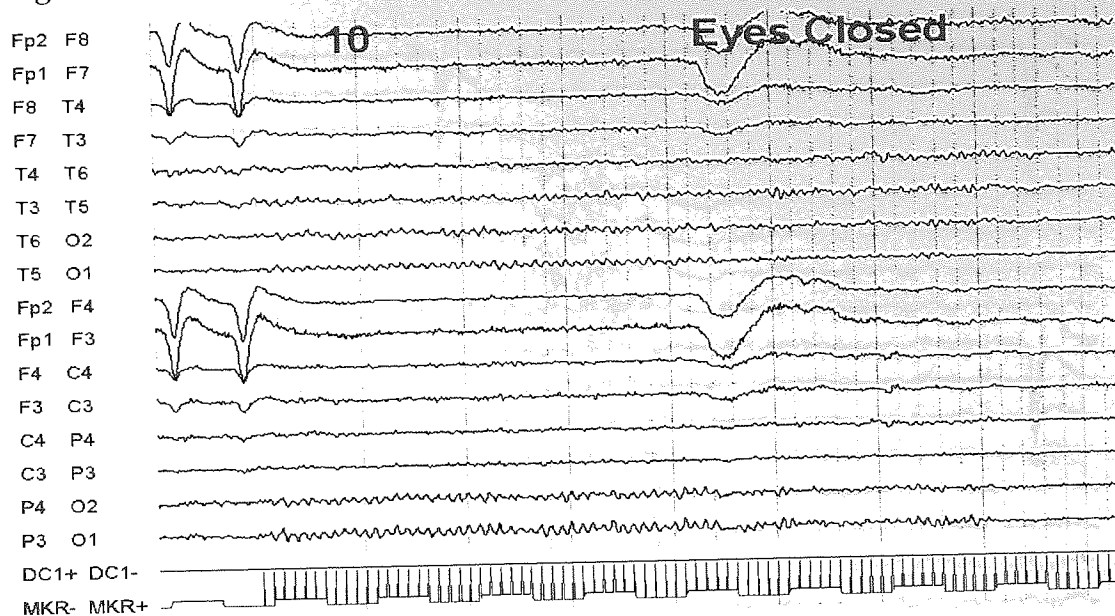
Figure 2.2: Lambda activity seen over occipital electrodes in the resting record with the eyes open



#### 2.4.1 Photic Driving

The photic driving response, also termed flicker following, is a rhythmic waveform occurring at the stimulus rate or at sub or supraharmonics of the flash rate (figure 2.3). It occurs over the occipital electrode and parieto-occipital regions (Harding, 1980) and is normally symmetrical although may display a lower amplitude over one hemisphere (Jeavons, 1982). Photic driving is especially common at flash rates of 8-20 flashes per second (Kasteleijn-Nolst Trenité, 1989) and is usually more prominent at lower flash frequencies. Reports suggest it occurs in 74% of photosensitive patients and 94% of control subjects without epilepsy (Kasteleijn-Nolst Trenité, 1989) and it is viewed as a normal response to intermittent photic stimulation (Harding, 1980).

Figure 2.3: Photic driving in response to 10 flash per second diffuse photic stimulation

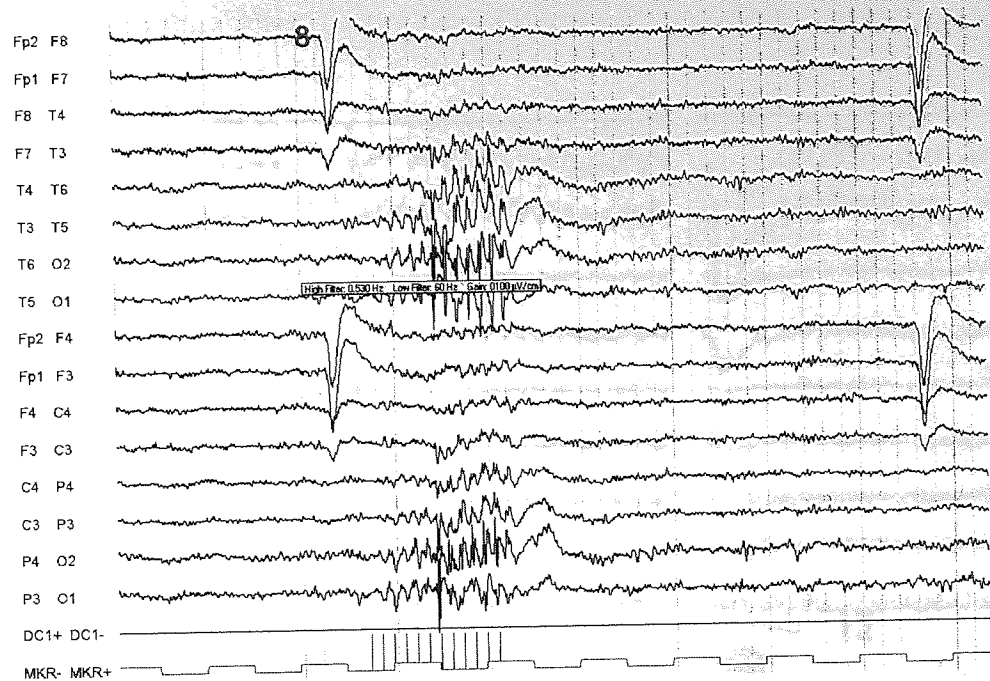


### 2.4.2 Occipital spikes

Occipital spikes occur in the occipital regions and are also time locked to the stimulus (figure 2.4). They are always electronegative to the occipital electrode (Harding, 1996). The main component is negative with small positive components immediately before and after (Panayiotopoulos et al, 1972), displaying maximal amplitude at the occipital electrodes with average reference recording (Panayiotopoulos et al, 1972). The occipital spike does not represent an exaggerated VEP as some authors have suggested, as the negative occipital spike occurs on the second positive component of the VEP (Harding and Dimitrakoudi, 1977). If monocular stimulation is performed the amplitude of the occipital spikes is reduced.

The clinical significance of occipital spikes has been debated. They may frequently act as a precursor to photoparoxysmal response (Harding, 1996). Reports suggest that 47% of patients displaying occipital spikes have epilepsy (Binnie and Jeavons, 1992), although other studies suggest 48.8% of patients with occipital spikes have epilepsy and 46.6% have no history of seizures and only 4.4% had photosensitive epilepsy (Maheshwari and

Figure 2.4 Occipital spikes, seen with some anterior spread



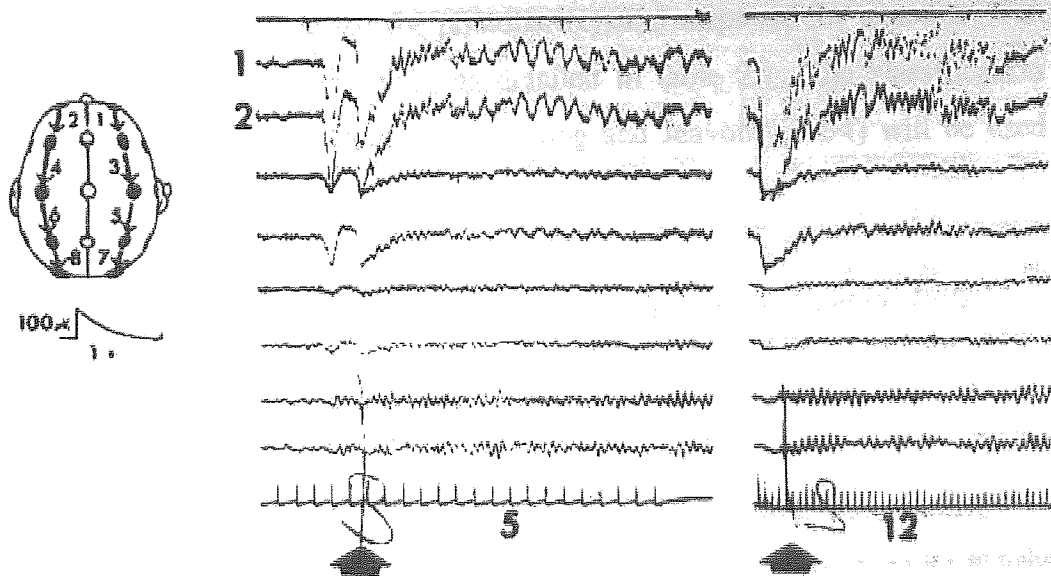
Jeavons, 1975). Now occipital spikes are not regarded as clinically significant (Jeavons, 1982, Jeavons, 1985, Kasteleijn-Nolst Trenité, 1989, Harding and Jeavons, 1994, Harding and Fylan, 1999).

### 2.4.3 The photomyoclonic response

The photomyoclonic response (PMR) consists of anterior spikes occurring at the same temporal frequency as the flash rate (Jeavons, 1982) (Figure 2.5). The spikes are associated with rhythmic action potentials in orbital and other facial muscles (Kasteleijn-Nolst Trenité, 1989) sometimes the patients shoulders may also go into spasm. The PMR occurs when the eyes are closed and is more commonly evoked if the stimulus is close to the patients eyes or it is of high intensity (Jeavons, 1982, Kasteleijn-Nolst Trenité, 1989).



Figure 2.5: The photomyoclonic response taken from Harding and Jeavons, 1994, pp74



The photomyoclonic response is not thought to be indicative of photosensitive epilepsy (Hess et al, 1974, Jeavons, 1982, Kasteleijn-Nolst Trenité, 1989, Harding, 1994). Bickford and colleagues were the first to differentiate between the photomyoclonic response which appears to have no clinical significance (Jeavons, 1969) and the photoparoxysmal response which can be regarded as evidence of convulsive tendency (Bickford et al, 1952).

#### 2.4.4 The photoparoxysmal response

The photoparoxysmal response (PPR), also termed the photoconvulsive response (PCR) in the literature, is a transient abnormality elicited by photic and pattern stimulation. There are various definitions depending on the study, (for example Quirk et al, 1995a), but generally the classic PPR has a 3Hz slow wave component (Jeavons, 1982) and activity may be regular or irregular with single or multiple spikes interspersed by the slow wave (Wilkins et al, 1980). The classic photoparoxysmal response is generalised

(Brinciotti et al, 1994), fairly symmetrical with maximal amplitude in fronto-central regions (Wilkins et al, 1980).

Various authors have classified the photoparoxysmal response for example Waltz et al, 1992 split the PPR into four types as detailed in table 2.1. The classification of the photoparoxysmal response detailed by Harding and Jeavons (1994) will be used in this study (table 2.2).

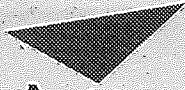
*Table 2.1: Classification of the photoparoxysmal response, Waltz et al, 1992*

<u>Type:</u>	<u>Activity:</u>
1	Spikey, occipital following response.
2	Parieto-occipital spikes with a biphasic slow wave.
3	Parieto-occipital spikes with a biphasic slow wave and spreads to the frontal regions.
4	Generalised high amplitude spike/polyspike and wave activity which outlast the stimulus.

*Table 2.2: Classification of the photoparoxysmal response, Harding and Jeavons, 1994*

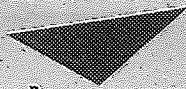
<u>Type:</u>	<u>Activity:</u>
I	Bursts of spikes and wave with the slow component at 3 Hz.
II	Bursts of high amplitude theta (4-7 Hz) with spikes.
III	Bursts of polyspikes or polyspike and wave.
IV	Bursts of spikes at the same rate as the flash extending into anterior regions.
V	Discharges of 3 Hz spike and wave lasting longer than five seconds post cessation of the stimulus, associated with clinical absence.
VI	Bilateral high amplitude slow waves without spikes.

Figures 2.6-2.11 Show examples of each type of PPR from Harding and Jeavons, 1994 classification.



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The PPR can be viewed as evidence of disruption of the electrical activity in the visual cortex and spreading disruption to other areas of the cortex, hence its generalised appearance. PPRs are rarely seen in the general population with their incidence being suggested at less than 2% (Jayakar and Chiappa, 1990). The significance of this is unknown but photoparoxysmal responses in individuals without epilepsy most likely represents increased excitability of the cortex which is insufficient to initiate a clinical seizure. Five percent of patients with seizure disorders display PPRs (Wilkins et al, 1980). Jeavons found that 2-3% of patients referred for an EEG display photoparoxysmal responses but states that this is not necessarily indicative of clinical symptoms but may represent a lowered convulsive threshold (Jeavons, 1982). Although other studies have suggested that the occurrence of epilepsy in patients displaying PPRs can be as high as 95% (Kasteleijn-Nolst Trenité, 1989, Binnie and Jeavons, 1992, Harding, 1994)

If the patient is sensitive to both pattern and photic stimulation they are more likely to display generalised polyspike and wave to IPS than those patients who are just pattern sensitive (Wilkins et al, 1980). Brinciotti and colleagues found similar results with the most common type of abnormalities in patients who were pattern and photosensitive being generalised 4-5Hz polyspike and wave activity. Whereas in patients who were only pattern sensitive generalised polyspike and wave activity was only seen in 15% and focal sharp wave and poly/spike and wave complexes were more frequently seen in occipital regions, often asymmetrically (Brinciotti et al, 1994).

There is some debate over the clinical significance of the photoparoxysmal response which outlasts the termination of the stimulus. Some studies suggest that the clinical significance increases if the PPR outlasts the stimulus train with 95% of patients showing a prolonged PPR having epilepsy (Binnie and Jeavons, 1992). If the individual does not have epilepsy and displays a prolonged PPR it is highly likely that a close family member will have epilepsy (Reilly and Peters, 1973, Harding and Jeavons, 1994). However it has been argued that photoparoxysmal responses which outlast the termination of the stimulus have no clinical significance (Jayakar and Chiappa, 1990) and whether a PPR is

prolonged or self limits may simply reflect the time taken for the technician to halt the stimulus.

The length of the discharge regardless of whether or not it outlasts the termination of the stimulus has been reported to be of clinical significance. With all patients displaying clinical features if the PPR is of 3 seconds duration or longer and 71% of patients showing clinical features if the discharge is less than 3 seconds in duration (Kasteleijn-Nolst Trenité et al, 1987). The most common clinical feature reported was pain in the eyes, reported by 39% of the patients (Kasteleijn-Nolst Trenité et al, 1987). Consciousness was the only clinical variable that was found to be directly related to the duration of the PPR with a higher probability of a reduction in consciousness with increased length of photoparoxysmal response (Kasteleijn-Nolst Trenité et al, 1987). Fylan and her colleagues found that photoparoxysmal responses evoked by diffuse IPS had more clinical significance than those induced by patterned IPS. Seventy six percent of patients showing photoparoxysmal responses to diffuse intermittent photic stimulation had experienced recent seizures compared to 24% of patients showing PPRs to patterned photic stimulation, suggesting that diffuse IPS is a more reliable predictor of seizure control (Fylan et al, 1999).

### **Chapter 3: Therapy for photosensitive epilepsy**

Various methods of treatment have been applied to photosensitive epilepsy, the most basic being avoidance of the stimulus and other simple behavioural modifications associated with the stimulus. This is most effective in television epilepsy where the patients' seizures are induced by watching the television. Simple procedures can reduce the number of seizures such as viewing the television in a well-lit room which reduces contrast between the stimulus and background environment (Binnie et al, 1980a, Jeavons and Harding, 1970, Jeavons et al, 1977, Jeavons, 1982). Sitting at least two metres away from the television decreases the retinal area stimulated (Hess et al, 1974, Jeavons, 1982). Covering one eye if the patient must approach the television also decreases the amount of retinal-cortical stimulation by not triggering the binocular cells in the visual cortex, and so provides some protection against seizures (Hess et al, 1974, Kasteleijn-Nolst Trenité, 1989, Binnie and Jeavons, 1992, Harding, 1994). However, if the patient is sensitive to a larger number of flash or spatial frequencies then a greater number of environmental stimuli are potentially hazardous and may not be as readily identifiable.

#### **3.1 Antiepileptic drug therapy**

Antiepileptic drugs (AEDs) are by far the most effective way of treating photosensitive epilepsy if the stimulus can not be avoided or if the patient also experiences spontaneous seizures. With acute administration virtually all the major AED groups will result in suppression of photosensitivity, although unfortunately this is not generally predictive of their chronic effects (Binnie et al, 1986). The most effective AEDs in the treatment of photosensitive epilepsy are ethosuximide (particularly if the patient experiences associated absences), benzodiazepines and sodium valproate. Valproate is clearly the most potent and has been considered the drug of choice for the treatment of PSE for many years. More recently developed AEDs may also prove effective, in particular Lamotrigine (Binnie, 1986) and Levetiracetam (UCB L059) (Kasteleijn-Nolst Trenité et al, 1996) look promising.



The use of antiepileptic drugs for the treatment of epilepsy commenced in 1857 when Locock discovered that potassium bromide was effective in controlling seizures in what is now termed catamenial epilepsy (Porter and Meldrum, 1995). Previously epilepsy had been treated with a variety of methods including trepanning, holy water, herbal remedies and animal extracts. Clinicians began to use phenobarbital in 1912 and in 1938 the efficacy of phenytoin was discovered when it was applied to the prevention of experimental seizures in cats (Porter and Meldrum 1995). From this time until the 1960s many new experimental models of epilepsy were developed alongside improvements in the testing of drugs and consequently many of the AEDs used today were developed in this period, such as ethosuximide, sodium valproate and carbamazepine. Antiepileptic drug development then slowed for a time due to the enactment of requirements for proof of drug efficacy in 1962 (Porter and Meldrum, 1995). In the 1990s AED development again benefited from the greater understanding of the mechanisms of the epilepsies and advancements in the pharmaceutical industry and there has again been a surge of new drugs arriving on the market such as vigabatrin, lamotrigine and oxcarbazepine.

There is conflicting evidence to suggest the commencement of antiepileptic drug treatment after a single unprovoked seizure, with a meta analysis of the data showing the risk of seizure recurrence being 51% (Berg and Skinner, 1991). Although a randomised study comparing AED treatment to no treatment demonstrated that at 24 months post the initial seizure 51% of patients who did not receive treatment had experienced a further seizure compared to only 26% of the treated group (First Seizure Trial Group, 1993). Regular antiepileptic drug treatment is usually recommended after two or more unprovoked seizures with an interval between them of less than 12 months (Wallace et al, 1998). Approximately 80% of patients can be well controlled with one drug (Sander, 1993, Shorvon et al, 1997). Social and occupational opportunities are increased and detrimental psychosocial effects of epilepsy are reduced if the patients' seizures can be controlled (Ridsdale et al, 1996). The risk of physical injury and seizure related death is also reduced (Zielinski, 1974, Hauser et al, 1980) therefore it is important that seizures be treated effectively.

For the purpose of drug treatment the epilepsies are classified according to seizure type, this is of primary importance in the determination of antiepileptic drug (Wallace et al, 1998). Drugs used for the treatment of the two major seizure groups (partial and generalised) are of two pharmacological classes and are different in their clinical effects (Porter and Meldrum, 1995). In deciding what AED is to be used the patients seizure type must be correctly identified using a combination of clinical history with eye witness accounts and evidence from the EEG (if available/appropriate) (Feely, 1999). It is essential that the seizure type be correctly identified as drugs that are effective for one type of seizure may aggravate other types (Porter and Meldrum, 1995).

The individual patient must also be considered when an antiepileptic drug is chosen e.g. pregnant, of childbearing potential, elderly, overweight (Feely, 1999), as factors such as these will effect drug efficacy and the incidence of adverse effects.

Generally AEDs suppress epileptic activity by either decreasing excitation or increasing inhibition within the central nervous system. These effects will then have limiting consequences upon the epileptic discharge itself and/or on the spread of the epileptic activity, but may also have effects upon wider mechanisms of the CNS and therefore on behaviour (Rosen, 1984).

### **3.1.1. Common drugs used in the treatment of partial and generalised seizures**

There are eight major groups of AEDs. Table 3.1 below illustrates these with examples of common AEDs. Generally drugs used for the treatment of partial seizures and generalised tonic clonic seizures are the hydantoins, the barbiturates, the benzodiazepines, with carbamazepine being the drug of choice for simple partial seizures and secondarily generalised partial seizures, and primidone being the drug of choice for complex partial seizures.

Ideally further classification of type of seizure and if possible epileptic syndrome increases the chance of choosing an efficacious AED, however detailed discussion of the specific treatments of individual epileptic syndromes is beyond the scope of this chapter.

*Table 3.1: The major antiepileptic drug groups*

<b>Class of AED:</b>	<b>Common Examples:</b>
Barbiturates	Phenobarbitone, Primidone,
Hydantoins	Diphenylhydantoin, Phenytoin, Ethytoin
Dibenzazepines	Carbamazepine
Oxazolidinedions	Trimethadione (Troxidone)
Succinimides	Ethosuximide
Benzodiazepines	Diazepam, Clobazam, Clonazepam
Sulphanamides	Acetazolamide, Sulthiame
Short chain fatty acids	Sodium Valproate

There has been a move to limit the use of sedative antiepileptics such as the barbiturates and so they are less frequently used as treatment for the epilepsies. Recently the new drugs of the 1990s have been found to be effective in the treatment of partial (oxecarbazepine and vigabatrin) and generalised tonic clonic seizures (lamotrigine).

All the drugs above can be used to treat generalised seizures with the addition of sodium valproate, which is the drug of choice for absences, as is ethosuximide. Valproate is also the primary drug for many specific myoclonic syndromes and can also be used to treat atonic seizures, as can lamotrigine and some of the benzodiazepine group (although others may aggravate this type of seizure), although atonic seizures are often refractory.

### **3.1.2 Mechanisms of action**

The clinical aspects of seizures are highly correlated with seizures induced in experimental animals and these animal models have been used to test the antiepileptic properties and the mechanisms of developing AEDs. Minimal threshold tests identify drugs which raise seizure threshold (such as ethosuximide and sodium valproate) and supramaximal tests identify drugs which prevent seizure spread (such as phenytoin,

carbamazepine and sodium valproate) (Swinyard et al, 1989). Generalised seizures (especially absences) are correlated with experimental seizures elicited by the subcutaneous administration of pentylenetetrazol and drugs such as ethosuximide, which are effective against such seizures, diminish  $CA^{2+}$  entry (through T type or low threshold calcium channels) (Porter and Meldrum, 1995).

The experimental animal model of partial seizures is the maximal electroshock test (MES) and drugs effective against MES and used in the treatment of partial seizures alter ionic transportation across excitable cell membranes. For example phenytoin decreases cell firing due to its action on sodium ion conductance mechanisms (Porter and Meldrum, 1995). However more than one mechanism is probably responsible for the various seizure types and the AEDs have many different mechanisms of action despite structural similarities between them (Porter and Meldrum, 1995).

The mode of action of an AED at the cellular level is complex. The facilitation of inhibitory feedback mechanisms, membrane stabilisation and decrease of excitatory transmitter release via changes in synaptic transmission are all involved (Meldrum, 1983). The result of these actions is an inhibition of ictal activity in the epileptic focus and an impairment of synaptic activity, thus preventing seizure propagation (Bleck and Klawans, 1990). It was previously thought that generally the antiepileptic properties of AEDs were achieved through the enhancement of inhibitory processes mediated by GABA. Benzodiazepines, barbiturates, phenytoin and sodium valproate primarily work in this fashion. However more recent evidence suggests changes in GABA levels do not coincide with the time course of the AEDs therapeutic action. GABAergic inhibition may be enhanced in a number of ways; facilitation of GABA release, action on benzodiazepine receptors or the ionophore/barbiturate site, inhibition of GABA reuptake or inhibition of GABA transaminase (MacDonald and Kelly, 1993). Most antiepileptic drugs increase GABA activity by acting on the picrotoxin-binding site on the GABA benzodiazepine receptor complex. AEDs that enhance GABA inhibition are most effective against myoclonic seizures (MacDonald and Kelly, 1993).

Other antiepileptic drugs act on decreasing excitatory mechanisms; for example phenobarbitone reduces glutamate transmission by preventing calcium ions entering presynaptic terminals (Meldrum, 1993), therefore preventing the potassium channel from opening and glutamate being released.

Membrane stabilisation occurs in a variety of different ways depending on the antiepileptic drug in question. Hydantoins e.g. phenytoin reduce the rise of sodium ions intracellularly after the action potential, reducing excitability, and also impairing the influx of calcium ions. Thus stabilising the membrane and preventing neurotransmitter release. Diphenyldeantoin, carbamazepine, valproate and diazepam (in high concentrations) also block sodium channels in order to reduce membrane excitability. AEDs that effect sodium channels are most effective against generalised tonic-clonic and partial seizures, particularly those which delay the recovery of inactivated sodium channels (MacDonald and Kelly, 1993).

AEDs may decrease excitatory neurotransmitter release by a variety of mechanisms such as effecting the synthesis of glutamate, aspartate, and other excitatory aminoacids by decreasing the maximum rate at which they are synthesised. From the evidence provided by animal cell studies this looks like the most promising mechanism of antiepileptic activity. Selective decrease of synaptic release and postsynaptic action also result in an impairment of excitatory transmission. Most antiepileptic drugs decrease excitatory neurotransmitter release by inhibiting calcium calmodulin dependent protein kinase activity, (Meldrum, 1983) which is involved in the mechanism that allows increasing numbers of calcium ions to enter the presynaptic terminal, which in turn triggers the release of the neurotransmitter.

Since the early 1990s more is now known about the mechanisms of the epilepsies and the new wave of AEDs are being designed with specific mechanisms in mind. Generally substances are being developed that enhance GABAergic transmission, thereby increasing inhibitory mechanisms (such as vigabatrin, the first "designer" AED). Or alternatively focus has been placed upon the reduction of excitatory transmission (usually

focussing on glutamatergic pathways) or the modification of ionic conductances (Porter and Meldrum, 1995), thereby altering ionic transport to the presynaptic cell and controlling the release of the desired neurotransmitter.

### **3.1.3 Basic pharmacology and pharmacokinetics**

Many of the classes of antiepileptic drugs are structurally similar, sharing a common heterocyclic ring structure. In addition to this structure they have a variety of substituents which determine their chemical group (barbiturate, hydantoin, oxazolidineone, succinimide or acetylurea) and which also determines the AEDs pharmacologic class (i.e. its effectiveness in MES or antipentylentetrazol tests) (Porter and Meldrum, 1995). Other antiepileptic drugs such as carbamazepine, sodium valproate, the benzodiazepines and the newer AEDs (vigabatrin, lamotrigine, felbamate, gabapentin etc) are dissimilar to each other in their chemical structure (Porter and Meldrum, 1995).

Generally AEDs share similar pharmacokinetic properties. Absorption is usually good with 80-100% of the dose reaching the circulation. Most AED clearance relies on hepatic mechanisms, many being converted to active metabolites (e.g. benzodiazepines, primidone) (Porter and Meldrum, 1995). Clearance from the plasma is usually relatively slow with many AEDs being long acting, half-lives are usually more than 12 hours (Porter and Meldrum, 1995), allowing once or twice daily dosing.

Concomitant AEDs may affect antiepileptic drug metabolism, as may other drugs, including those bought over the counter (e.g. aspirin). Metabolism is also affected by various disease states such as renal, and hepatic disease and can be altered by respiratory, urinary and other infections (Gardner-Thorpe, 1977).

### **3.1.4 Adverse Effects**

Not only does a drug need to be clinically efficacious but it also needs to be relatively free of adverse side effects. Antiepileptic drugs tend to be similar in their efficacy as

regards seizure control (except in specific syndromes such as photosensitive epilepsy) and so the choice of a drug is largely determined by its adverse effects (Mattson et al, 1985). All antiepileptic drugs are potentially toxic, although most adverse effects are transient and reversible. The incidence of adverse effects increases when AEDs are combined (Greenwood, 2000), therefore monotherapy is preferred if appropriate.

Adverse effects can be classified into three main types; idiosyncratic effects, i.e. effects which are peculiar to the individual patient, acute dose related effects, implying that these will improve with a reduction in dosage (Greenwood, 2000) and chronic toxic effects i.e. effects which develop over an extended period of drug use. Teratogenicity of AEDs may also be thought of as a specific class of adverse effect.

Idiosyncratic reactions usually occur at the start of the treatment and include transient dermatological symptoms (e.g. Stevens-Johnson syndrome reportedly associated with lamotrigine and carbamazepine treatment, and Lupus associated with phenobarbital), acute hepatic toxicity (found in children taking sodium valproate) and haematological effects. Acute dose related adverse effects again occur at the beginning of treatment. If AEDs are commenced in a rapid manner or initial dosages are high then these effects are more likely to arise and are generally more serious (Greenwood, 2000). These adverse effects occur with all drugs, differing in their severity depending on each AED, usually remitting if the dosage is lowered. Common effects are drowsiness, dizziness, headache, nausea, and ataxia. Chronic toxic effects develop over a much slower time course and are not as clearly dose dependant; these include cognitive and behavioural changes (as seen with phenobarbital, phenytoin and sodium valproate).

The role of AEDs in teratogenesis is difficult to assess due to the combined factors of the seizures themselves and genetic predispositions. Generally children born to mothers taking AEDs have a two-fold increased risk of birth defects (Porter and Meldrum, 1995) and some AEDs have been linked to specific teratogenic effects and syndromes, such as phenytoin and the foetal hydantoin syndrome and sodium valproate and the foetal valproate syndrome.

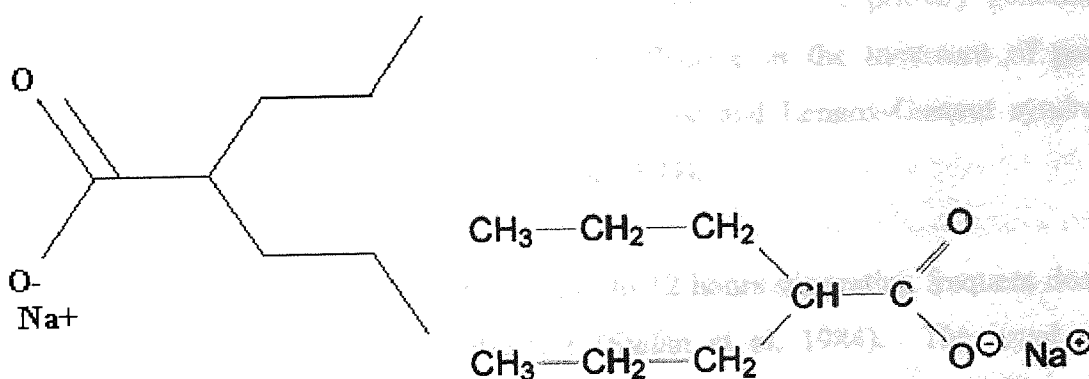


All adverse effects vary among patients and depend not only on the drug used, the patients' epilepsy and other medical conditions, but also on socio-economic factors such as culture, marital status, expectations, financial concerns and occupation (Greenwood, 2000). Ideally an efficacious drug completely free from adverse side effects is desired, unfortunately no such drug exists so a balance must be made between seizure control and minimal adverse effects taking into account the individual patient.

### 3.2 Sodium Valproate

Valproate is one of the most widely used AEDs with a broad spectrum of action and is particularly efficacious in the treatment of the primary generalised epilepsies. It was first synthesised by Burton in 1882 (Johnston, 1984) and was introduced onto the market in the UK in 1974 and has long been considered a first line drug for photosensitive epilepsy, absences and myoclonic seizures (Porter and Meldrum, 1995). More recently it has been used in the treatment of migraine and bipolar disorder (Bowden, 1998). Valproic acid (2 propylpentanoic acid or dipropylacetic acid) is a colourless liquid soluble in organic solvents with the molecular weight of 144.21 (Kupferberg, 1989). It is a short branched chain fatty acid or carboxylic acid with a chemical structure unlike other AEDs.

*Figure 3.1: The molecular structure and structural formula of sodium valproate*





It is usually used as its sodium salt (sodium valproate) (see figure 3.1) which is a white crystalline powder, soluble in water, that dissociates to valproic acid once in the body (Loscher, 1999). Its antiepileptic efficacy seems to be greatest when five to eight carbon atoms make up the chain (Porter and Meldrum, 1995), with more carbon atoms sedative effects are seen (Johnston, 1984). The active component of both the acid and the salt is assumed to be the valproate ion and its amides and esters are also effective in the reduction of epileptic activity (Redecker et al, 2000a, Redecker et al, 2000b).

It is well absorbed in humans with peak plasma levels being reached within one to two hours after oral administration, although this may be delayed by the intake of food (Porter and Meldrum, 1995). Bioavailability is almost 100% and is not affected by the age or sex of the patient (Shorvon, 1995). It is approximately 90% bound to plasma protein (Shorvon, 1995) but appears not to bind to brain proteins (Loscher, 1999) so that only 20% of the valproate concentration in the plasma is present in the brain (Loscher, 1999). Valproate is metabolised extensively by a variety of pathways including conjugation and beta and omega oxidation (Porter and Meldrum, 1995). Valproate is an enzyme inhibitor, i.e. it does not induce microsomal enzymes within the liver via its elimination and less than 5% of unchanged VPA is present in urine (Shorvon, 1995).

Administration of valproate decreases spike and wave activity (Jeavons et al 1975, Jeavons et al 1977, Stefan et al, 1984) and it is the drug of choice for generalised tonic clonic seizures. Consequently it is used in the treatment of the primary generalised epilepsies (Shorvon, 1995), although it is also effective in the treatment of partial seizures, specific syndromes including West syndrome and Lennox-Gastaut syndrome and is also used in status epilepticus (Davies et al, 1994).

Valproate has a relatively short half life of eight to 12 hours suggesting frequent dosing, although once daily dosing can be effective (Stefan et al, 1984). The usual adult maintenance dose is between 600-2500mg/day and 40mg/kg for children weighing up to 20Kg and 30mg/Kg for older children (Shorvon, 1995). As valproate binds extensively to serum proteins the total blood concentration may not accurately reflect the amount of

the drug available in the brain, which can make titration difficult (Loscher, 1999). Plasma levels of valproate fluctuate widely (Rowan et al, 1979) and display a curvilinear relationship to dose (Gram et al, 1980) with quoted therapeutic levels ranging from 50 to 100µg/mL (Porter and Meldrum, 1995). However as will be discussed later the significance of serum levels of valproate to its antiepileptic efficacy and its side effects are questionable. The controlling dose is usually obtained within a few weeks as there is no need to slowly titrate (Shorvon, 1995).

Valproate alters plasma and brain levels of other antiepileptic drugs such as phenobarbitone, phenytoin, carbamazepine (Shorvon, 1995) and lamotrigine (Yuen et al, 1992) by inhibiting the metabolism or protein binding of the other drugs. Valproate's own pharmacokinetic properties may also be changed by other antiepileptic drugs consequently altering its plasma and brain concentrations (Loscher, 1999).

### **3.2.1 The use of sodium valproate in the treatment of photosensitivity**

Valproate has been used in the treatment of photosensitive epilepsy for over 20 years and is considered the drug of choice for the condition. It controls (i.e. abolishes clinical manifestations of PSE) approximately 80% of patients (Harding et al, 1978), abolishing photoparoxysmal responses in a large proportion. Although the dosage needed to affect PPRs tends to be higher than that which normalises the background EEG (Herrick and Maheshwari, 1975, Jeavons et al, 1980). The duration of the PPR seems to be the measure that bears the most relation to dosage. As the dose of VPA increases the duration of the abnormalities evoked with IPS decrease, until they are abolished (Darby et al, 1986). This suggests that valproate effects the generalisation of the photoparoxysmal response rather than having a direct effect in the trigger/source of the abnormality. On withdrawal of valproate, patients' photosensitive ranges tend to return to their previous untreated levels within seven months (Harding and Jeavons 1994).

Sodium valproate does not have any effect on occipital spikes (Jeavons et al, 1975, Binnie et al, 1980b). If occipital spikes are viewed as evidence of hyperexcitability in the

visual cortex, and effectively as a precursor to photoparoxysmal responses, then this again is indicative of valproate's control of the generalisation of photosensitive epileptiform activity rather than the initiation (Herrick and Harding, 1978). Binnie et al. propose that this is further alluded to by the fact that at lower dosages of valproate, when photosensitivity is not fully controlled, abnormal responses to IPS may still be seen in posterior regions of the brain (Binnie et al, 1980b). This and other studies (Darby et al, 1986) add further support to the idea that valproate affects the spread of photoparoxysmal activity rather than the activation mechanism underlying its initiation.

There is some laboratory evidence that sodium valproate can control pattern sensitivity. Darby and colleagues found that as they increased the dose of valproate photoparoxysmal responses were significantly less likely to occur in response to patterns of striped lines (Darby et al, 1986).

### **3.2.2 Mechanisms of action of sodium valproate**

Valproate's broad spectrum of clinical efficacy suggests multiple modes of action. The mechanisms postulated can be loosely split into valproate's neurochemical and neurophysiological effects. Neurochemically, initial explanations focused upon valproate's alteration of the GABAergic system, whereas more recently attention has been drawn to its effects on other neurotransmitters; specifically aspartate and gamma-hydroxybutyrate (GHB). Researchers have investigated valproate's modification of sodium channels, cellular potassium conductance and calcium currents in search of neurophysiological explanations for its antiepileptic properties. More recently theories involving brain histamine and guanosine 3',5'-monophosphate (cGMP) have been put forward as further mechanisms of valproate's action.

With valproate therapy raised levels of GABA have been found in the brain (Williams et al, 1980) therefore suggesting that valproate facilitates GABAergic transmission and hence inhibition. The precise mechanisms of this are uncertain but generally there are three mechanisms by which increased brain GABA levels could be explained (Loscher,

1999). GABA reuptake may be inhibited, GABA synthesis may be increased or a more indirect effect on GABA levels may be achieved by an increase of postsynaptic GABA function, which would in turn create an inhibition of GABA turnover, and consequently increase presynaptic GABA levels. It has been suggested that valproate may inhibit GABAtransaminase activity, or valproate desensitises GABA autoreceptors, thereby facilitating the release of the transmitter (Johnston, 1984). Unlike most antiepileptic drugs, which affect GABAergic transmission, valproate does not appear to act directly on the GABA recognition site, the benzodiazepine receptor or the picrotoxin/barbiturate ionophore site (Loscher, 1999). In vivo valproate mimics the behavioural effects of GABA itself or GABA agonists (Chapman et al, 1982). Although valproate does act on GABAergic systems, protection against seizures can be demonstrated with dosages and at times when the GABA content of the brain is not altered (Morre et al, 1984) i.e. the antiepileptic effect occurs before the increase in brain GABA levels. The antiepileptic effect can remain for 3 hours after GABA levels have returned to normal levels (Harding et al, 1978). It is therefore difficult to explain valproate's broad spectrum of antiepileptic action purely on the basis of its effects on GABAergic mechanisms, it is more likely that its effects on other alternative mechanisms explain its wide therapeutic value (Loscher, 1999).

In the search for the mode of action of antiepileptic drugs, attention is now turning to their effects on amino acids. Valproate and its analogues induce a reduction in aspartate within the brain (Schechter et al, 1978, Chapman et al, 1982), specifically in astroglial cells (Loscher, 1999) either through its effect on aspartate synthesis or on the release of aspartate (Meldrum, 1986). Whatever manner in which the reduction of aspartate is reduced it seems that it is independent from valproate's effect on GABA (Chapman et al, 1983). The time course of this action is similar to that of its antiepileptic effects and it may be that this also contributes to valproate's anticonvulsant properties although its importance is so far unknown. However it has been suggested that valproate's effects on aspartate levels could account for its efficacy in the treatment of myoclonic seizures (Johannessen, 2000).

Gamma-hydroxybutyrate (GHB) is a product of GABA metabolism and has been shown to suppress generalised spike and wave discharges (Maitre et al, 1990) and absence-like seizures in experimental animals (Loscher, 1999). An increase in GHB has been found with valproate therapy which is both time and dose dependant (Vayer et al, 1988) and may explain its effectiveness in absence epilepsy.

Valproate affects other amino acids for example an increase in glycine concentration has been found in brain tissue (Loscher, 1999) although there is evidence that this is not related to its antiepileptic activity. In animals valproate is also seen to increase taurine concentrations in the cerebellum and the cerebral cortex (Williams et al, 1980), but again there is no evidence this is directly related to its antiepileptic effects (Loscher, 1999).

Valproate also alters the transmission of other neurotransmitters. NMDA receptors mediate excitation and valproate is an antagonist of NMDA which may explain its use in focal and generalised seizures (Loscher, 1999). Its effect on serotonin and dopamine are probably not related to its anti epileptic activity but may explain the efficacy of valproate in the treatment of psychological disorders (Loscher, 1999).

Any action that reduces potassium ions leaving cells or increases the entry of sodium or calcium ions can result in burst firing in neurones. Conversely therefore any substance which increase potassium conductance or inhibits sodium or calcium conductance may have a potential for antiepileptic activity. Chapman et al propose that this action on membranes rather than on a specific receptor/enzyme site as an explanation of valproate's therapeutic action (Chapman et al, 1983). This in turn may secondarily produce changes of neurotransmitter/enzyme activity. Valproate has been found to effect ion channels. Administration of valproate blocks sodium and potassium channels (Bleck and Klawans, 1990) and more specifically inhibits sodium currents (Zona and Avoli, 1990). This delayed recovery from inactivation of sodium channels and has been documented as a direct result of valproate administration (Van den Berg et al, 1993), this is consistent with a decrease of sodium conductance (Loscher, 1999). Whatever the chemical mode of action of valproate at a cellular level it raises the threshold necessary for the paroxysmal

depolarising shift (Griffith and Taylor, 1988). So consequently inhibits the spontaneous firing of neurones (Chapman et al, 1982), particularly sustained high-frequency repetitive firing (Bleck and Klawans, 1990, Maclean and MacDonald, 1986). This suggests that valproate reduces the inward sodium current (Maclean and MacDonald, 1986), which could explain its efficacy against partial seizures (Porter and Meldrum, 1995).

Valproate's antiepileptic activity may also be exerted via its effects on potassium channels. High concentrations of valproate increase membrane conductance of potassium (Johnston, 1984, Porter and Meldrum, 1995). Elevated levels of potassium ions can produce epileptiform activity in hippocampal slices (Johnston, 1984). Suggesting a reduction of potassium ions may diminish epileptic activity, however in the *xenopus laevis* where the effect has been studied in great detail it has been concluded that this effect is too small to explain valproate's antiepileptic properties (Loscher, 1999).

More recent research has focussed on alternative mechanisms to explain valproate's action, such as elevations in brain histamine concentration (Vohora et al, 2001) and decreases in guanosine 3',5'-monophosphate (cGMP) which is time related to dosing (Loscher, 1999). It is clear there are many plausible mechanisms to explain valproate's broad spectrum of clinical efficacy and adverse effects profile and it is certain that a combination of these mechanisms are responsible.

### **3.2.3 Adverse effects associated with sodium valproate**

Like any drug valproate has side effects which are mild and transient; the most commonly reported being drowsiness (less likely with monotherapy), mild ataxia, dizziness, gastrointestinal complaints and tremor with high plasma concentrations (Laljee and Parsonage, 1980, Clark et al, 1980, Dinesen et al, 1984). Tremor is usually mild and can occur rapidly (within three months of commencing treatment) or over a longer time period (up to 12 months), (Hyman et al, 1979). It can be reduced by decreasing the dosage of valproate as can many of these dose-related side effects, slow titration of the

drug may also be useful in the elimination of unwanted treatment outcomes (Porter and Meldrum, 1995).

Unlike many antiepileptic drugs, valproate treatment is relatively free from behavioural and cognitive adverse effects (Chapman et al, 1983). Sodium valproate can enhance both mood (Mattson et al, 1989) and cognition, patients becoming more alert and co-ordinated after valproate therapy. These cognitive effects can be evident after just three months of therapy and also include improvements in word fluency, concentration and motor speed (Mattson et al, 1989) possibly due to the decrease in epileptic activity.

Two of the most severe side effects of valproate, idiosyncratic hepatotoxicity and pancreatitis occur most often when it is used to treat children (Dreifuss, 1989a). Those patients at greatest risk tend to be under two years of age and on polytherapy (Porter and Meldrum, 1995). The cause of this hepatotoxicity is uncertain and an underlying congenital metabolic disturbance has been suggested (Shorvon, 1995), such as abnormal cytochrome P-450 dependant metabolism (Dreifuss, 1989b). Linked with these disorders Verrotti et al found a decrease of triglycerides (TG) and low density lipid (LDL) cholesterol and an increase of high density lipid (HDL) cholesterol in children treated with sodium valproate, which could increase the risk of atherosclerosis and insulin resistance. They suggest that hepatic injury from valproate therapy may be the cause of these changes (Verrotti et al, 1997).

When considering the treatment of photosensitivity, side effects which are particularly relevant are those, which affect females. It has been well established that valproate is a powerful teratogen and should therefore be avoided by women who are, or are likely to become, pregnant. There is now evidence that valproate may also be involved in the development of the polycystic ovary syndrome (PCOS). These issues will be subsequently discussed in further detail. Two other common adverse effects of valproate which create particular psychological problems for women taking the drug are hair loss and weight gain, which can often lead to non-compliance and discontinuation of treatment.



Thinning of the hair seems to occur in approximately 8% of patients (Clark et al, 1980). This can be transient (Mattson et al, 1989) and usually occurs in the first six months of treatment (Shorvon, 1995). Changes in the texture of the hair may be seen following re-growth, with 2-3% of VPA-treated patients reporting re-growth of curly hair (Jeavons et al, 1977 and Clark et al, 1980). The mechanisms of this side effect are unknown but it appears to be dose related (Shorvon, 1995), as alopecia tends to occur with plasma concentrations of 23-65µg/ml (Froscher et al, 1979). At high concentrations incidences of up to 28% have been reported (Mercke et al, 2000), much higher than those seen with other AEDs such as carbamazepine.

Increased weight gain occurs in 20% (Corman et al, 1997) to 50% (Dinesen et al, 1984, Mattson et al, 1992) of patients treated with sodium valproate. Some reports state that weight gain is most likely to occur in women and particularly in adolescence or childhood (Corman et al, 1997), whereas others (Biton et al, 2001) report that there is no difference between genders in the potential to gain weight with valproate treatment. Indeed Biton and colleagues suggest that no predictive factors for weight gain have been identified (Biton et al, 2001). However there is some evidence that the most severe weight gain occurs in those patients who had below or within normal body mass index (BMI) scores prior to valproate therapy (Corman et al, 1997).

The reasons for such a gain are unknown, there are reports of increasing appetite, possibly through lower blood glucose and higher insulin levels (Demir and Aysun, 2000), due to insulin resistance, although weight gain can also occur in patients who report no changes in appetite (Clark et al 1980). A study by Gidal and colleagues suggested that the weight gain might be associated with the patients' clearance of 2-ene-valproate. Patients who display weight gain on valproate therapy demonstrate slower clearance of this metabolite and also have lower energy expenditure than those patients who do not gain weight on valproate, patients taking other AEDs and volunteers without epilepsy taking valproate (Gidal et al, 1996)



The gain in weight can be seen within 10 weeks of commencing valproate therapy (Biton et al, 2001) and has been seen to continue for up to four years in some patients (Corman et al, 1997). The increase can be over 10% of the patient's weight prior to treatment (Mattson et al, 1989) and is frequently socially and clinically significant (Corman et al, 1997, Mirza et al, 1999) leading to discontinuation of valproate therapy in some cases (Shorvon, 1995, Mattson et al, 1989). Strategies to compensate for the increase in weight, such as change in diet and exercise regimes, are often ineffective (Corman et al 1997) but after terminating treatment with valproate most patients gradually return to their original weight, although this can take years (Mattson et al, 1989).

Apart from the psychosocial stigma associated with weight gain there are also obvious health risks of being overweight including links with reproductive endocrine disorders such as the polycystic ovary syndrome.

### **3.2.3.1 The polycystic ovary syndrome and its association with valproate**

A further side effect that is relevant to the treatment of women is its association with the polycystic ovary syndrome (PCOS). This is currently a somewhat contentious issue, but recent evidence (Isojarvi et al, 1995) suggests that valproate treatment is associated with a higher risk of developing PCOS. It is of further concern as it has been suggested that women commencing valproate therapy before the age of 20 years, (as with women treated for photosensitive epilepsy) are more at risk of becoming obese and developing the polycystic ovary syndrome (Vainionpaa et al, 1999). This risk may increase further amongst children commencing therapy before or during puberty (Betts et al, 2001).

Polycystic ovaries are characterised by the development of enlarged ovaries through thickening of the stroma, with multiple cysts. The polycystic ovary syndrome is defined by evidence of polycystic ovaries (PCO) coupled with at least one of the following symptoms; obesity, menstrual disturbance (primarily oligomenorrhea or amenorrhea), hyperandrogenism, infertility and endocrine abnormalities. The most likely cause of PCOS is an elevation of testosterone and luteinising hormone (LH) which disrupts the

menstrual cycle. Abnormalities in insulin and glucose metabolism have been implicated along with dysfunction in the control mechanisms of the hypothalamic, pituitary, ovary and adrenal (HPOA) axis. It appears that women with PCOS produce increased amounts of insulin, which then results in an elevation in testosterone release.

The prevalence in the general population is approximately one in five, but some studies report a higher prevalence of PCOS in women with epilepsy, particularly those with temporal lobe epilepsy (Herzog, 1996). This association has been attributed to both the mechanisms of epilepsy itself and the effects of AEDs. Although other studies suggest there is no evidence of an increased prevalence (Murialdo et al, 1997, Luef et al, 2002) although it is difficult to make a comparison due to differing diagnostic criteria used and different types of epilepsy being investigated.

Epilepsy affects the gonadotrophin-releasing hormone (GnRH) pulse generator resulting in abnormal LH pulsivity, therefore disrupting the menstrual cycle and possibly triggering the development of PCOS. Bilo et al describe increased LH pulsivity in untreated patients (Bilo et al, 1998) and Drislane and colleagues report higher pulse frequencies in women taking antiepileptic medications with temporal lobe epilepsy, and PCOS, suggesting a relationship with left temporal EEG foci (Drislane et al, 1994). However, in women who do not have epilepsy there is no evidence that valproate effects the pulsatile LH secretion (Lado Abeal et al, 1994).

There appears to be a high occurrence of hyperandrogenism, hyperinsulism and polycystic ovaries in women treated with valproate (Isojarvi et al, 1993) compared to women treated with other antiepileptic drugs. Sixty to eighty percent of valproate treated women were found to develop the PCOS (Isojarvi et al, 1998). Almost all women investigated displayed some form of menstrual irregularity. However it may be that this is due to a protective effect of other AEDs rather than valproate inducing the syndrome.

This occurrence of the polycystic ovary syndrome with valproate treatment appears to be unrelated to the type of epilepsy (Isojarvi et al, 1999) suggesting that valproate is one of

the factors associated with the development of the syndrome rather than the epilepsy itself. Although other authors have not found any difference in the incidence of PCOS between women treated with valproate and women without epilepsy who are free from medication (Bauer et al, 2000) or women treated with other AEDs (Murialdo et al 1998). However Murialdo et al did find that testosterone levels were higher in women treated with valproate as did other authors (Luef et al, 2002) and in a previous paper this research group reported that polycystic ovaries and ovulatory dysfunction were associated with valproate therapy (Murialdo et al, 1997).

Within the epileptic population the polycystic ovary syndrome is less common in women taking enzyme-inducing AEDs than in those with epilepsy not taking AEDs (Herzog, 1996). It is suggested that the increased frequency of PCOS in women taking sodium valproate simply reflects the fact that valproate does not lower androgen levels unlike enzyme-inducing drugs. However, Isojarvi and his colleagues suggest that valproate may well increase the incidence or at least the expression of PCOS, possibly via its association with obesity and hyperinsulism (Isojarvi et al, 1998).

Insulin regulation is pivotal in the expression of PCOS. In women at risk of the polycystic ovary syndrome a decrease in insulin levels stimulates glucose disposal indicating insulin sensitive resistance. There then occurs a compensatory hypersecretion of insulin which can lead to the expression of PCOS via its effects upon sex hormone binding globulin (SHBG) and gonadotrophins and its direct effect on ovarian function. Obesity can change insulin regulation and it seems plausible that valproate-induced obesity is the mechanism by which the expression of PCOS is increased in women receiving valproate therapy. Indeed weight gain is seen in women on valproate with the syndrome particularly those that are postpubertal (Vainonpaa et al, 1999). However there is controversy over changes in insulin concentration, with lower concentrations found in women treated with sodium valproate without hyperandrogenism (Vainonpaa et al, 1999) and no change found in both pre- and postpubertal girls who had gained weight with valproate treatment (Rattya et al, 1999a).

With replacement of valproate therapy by lamotrigine the symptoms of PCOS can be reversed (Isojarvi and Tapanainen, 2000) with a decrease of serum testosterone concentration coupled with the disappearance of the polycystic ovarian changes, weight loss and the reinstatement of menstruation. This occurred before the complete withdrawal of valproate so may suggest a protective effect of lamotrigine. However similar changes can be obtained with a reduction of body weight not necessarily associated with the transference from valproate therapy (Genton et al, 1999). So by reducing valproate therapy the patients' weight may have decreased and therefore the symptoms of PCOS improved. This does not rule out valproate's involvement in the polycystic ovary syndrome but again suggests its effects are mediated through its adverse effect of weight gain.

However, the polycystic ovary syndrome has also been seen in women undergoing valproate treatment who are not obese. In these women the incidence is lower than that of obese women but is still higher than that expected from the general population (Isojarvi et al, 1999). The mechanisms in non-obese women could lie within raised testosterone levels, which also appear evident with valproate therapy. As was discussed previously polycystic changes disappeared in association with decreased testosterone levels following withdrawal of valproate (Isojarvi and Tapanainen, 2000).

The results of animal studies, although contradictory at times and differing from those of human studies, suggest that valproate has an effect on ovarian structure with evidence that ovarian weight can both increase (Tauboll et al, 1999a) and decrease (Roste et al, 2000) following the administration of valproate. However these studies do confirm an increase in follicular cysts (Tauboll et al, 1999a, Roste et al, 2000) and changes in endocrine function as seen in human studies.

Although the evidence looks convincing, it should be taken into account that primarily one research group (the Finnish group headed by Isojarvi) has performed most of the research into valproate's association with the polycystic ovary syndrome. Although recent research by Betts and his colleagues suggest that women with epilepsy are more

vulnerable to the PCOS which can be triggered by taking valproate, particularly if taken in adolescence, and that withdrawal of valproate can reverse the symptoms (Betts et al, 2001). Polycystic ovary syndrome appears to be a major, current issue in the treatment of women with epilepsy and various in-depth studies are currently being undertaken with alternate hypotheses of valproate's involvement, including its effect on epoxide hydrolase activity (Hattori et al, 2000) which affects ovarian oestrogen production.

Focus has also shifted to valproate's reproductive endocrine effects in men where hyperandrogenism has also been reported (Rattya et al, 1999b) as have increased serum levels of androstenedione (Rattya et al, 2001). Animal studies in this area also suggest gonadal changes in male as well as female rats with reports of decreased testicular weight and a reduction in spermatogenesis in the former (Tauboll et al, 1999b).

### **3.2.2.2 The teratogenicity of sodium valproate**

Valproate is one of the antiepileptic drugs most likely to cause birth defects in children exposed to it in-utero (Kaneko et al, 1999) and is the only AED with a dose-response relationship to foetal abnormalities. A daily dose of 1000mg or a high peak blood level appear to be correlated with an increased risk of foetal malformations (Lindhout and Omitzigt, 1992). Generally malformations are more likely to occur if the blood level is over 70µg/mL (Kaneko et al, 1999). There is an increased risk of neural tube defects with first trimester exposure. Approximately 2% of children exposed to valproate in-utero develop such defects, particularly spina bifida. This incidence is approximately 20 times higher than that of the general population.

Other malformations are associated with the maternal use of sodium valproate and indeed a collection of these have been described as the foetal valproate syndrome (Diliberti et al, 1984). The features expressed in this syndrome include craniofacial malformations (such as small antiverted nose, flat nasal bridge, long upper lip) and abnormalities of distal digits (thin, overlapping fingers and toes, hyper-convex nails) (Jager-Roman et al, 1986). Further abnormalities associated with maternal valproate therapy are skeletal

malformations, cardiovascular and urinogenital defects. The risk of such abnormalities is increased if valproate is prescribed as monotherapy (2.5%) in comparison to its use in polytherapy (1.5%) (Lindhout and Schmidt, 1986).

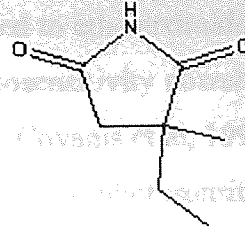
The precise mechanism of valproate-induced teratogenesis is unknown. It was originally proposed that decreased folate levels as a result of valproate therapy could be a possible mechanism (Meadow, 1968) but the association between low folate levels and foetal abnormalities has since been disputed (Hall, 1977) as use of folic acid does not protect against the abnormalities. Nau and Hendrickx suggested that alterations in intracellular pH might explain the teratogenicity of valproate (Nau and Hendrickx, 1987), whereas Lindhout proposes interference with lipid metabolism or alterations in zinc concentrations as possible mechanisms (Lindhout, 1988).

Alterations in proliferative rate of cells involved in neural tube closure can result in neural tube defects and it has been shown that in culture valproate can inhibit the proliferation of neuronal cells (Bennett et al, 2000). This effect seems to increase with an increase in the chain length of analogues of valproate (Bojic et al, 1998). Whatever the mechanism of valproate induced teratogenesis, it appears that it is markedly different from that of its antiepileptic action and that of teratogenicity of other antiepileptic drugs.

### **3.3. Ethosuximide**

Ethosuximide (Zarontin or 2-Ethyl-2-methylsuccinimide) is a succinamide, which as introduced onto the UK market in 1958. It is a soluble crystalline compound, molecular structure described in figure 3.2, with a molecular weight of 141.1694, empirical formula  $C_7H_{11}NO_2$ .

Figure 3.2: The molecular structure of ethosuximide



Ethosuximide is well absorbed and almost completely bioavailable. Its peak serum levels are usually reached 3 hours after oral administration (Shorvon, 1995). The half-life of the drug is very variable ranging from 20-70 hours depending on the patient, this is particularly true in children (Shorvon, 1995).

Ethosuximide is the drug of choice for generalised absence and atypical absence seizures (Santavuori, 1983). It is useful in refractory absences when combined with sodium valproate (Rowan et al, 1983).

The normal maintenance dose is 500-2000mg daily with a starting dose of 250mg with weekly increments of 250mg. In children the dosage is 250mg/day for one to six year olds and 500-1000mg/day for six to 12 year olds (Shorvon, 1995). Optimum serum levels are 300-700 $\mu$ mol/l.

Ethosuximide is not protein bound and does not significantly interact with other antiepileptic drugs, although it does slightly increase phenytoin levels and carbamazepine, phenobarbitone and primidone can slightly reduce ethosuximide levels (Shorvon, 1995).

### **3.3.1 The use of ethosuximide in the treatment of photosensitivity**

There is very little data available in the literature regarding studies that have investigated ethosuximide's efficacy in the treatment of photosensitive epilepsy. Harding and his colleagues found that less than half of the patients displaying photosensitivity improved



with ethosuximide therapy (Jeavons et al, 1975) and Jeavons et al found that none of their 65 photosensitive patients responded to ethosuximide (Jeavons et al, 1986). Covanis and colleagues found that marked photosensitivity correlated with a poor clinical response in patients treated with ethosuximide (Covanis et al, 1992). This suggests that ethosuximide should not be used as a first line drug in photosensitive epilepsy, although it is still used in combination with valproate mainly in children displaying photosensitivity who are experiencing refractory absence seizures (Rowan et al, 1983).

### **3.3.2 Mechanisms of action of ethosuximide**

There is very little data on the mechanisms of ethosuximide available in the literature. It appears to reduce low threshold calcium currents (Coulter et al, 1989) indicating a direct blocking action at calcium channels. This seems to occur specifically in thalamic nuclei (Pellegrini et al, 1989) resulting in decreased effectiveness of thalamocortical volleys and therefore reducing spike and wave discharges (Pellegrini et al, 1989). Spinal cord hyperexcitability also seems particularly susceptible to the effects of ethosuximide, decreasing activity in projections to higher brain areas and therefore limiting the spread of generalised discharges (Matthews and Dickenson, 2001).

### **3.3.3 Adverse effects associated with ethosuximide**

Generally about 40% of patients treated with ethosuximide experience adverse effects (Shorvon, 1995). These are usually lethargy, dizziness, ataxia and headache and are normally mild and transient (Santavuori, 1983) and resolve at lower dosages (Shorvon, 1995). Insomnia, nausea and abdominal pain are also commonly reported and are again often mild and self limiting (Shorvon, 1995). A skin rash is found in five percent of patients (Shorvon, 1995) and can be similar to Stevens-Johnson syndrome (Santavuori, 1983). Depression and confusion are occasionally seen presenting in the first few weeks of therapy (Shorvon, 1995) and mild irritability, aggression and anxiety may also occur (Shorvon, 1995). Haematological side effects are again usually mild and the most common to occur is leucopenia (Shorvon, 1995). Lupus (Casteels et al, 1998) and renal



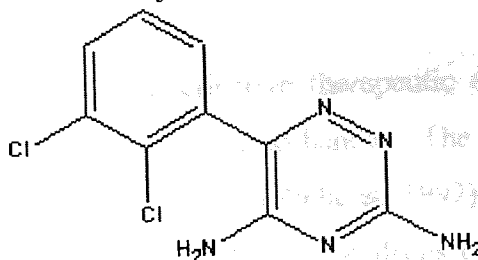
hepatic problems (Takeda et al, 1996) can occur but are relatively uncommon (Shorvon, 1995).

### 3.4. Lamotrigine

Lamotrigine (LTG) is a recently developed AED, introduced onto the market in the UK 1991, which appears promising for the treatment of photosensitive epilepsy (Binnie et al 1986b). Animal studies suggest that it is not teratogenic (Morrell, 1996) and its substitution for sodium valproate seems to reduce the expression of the polycystic ovary syndrome (Isojarvi et al 1998).

Lamotrigine is a phenyltriazine derivative with a molecular weight of 256.09, empirical formula:  $C_9H_7Cl_2N_5$  (Yuen, 1991) its chemical formula 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,3-triazine (Gram, 1989) is shown in figure 3.3 below.

*Figure 3.3: The molecular structure of Lamotrigine*



It was originally thought to have antiepileptic properties due to the fact that it is an antifolate. However there is now some argument as to whether indeed lamotrigine does display antifolate properties in humans (Sander and Patsalos, 1992). Whether or not lamotrigine is an antifolate is probably not related to its antiepileptic activity, as modification of the drug in development decreased its antifolate effects but increased its antiepileptic efficacy (Peck, 1992).

Lamotrigine is a white powder, soluble in water and 98% soluble in the blood stream (Richens, 1992). It is rapidly and completely absorbed from the gastrointestinal tract,

reaching peak serum levels usually within three hours (Peck, 1992). Its half-life is approximately 25 hours making once-daily dosing feasible (Ramsey et al 1991). Lamotrigine is chemically unrelated to other antiepileptic drugs and is advantageous in polytherapy, as it does not appear to affect blood levels of concomitant drugs. However its metabolism is accelerated if it is taken with enzyme inducing AEDs and consequently its half-life is reduced. If taken concomitantly with valproate, lamotrigine's half-life is lengthened to 30-90 hours as valproate inhibits the metabolism of lamotrigine. A further consequence of this interaction between the two drugs is that valproate serum levels are reduced by 25% (Yuen et al, 1992). Lamotrigine's half-life is also longer in renal failure patients if renal and plasma clearance is compromised (Richens, 1992).

It is converted to glucuronide metabolite 2-N glucuronic acid in the liver which is excreted in the urine (Yuen and Peck, 1998). Children metabolise lamotrigine quicker than adults do (Richens, 1992). It can be taken before or after food, with little delay in absorption if taken with food with maximum concentrations at 3.1 hours compared to 1.5 hours if fasting (Richens, 1992).

There is a large difference between effective therapeutic dosage and sedating dosage (Peck, 1992) which makes it an easier drug to handle. The normal maintenance dose is 200-400mg/day for adults and the elderly (Richens, 1992) usually given in two daily doses. It does not interact with other antiepileptic drugs or with the contraceptive pill (Richens, 1992) making it a useful drug in the treatment of women of childbearing age with epilepsy.

Lamotrigine is efficacious in the treatment of partial and generalised tonic-clonic seizures (Binnie et al, 1986, Jawad et al, 1989, Sander et al 1990a, Loiseau et al, 1990 and Messenheimer et al, 1994) as well as generalised absences and myoclonic jerks in children (Richens and Yuen, 1991). It also appears to be effective for the control of seizures associated with Lennox-Gastaut syndrome (Motte et al, 1997, Schlumberger et al, 1991). Open label studies have suggested it is more efficacious in the reduction of tonic clonic seizures than partial seizures (Binnie, 1992). With seizure severity being

reduced if seizures are not completely abolished (Smith et al, 1992). In children lamotrigine appears to be most effective in partial and atypical absence seizures (Gibbs et al, 1992).

### **3.4.1 The use of lamotrigine in the treatment of photosensitivity**

To date only one study concerned with the administration of lamotrigine to patients displaying photosensitivity has been reported in the literature. Binnie et al, (1986) investigated the effect of the acute administration of 120 or 240mg LTG in six photosensitive patients. The results showed that all six patients demonstrated a reduction in their photosensitive range. In two patients photosensitivity was completely abolished. The onset of the effect ranged from 1.5-6.5 hours post lamotrigine administration. The effect was still evident 24 hours after dosing in four of the six patients. This study along with numerous anecdotal reports suggests that lamotrigine may be useful in the control of photosensitive epilepsy.

### **3.4.2 Mechanisms of action of lamotrigine**

Lamotrigine's mode of action is primarily the stabilisation of voltage dependant sodium channels within the neurone, thus stabilising the neuronal membrane preventing depolarisation and so impeding subsequent glutamate release (Lang et al, 1993) therefore decreasing excitation (Peck, 1991). It also appears to inhibit GABA release but on a much-diminished scale compared to its effects on glutamate (Leach et al, 1991). It does not reduce glutamate release via potassium channels (Peck, 1992) but does limit excitation in hippocampal cells by modulating the outward potassium current in the guinea pig (Grunze et al, 1998).

Evidence that lamotrigine prevents the opening of sodium channels resulting in decreased release of glutamate is provided by in vitro studies (Leach et al, 1991). Lamotrigine inhibits binding of [<sup>3</sup>H] batrachotoxin A20- $\alpha$ -benzoate, which binds to sodium channels and relates to their activation, suggesting a possible mechanism by which Lamotrigine

blocks sodium channels (Lang et al, 1993). It appears that Lamotrigine binds to fast inactivated sodium channels rather than those that are at rest, thereby slowing their recovery after depolarisation and hence inhibiting further activation at these sites (Kuo and Lu, 1997). Lamotrigine's blockade of sodium channels is use dependant in that it blocks the channels to a greater extent during repetitive activation (for example as a result of epileptic sustained firing) (Coulter, 1997) and slows the time course of recovery from inactivation (Coulter, 1997). It has been suggested that the control of repetitive action potential firing is due to a negative shift of the steady state inactivation curve resulting from the reduction of amplitude of the voltage gates inward sodium current (Zona and Avoli, 1997)

Lamotrigine's effect on glutamate release is probably predominate in its antiepileptic properties although it also inhibits aspartate release (Leach et al, 1986). The clinical significance of this is so far unknown.

### **3.4.3 Adverse effects associated with lamotrigine**

The most commonly reported side effects of lamotrigine are headaches, ataxia, diplopia, nausea, drowsiness and insomnia (Betts, 1992). These are usually mild and non-specific (Smith et al, 1992). No changes have been reported in studies comparing lamotrigine to a placebo in regards to electrocardiogram, vital signs, weight, haematological characteristics, electrolytes, liver function tests and folate levels (Betts et al, 1991).

Studies assessing the effects of lamotrigine on central nervous system function suggest that it has no adverse cognitive effects and in fact cognitive function may be slightly improved with treatment, particularly in terms of short term memory and mental speed (Aldenkamp et al, 1997). Vigilance is also not impaired with lamotrigine therapy (Bonanni et al, 2001). No significant difference has been found in the incidence of anxiety and depression, comparing lamotrigine and placebo (Smith et al, 1992, Betts 1992). In fact lamotrigine is now used in the treatment of bipolar disorder and positive

effects on mood have been documented (Smith et al, 1992) independent from its antiepileptic effect (Besag, 1992).

More serious adverse effects have been reportedly associated with lamotrigine therapy, in particular multiorgan dysfunction and disseminated intravascular coagulopathy (DIC), which in a limited number of cases have been fatal. It has been proposed however that these conditions may in fact be related to the patients' epilepsy itself rather than the drug treatment (Yuen, 1991).

The most frequently reported serious adverse effect is skin reaction, in the form of a rash, which generally occurs within eight weeks of the commencement of lamotrigine therapy. Most rashes are mild and disappear with the cessation of therapy (Smith et al, 1992). However about 3% of patients withdraw from therapy due to skin rash (Yuen, 1992) and in rare cases potentially fatal rashes may develop such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). The approximate incidence of such events is 1 in 1000 (Yuen, 1992). This is increased in children under the age of 12, possibly due to its relationship with lamotrigine hypersensitivity, which is more commonly found in children (Besag, 1992). Indeed 10% of children treated withdraw therapy due to adverse effects (Besag, 1992). Serious skin reactions are associated with polytherapy with valproate (due to its effect on lamotrigine's metabolism) and initial high dosages of lamotrigine in monotherapy. The risk of such a reaction can be drastically reduced by initiating lamotrigine therapy with very small increments (commencing at 25mg/day) over a longer than usual time period. (Yuen, 1992).

Lamotrigine does not appear to induce teratogenesis or infertility in animal studies (Peck, 1992, Morrell, 1996) and the Glaxo Wellcome pregnancy register for lamotrigine and other reports do not provide evidence to suggest that it does in humans (Jovic, 1999).

### **3.5 Other forms of therapy used in photosensitive epilepsy**

#### **3.5.1 Conditioning of the photoparoxysmal response**

Various different methods of conditioning have been applied as therapy for photosensitive epilepsy: monocular conditioning (Braham, 1967, Harding et al, 1969), repetitive stimulation with flash frequencies outside the patients' photosensitive range (Forster et al, 1964) and stimulation with additional ambient lighting (Harding et al, 1969). Unfortunately photosensitivity is not really an appropriate target for conditioning therapy due to the fact that in photosensitivity the photoparoxysmal response is the unconditioned response and the light stimulus is the unconditional stimulus, all methods have concentrated on creating an association between the PPR and a conditioned stimulus. According to conditioning theory only the association between the conditioned stimulus and the response can be altered, not the association between the unconditioned stimulus and the unconditioned response (Harding and Jeavons, 1994). Consequently all methods have been relatively unsuccessful (Harding and Jeavons, 1994). However a recent case report suggests that countermeasures, such as rapid relaxation and imagery techniques at the onset of seizure precipitants can reduce seizures induced by visual stimuli, with the reduction remaining after the withdrawal of medication (Noeker and Haverkamp, 2001). Although this suggests that seizures may have been brought on by anxiety resulting from the patient's photophobia rather than photosensitivity.

#### **3.5.2 The use of spectacles in photosensitivity**

Polarised spectacles have been used on the basis that if the light intensity of a particular stimulus can be reduced then the likelihood of a seizure being provoked will be diminished. To be effective the lenses need to absorb approximately 90% of the incident light resulting in much darker spectacles that may not be cosmetically acceptable. Polarised spectacles reduce the light intensity in the surrounding environment but do not alter the flicker of the stimuli. Spectacles have been designed which have incorporated a light sensitive device, which detects flicker and then provides a source of bright light in



response in an attempt to reduce contrast and so reduce the epileptogenic nature of the flicker (Harding et al, 1969). The spectacles were very successful in trial with photosensitive patients but need to be custom made and so tend to be expensive, also the technique of covering one eye appears to be just as effective in the majority of patients (Harding and Jeavons, 1994). Spectacles have been devised, on the basis of this phenomena that monocular stimulation is less evocative, using frosted or heavily polarised filters in one lens (Wilkins et al, 1975). However these again are not particularly cosmetically appealing and also cause eyestrain and headaches in some patients (Wilkins et al, 1977).

Some investigations have been carried out to devise spectacles using coloured lenses to provide protection for photosensitive patients (e.g., Takahashi and Tsukahara, 1992). This is based on the fact that some coloured light is more provocative than other colours, so by altering the colour (hue) and depth of colour (saturation), by using tinted lenses that absorb certain colours, this may reduce the hyperexcitable response of the visual neurons. Capovilla and colleagues reported an abolition of photoparoxysmal responses in 64 of 83 patients (71%) using experimental blue lenses (Capovilla et al, 1999). Arnold Wilkins has extended this work to develop coloured lenses for his patients. The patients choose their own coloured lenses, the majority choosing a rose or purple colour. In 3 of 24 photosensitive patients a reduction of seizures occurred that could be solely attributed to using the lens, reduction of seizures occurred in other patients but additional changes in medication had also taken place. However 13 patients reported a reduction in subjective sensations (e.g. dizziness and aura) with environmental visual stimuli suggesting this may be a useful alternative to pharmacological treatment (Wilkins et al, 1999).

## **Chapter 4: Main study**

### **4.1 Rationale**

The current first line drug for the treatment of photosensitive epilepsy is sodium valproate. Valproate as described previously, is a powerful teratogen and should be avoided by women who are, or are likely to become, pregnant. With increasing evidence that sodium valproate may be associated with the expression of the polycystic ovary syndrome, or at least with some endocrine abnormalities, coupled with the higher incidence of photosensitive epilepsy in females, it is clear that an alternative treatment for photosensitive epilepsy is required. Additionally valproate does not adequately control pattern sensitivity, which is common in patients who are photosensitive (Park et al, 1982). Lamotrigine appears to be a promising substitute for valproate with evidence of efficacy in photosensitivity with acute administration (Binnie et al, 1986). This study attempts to determine the usefulness of lamotrigine as a treatment for photosensitive epilepsy with chronic administration.

### **4.2 Pilot study**

A retrospective review of records of photo and pattern sensitive patients on the Aston register was carried out. All patients had been treated chronically with lamotrigine. Patients were either drug naïve, new onset patients or transferring from valproate to lamotrigine due to clinical considerations, primarily desired pregnancy or evidence of endocrine abnormalities or ovarian cysts. The effect of lamotrigine was measured by the EEG response to intermittent photic stimulation.

#### **4.2.1 Methodology**

Twenty patients were involved in the study, 17 females and three males. The age range was 14-52 years, the mean age was 25.9 years. Ten patients had been previously treated with valproate and seven had not received previous drug therapy. Three were taking



concomitant AEDs (Phenytoin, Clobazam and Phenobarbitone), the dosages of which remained constant during lamotrigine treatment.

Lamotrigine was introduced to patients with small increments in dosage over a period of approximately five months to avoid the risk of rash. The dosage of lamotrigine varied from 25-600mg/day with a mean dosage of 243.75mg/day. Dose escalation was not completed in all patients but they were still included in the assessment as it was felt that patients on a small dosage should be included in the pilot study to investigate the effects of lower dosages of lamotrigine on photosensitivity. Duration of follow up ranged from 3-60 months with mean duration being 20.85 months.

Patient records were examined retrospectively. All patients had undergone EEG testing at least twice, prior to and during lamotrigine therapy. Drug dosage at the time of testing was recorded. EEG testing was carried out at either the Clinical Neurophysiology Unit, Aston University or at the Peter Jeavons Neurophysiology Unit, Queen Elizabeth Psychiatric Hospital and included IPS conducted following clinical protocol used at the Clinical Neurophysiology Unit, Aston University (see appendix A). Patients were tested with either diffuse flash or with a grid in place.

Each patients photosensitivity range (SR) (i.e. the upper limit of sensitivity minus the lower limit of sensitivity), and in drug naïve patients the sensitivity range was compared between baseline (no medication) and at the highest dosage of lamotrigine achieved. Categorisations were made according to change in the sensitivity range. If patients had been previously treated with valproate then a baseline sensitivity range was taken with the optimum controlling dosage of valproate and compared to the range on the highest lamotrigine dosage achieved. A similar comparison was made for patients taking concomitant AEDs.

Four categorisations were used; abolition, improvement, no change and deterioration. These categories were based on a similar study of valproate (Harding et al, 1978). In order to be categorised as abolished the second EEG record would show no evidence of

photosensitivity with IPS. (In patients transferring from sodium valproate previous evidence of photosensitivity would be needed at baseline, indicating that valproate therapy had not completely abolished EEG evidence of photosensitivity). Patients were deemed to have improved if there was a decrease of 78% or greater in the sensitivity range, (i.e. less sensitive to IPS). Similarly patients were deemed to have deteriorated if there was an increase of 78% or greater in the range, i.e. more sensitive to IPS. If there was a change of less than 78% in the range in either direction or the sensitivity range remained unaltered then a category of no change was recorded. The 78% cut off level was taken, as this represents a difference of two standard deviations from the normal variation of the sensitivity range over time (Harding et al, 1978).

#### **4.2.2 Results**

Figure 4.1 demonstrates the effect of lamotrigine on the sensitivity range in patients transferring from valproate. Five patients improved on changing to lamotrigine, i.e. their ranges were reduced by at least 78%. In four of these patients all evidence of photosensitivity, as seen on the EEG, was completely abolished. In two patients, changing from valproate to lamotrigine did not alter the sensitivity range. Deterioration occurred in three patients; i.e. the sensitivity range increased by more than 78%.

Figure 4.2 demonstrates the effect of lamotrigine on drug naïve patients or those taking concomitant AEDs. In five patients at follow up there was no longer any evidence of photosensitivity. However in the remaining five patients the sensitivity range did not alter beyond the 78% level in either direction.

The effect of dosage was examined in those patients who were previously untreated or who were taking concomitant AEDs. Mean dosage for patients whose photosensitivity was abolished was 201mg/day compared to 120mg/day for patients whose photosensitivity remained unchanged. An independent samples t-test was performed comparing dosages of patients showing abolition of photosensitivity with dosages of patients whose photosensitivity remained unchanged.

Figure 4.1: Effect of LTG treatment on the SR of 10 patients previously treated with VPA

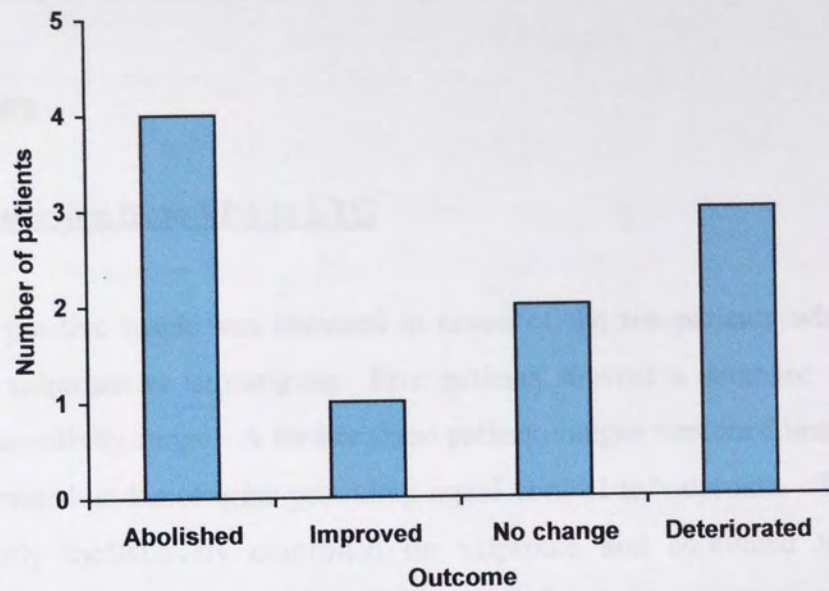
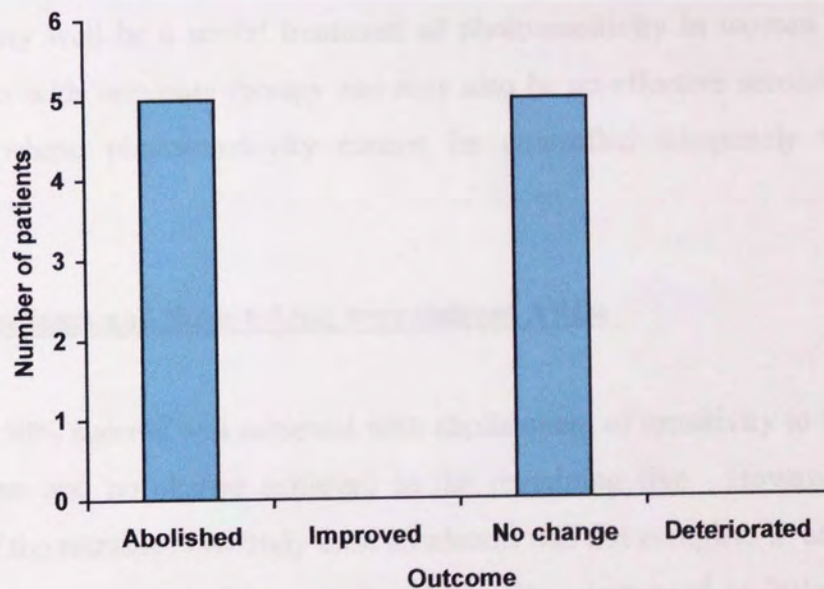


Figure 4.2: Effect of LTG treatment on the SR of 10 patients (drug naïve or taking concomitant AEDs)



The results were non-significant ( $t(8) = 0.82$ ;  $p = 0.437$ ). However the data displayed high standard deviations and each respective group (i.e. abolished and no change)

contained significant outliers. An independent samples t-test was repeated after the removal of outliers, the result remained non-significant ( $t(6) = 2.26; p = 0.65$ ).

### **4.2.3 Discussion**

#### **Patients transferring from VPA to LTG**

Effectively a positive result was obtained in seven of the ten patients who transferred from sodium valproate to lamotrigine. Five patients showed a decrease of more than 78% in their sensitivity range. A further three patients ranges remained unaltered, which may be interpreted as lamotrigine providing equal control to valproate. Three patients were previously ineffectively controlled on valproate and continued to experience absence seizures and myoclonic jerks. These clinical manifestations were resolved on lamotrigine. Although the sensitivity range deteriorated in three patients, one of these patients is now clinically controlled and has not experienced any further seizures since transferring to lamotrigine. Essentially equal or improved control compared to valproate was achieved in 70% of patients transferring to lamotrigine. This suggests that lamotrigine may well be a useful treatment of photosensitivity in women experiencing adverse effects with valproate therapy and may also be an effective second line therapy for patients whose photosensitivity cannot be controlled adequately with sodium valproate.

#### **Drug naive patients and those taking concomitant AEDs**

In this group 50% success was achieved with abolishment of sensitivity to IPS occurring in five patients and no change achieved in the remaining five. However due to the constraints of the retrospective study dose escalation was not complete in all the patients. Mean dosage in the unchanged group was 120mg/day compared to 201mg/day in the abolished group. Dose titration may play a role in lamotrigines effect on the sensitivity range, i.e. reduction of the SR is more likely to occur with higher dosages of LTG. Indeed valproate is more effective in its control of photosensitivity at high dosages



(Jeavons et al 1975). However the non-significant results from the pilot study would not suggest this, although these results may be explained by inadequate sample size.

#### **4.2.4 Conclusions**

These preliminary results suggest that the chronic administration of lamotrigine affects the sensitivity range and that in the majority of patients the range is reduced. Lamotrigine appears to be effective in the treatment of photosensitivity with chronic administration and could well be an appropriate substitute for sodium valproate in women of childbearing potential. Lamotrigine may also prove useful as a second line therapy for patients in which control of photosensitivity cannot be achieved with valproate treatment.

As with all retrospective studies the findings are limited by the restrictions of the design, however the evidence suggests that a prospective, more controlled study investigating the effects of lamotrigine in the treatment of photosensitive epilepsy is justified.

#### **4.3 Design of main study**

A prospective, longitudinal study was planned to investigate the effects of lamotrigine in the treatment of photosensitive epilepsy in adults and children over at least a 12 month follow up period. Ethical approval was obtained from the Human Science Ethical Committee at Aston University and from the Birmingham Health Authority Local Research Ethical Committee (South Birmingham).

##### **4.3.1: Adult protocol**

The original protocol required patients to attend for EEG testing once a week for one month and then once fortnightly for eight months. Patient recruitment was extremely slow with only two patients recruited by February 2000. The major obstacle to patient recruitment appeared to be the frequency of testing. The majority of patients who were deemed suitable for this trial had other commitments (work, family) and could not have

possibly committed to such a vigorous testing schedule. A further point is that patients do not enjoy intermittent photic stimulation, many find it unpleasant and can get distressed. Although patients are interested in the research and willing to help the thought of having IPS every two weeks is extremely off-putting to many patients. The following reduced testing protocol was therefore proposed as detailed in table 4.1. Intermittent photic stimulation was carried out as described in appendix A and pattern testing was performed following the clinical protocol used at the Clinical Neurophysiology Unit, Aston University, as described in appendix B.

#### **4.3.1.1 Patients**

It was intended that approximately 40 photo and pattern sensitive patients (numbers estimated from the departmental records of patients attending the Clinical Neurophysiology Unit, Aston University) were to be recruited from patient databases at either the Clinical Neurophysiology unit at Aston University or Birmingham University seizure clinic. The patients were to be within the age range of 16-65 years (The age range was decided upon as it is within the realms of the LTG monotherapy licence. In women over 65 years the side effects of teratogenicity and PCOS are unlikely to apply. Children under 16 were entered into the children's study.)

Patients were approached if they were current female patients of child bearing age taking sodium valproate and were offered the change to lamotrigine to avoid teratogenicity and sodium valproate associated adverse side effects of weight gain and reproductive endocrine disorders. Newly diagnosed patients discussed with their consultant the most appropriate medication for them, and if they then decided to commence lamotrigine therapy they were considered for the study. Male patients were also offered treatment with lamotrigine to avoid the adverse effects associated with sodium valproate in males such as weight gain and changes in testosterone levels (Nag et al, 1997).

All patients were diagnosed as being photo and/or pattern sensitive and had experienced at least one clinical seizure on the basis of which their doctor had advised medication.

Table 4.1: The final protocol for the adult study

Time scale	Medication Group A (changeover patients)	Test Group A	Medication Group B	Tests Group B
Baseline	VPA - 100% of original dose LTG - nil	EEG with full photic and pattern testing BDI Stroop BMI	Nil	EEG with full photic and pattern testing BDI Stroop BMI
Week 12	VPA - 100% of original dose LTG - 50mg/day	EEG with full photic and pattern testing BDI Stroop BMI	LTG - 50mg/day	EEG with full photic and pattern testing BDI Stroop BMI
Week 20	VPA - 100% of original dose LTG - 100mg/day	EEG with full photic and pattern testing BDI Stroop BMI	100mg/day	EEG with full photic and pattern testing BDI Stroop BMI
Week 28	VPA - 50% of original dose LTG - 150mg/day	EEG with full photic and pattern testing BDI Stroop BMI	LTG - 150mg/day	EEG with full photic and pattern testing BDI Stroop BMI
Week 36	VPA - Nil LTG - 200mg/day	EEG with full photic and pattern testing BDI Stroop BMI	LTG - 200mg/day	EEG with full photic and pattern testing BDI Stroop BMI
Month 15	LTG - As deemed appropriate by clinician	EEG with full photic and pattern testing BDI Stroop BMI	LTG - As deemed appropriate by clinician	EEG with full photic and pattern testing BDI Stroop BMI

Table 4.2 details the exclusion criteria for the study. Patients were split into two groups as detailed in table 4.3.

Recruitment for the trial was carried out between May 1998 and February 2001. Figure 4.3 details the recruitment of adult patients.

Table 4.2: Exclusion criteria for the adult study

I) Under 16 years old or over 65 years of age.
II) No evidence of photo or pattern sensitivity (as seen on the EEG).
III) Hypersensitivity to lamotrigine.
IV) Currently taking anti-epileptic medication other than sodium valproate.
V) Not experiencing adverse effects of sodium valproate or have little chance of becoming pregnant in the future.

Table 4.3: Adult patient groups

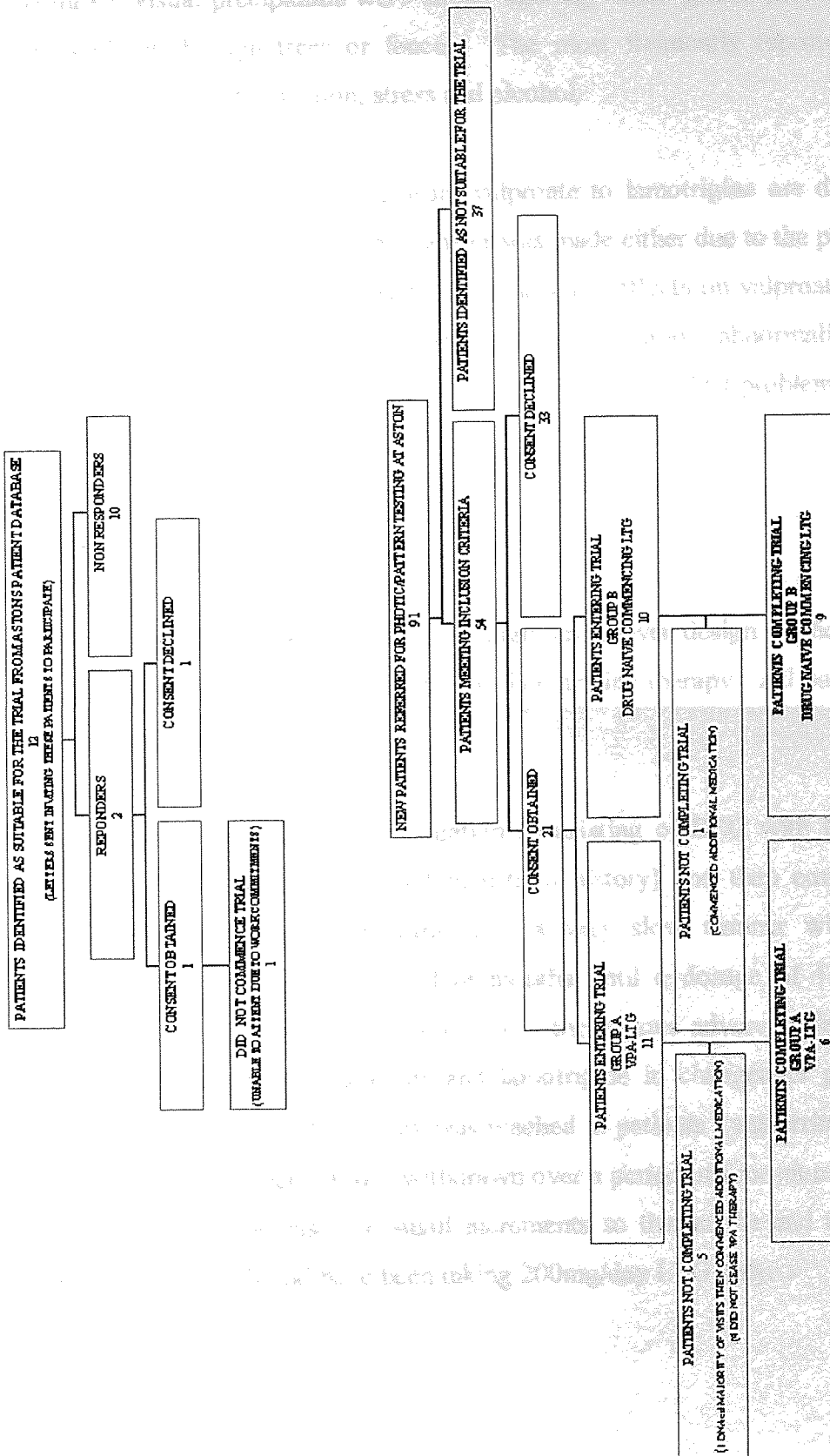
Group:	Description:
Group A	Current patients receiving valproate therapy whom are experiencing adverse effects or who may wish to become pregnant.
Group B	New onset patients requiring AED treatment.

As can be seen from figure 4.3, 103 patients were originally either identified from Aston's records as being suitable for the trial or were referred as prospective patients. However consent was only obtained in 22 of the 66 patients meeting the inclusion criteria. At the end of the study six of the eleven patients in the valproate changeover group completed the trial. Nine of the ten drug naïve patients were followed up to visit six, although some data were available for analysis for the tenth drug naïve patient, who did not commence concomitant medication until visit six, allowing analysis of the data from the previous visits.

The age range of the patients was 17-36 years with a mean age of 24.06 years, 20 were female and one patient was male and one female patient was left-handed. All patients experienced tonic clonic seizures (some with additional absence seizures) except one patient who had only ever experienced absences. The duration of the patients' epilepsy ranged from less than one year to 22 years with a mean duration of 10.68 years. Diagnosis of type of epilepsy was not given in seven of the patients, four were diagnosed with juvenile myoclonic epilepsy, one with primary generalised epilepsy and three with pure photo/pattern sensitive epilepsy.



Figure 4.3: Adult study recruitment May 1998-February 2001



Eight of the patients presented with both visual and non-visual seizure precipitants as summarised in figure 4.4. Two patients could not identify any precipitating factors. The most common visual precipitants were strobe lighting, video games played through the TV and sunlight through trees or fences. The most frequently reported non-visual precipitants were sleep deprivation, stress and alcohol.

The reasons for patients transferring from valproate to lamotrigine are documented in figure 4.5. Apart from one patient the transfer was made either due to the patient's desire to conceive or because they were experiencing adverse effects on valproate. Half of the patients in the transferring group experienced menstruation abnormalities and had evidence of polycystic ovaries on MRI scanning, two patients had problems with weight gain after commencing valproate therapy.

#### **4.3.1.2 Methodology**

The study was an open label trial, with a single cross-over design applied to group A patients, valproate therapy being compared to lamotrigine therapy. All patients acted as their own controls.

All patients underwent baseline investigation (consisting of EEG with full photic and pattern testing, height and weight and menstrual history) and then commenced LTG therapy. Lamotrigine was to be titrated in a very slow manner with very small increments in dose over a period of five months until a dosage of 100mg/day was reached. Slow titration was necessary to avoid the serious adverse effect of rash and adverse interactions between valproate and lamotrigine in changeover patients (Yuen, 1992). Once the dosage of 100mg/day was reached in patients transferring from sodium valproate, valproate was very slowly withdrawn over a period of four months, at the same time lamotrigine was increased in small increments so that at the end of nine months from baseline patients should have been taking 200mg/day LTG only.

Figure 4.4: Precipitants of clinical phenomena in adult patients

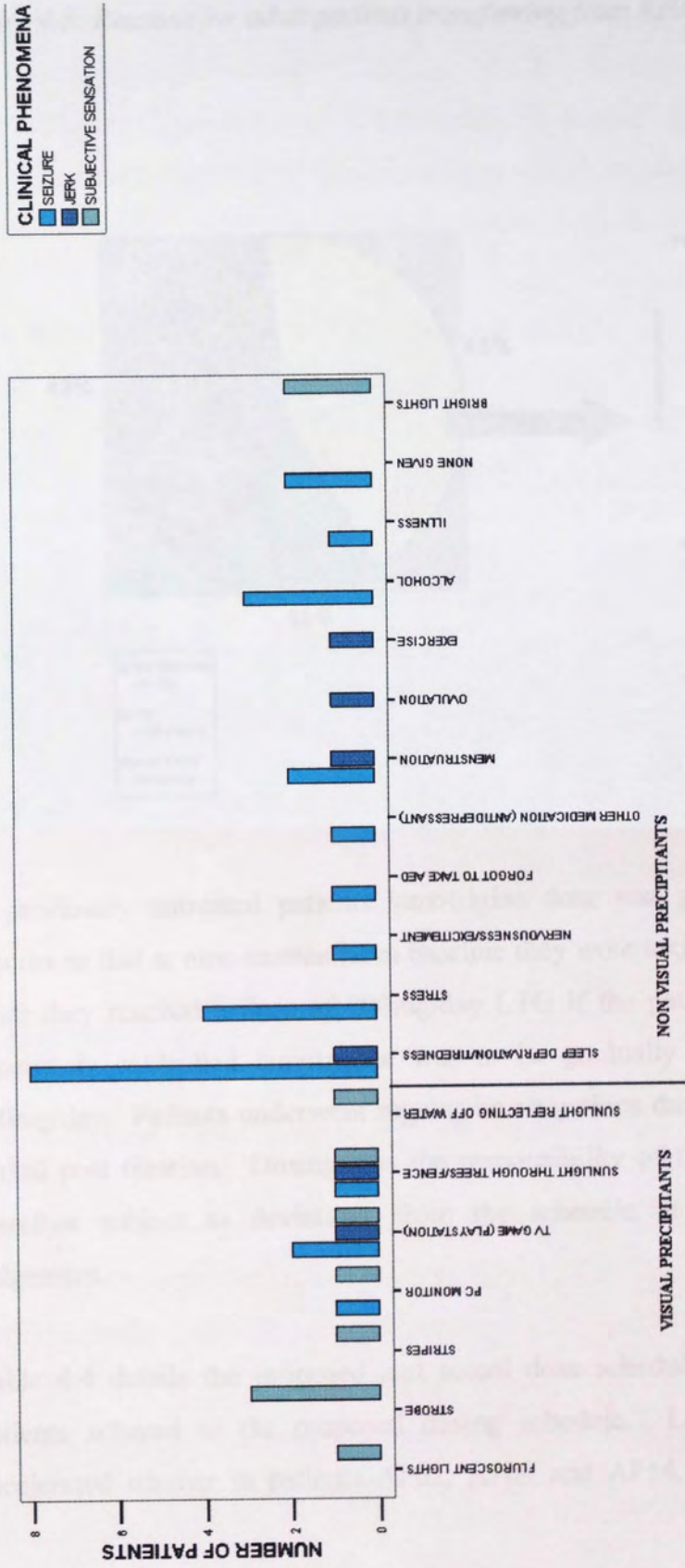
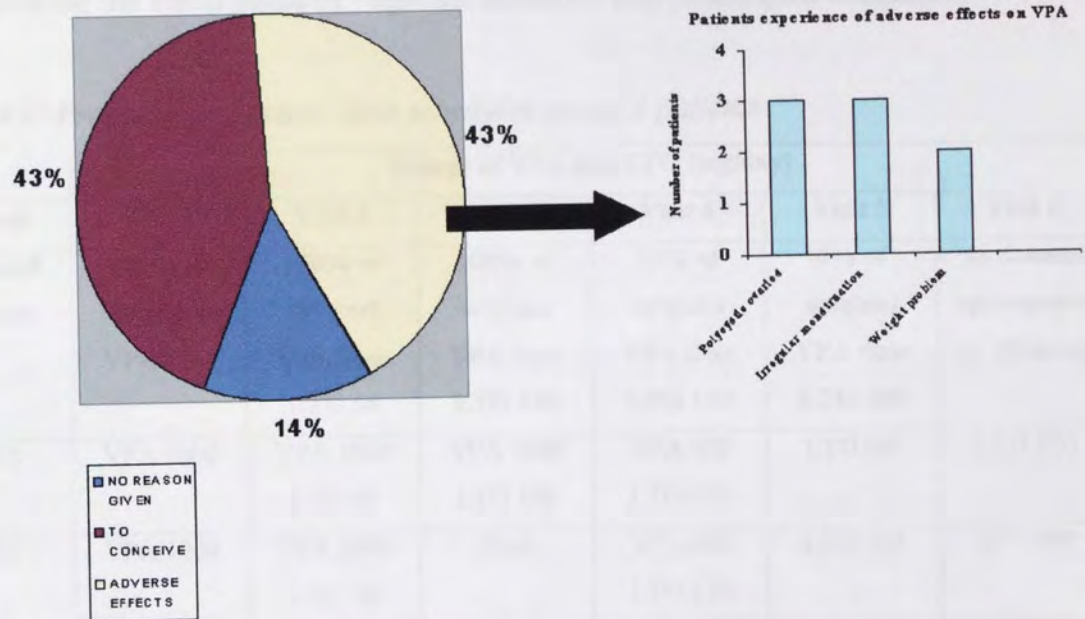




Figure 4.5: Reasons for adult patients transferring from VPA to LTG



In previously untreated patients lamotrigine dose was gradually increased over four months so that at nine months from baseline they were taking a dose of 200mg/day LTG. Once they reached a dose of 200mg/day LTG if the patients photosensitivity was not adequately controlled lamotrigine was to be gradually increased to a maximum of 600mg/day. Patients underwent regular investigations during this period and during the period post titration. Dosing was the responsibility of the referring clinician and was therefore subject to deviations from the schedule in accordance to their clinical judgement.

Table 4.4 details the proposed and actual dose schedules for group A patients. No patients adhered to the proposed dosing schedule. Lamotrigine was titrated in an accelerated manner in patients AP02, AP09 and AP14. Valproate was reduced in a

slower manner than that originally proposed in patients AP11 and AP14 and at an accelerated rate in patient AP17.

It is difficult to comment on the schedule of patient AP15 as due to retrospective recruitment and the patient being unable to attend appointments she did not visit for testing during the initial phase of valproate reduction and lamotrigine escalation.

*Table 4.4: Proposed and actual dose schedules group A patients*

Patient	Dosage of VPA and LTG (mg/day)					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
<b>Proposed schedule</b>	<b>100% of original VPA dose</b>	<b>100% of original VPA dose LTG 50</b>	<b>100% of original VPA dose LTG 100</b>	<b>50% of original VPA dose LTG 150</b>	<b>0% of original VPA dose LTG 200</b>	<b>As deemed appropriate by clinician</b>
AP02	VPA 1000	VPA 1000 LTG 50	VPA 1000 LTG 100	VPA 600 LTG 175	LTG300	LTG 500
AP09	VPA 1000	VPA 1000 LTG 50	DNA	VPA 600 LTG 175	LTG 300	LTG 300
AP11	VPA 1000	DNA	VPA 1000 LTG 100	DNA	VPA 400 LTG 200	LTG 350
AP14	VPA 1000	VPA 1000 LTG 10	VPA 200 LTG 100	DNA	LTG 250	LTG 250
AP15	VPA 1000	DNA	DNA	DNA	LTG 275	LTG 400
AP17	VPA 200	VPA 200 LTG 50	VPA 200 LTG 100	LTG 150	LTG 200	LTG 400

Note: DNA denotes that the patient did not attend for testing at that visit.

Table 4.5 details the proposed dose schedules for group B patients. Two patients (AP01 and AP06) completed the schedule as proposed. Three patients (AP04, AP12 and AP19) were clinically controlled on 100mg/day LTG and therefore lamotrigine was not increased further. One patient (AP08) followed the proposed dose schedule but at visit six was taking concomitant levetiracetam due to impaired concentration attributed to subclinical epileptiform discharges.

As can be seen from table 4.5 the dosing for patients AP03, AP07, AP13 and AP18 deviated from the proposed schedule. Patients AP03 and AP07 lamotrigine was titrated in a more rapid manner. In AP13 retrospective recruitment meant that she had already reached a dosage of 250mg/day LTG at her first follow up visit (visit three). Patient AP18's dosage initially increased at a slower rate than the proposed schedule, until visit five when it increased in an accelerated manner.

Table 4.5: Proposed and actual dose schedules group B patients

Patient	Dosage of LTG (mg/day)					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
<b>Proposed schedule</b>	Nil	LTG 50	LTG 100	LTG 150	LTG 200	As deemed appropriate by clinician
AP01	Nil	LTG 50	LTG 100	LTG 150	LTG 200	LTG 300
AP03	Nil	LTG 50	LTG 100	LTG 200	LTG 300	LTG 300
AP04	Nil	LTG 50	LTG 100	DNA	DNA	DNA
AP06	Nil	LTG 100	DNA	LTG 150	LTG 200	LTG 300
AP07	Nil	LTG 50	LTG 100	LTG 200	LTG 200	LTG 250
AP08	Nil	DNA	LTG 100	DNA	LTG 200	LTG 150 LEVE 1500
AP12	Nil	LTG 50	LTG 100	LTG 100	DNA	LTG 100
AP13	Nil	DNA	LTG 250	LTG 300	LTG 400	LTG 400
AP18	Nil	DNA	LTG 100	LTG 100	LTG 300	LTG 400
AP19	Nil	LTG 50	LTG 100	LTG 100	DNA	LTG 100

Note: DNA denotes that the patient did not attend for testing at that visit.

As a result of the frequent deviations from the proposed dosing schedule for the majority of measures analysis was carried out comparing baseline and final follow up visit attended.



The EEG with photic and pattern testing was used to determine the effect of lamotrigine both on the background EEG and on the sensitivity range. Menstrual histories (see appendix C) were taken to determine the effect of lamotrigine on the menstrual cycle in all female patients, and to record any improvement of menstrual cycle regularity in patients transferring from valproate to lamotrigine, particularly in those suffering from menstrual disturbance or ovarian cysts.

The psychological tests; the Beck Depression Inventory (BDI) and the Stroop test were used to determine any adverse effects of lamotrigine upon mood or concentration. The BDI was chosen as it has been previously shown that 50% of patients with epilepsy suffer from depression (Indaco et al, 1992). This appears to be as a result of the epilepsy itself rather than a reaction to a chronic disease (Perini et al, 1996). Lamotrigine appears to act as a mood stabiliser, as does valproate (Bowden, 1998) and indeed is now used in the treatment of bipolar disorder (Kotler and Matar, 1998). Improvements in mood in epileptic patients with lamotrigine treatment have been documented (Meador and Baker, 1997) and it would be fortuitous if the antiepileptic drug also has effects on epilepsy-associated depression.

The Stroop test has been described as a particularly sensitive and reliable measure in the investigation of cognitive effects of AEDs (Banks and Beran, 1991) and is one of the commonest neuropsychological tests used in the investigation of the cognitive effects of AEDs (Cochrane et al, 1998). Conflicting reports have been made regarding the effect of lamotrigine on the Stroop. For example, Banks and Beran (1991) documented a decrease in performance in the majority of patients treated with lamotrigine, whereas Meador and Baker reported no difference in scores on the Stroop between treatment with lamotrigine and a placebo (Meador and Baker, 1997).

All patients were asked to record any subjective experiences or seizures to provide data of the effect of lamotrigine on clinical manifestations of photosensitive epilepsy. Height

and weight were recorded regularly in all patients to investigate the effects of lamotrigine on the body mass index (BMI). Of particular interest are women transferring from valproate due to its association with weight gain.

#### **4.3.2. Children's Protocol**

The children's protocol is similar to that of the adults (appendix D). The effect of lamotrigine in the treatment of PSE was investigated in children aged 10-16 years.

##### **4.3.2.1 Patients**

The aim was to recruit approximately 20-25 children diagnosed as being photo or pattern sensitive from patient databases at either the Clinical Neurophysiology Unit at Aston University or Birmingham Children's hospital (as estimated from the records at the two establishments). Patients were within the age range of 10-16 years, chosen because it is within the age range of patients attending the Birmingham Children's Hospital from where patients were recruited. Patients over 16 years of age were entered into the adult study.

Patients were either currently taking sodium valproate, other antiepileptic drugs or were new onset PSE patients, previously untreated. Current patients taking sodium valproate whose photosensitivity was not controlled were transferred to lamotrigine. Newly diagnosed patients were randomised to either lamotrigine or valproate, as were patients taking other AEDs whose photosensitivity was not controlled. All patients were photo and/or pattern sensitive and had at least one clinical seizure on the basis of which their doctor advised medication. Table 4.6 details the exclusion criteria for the children's study. Patients were split into three groups as detailed in table 4.7.



Table 4.6: Exclusion criteria for the children's study

I) Under 10 years old or over 16 years of age.
II) No evidence of photo or pattern sensitivity (as seen on the EEG).
III) Hypersensitivity to lamotrigine.
IV) Currently taking VPA with full control of PSE.

Table 4.7: Children's patient groups

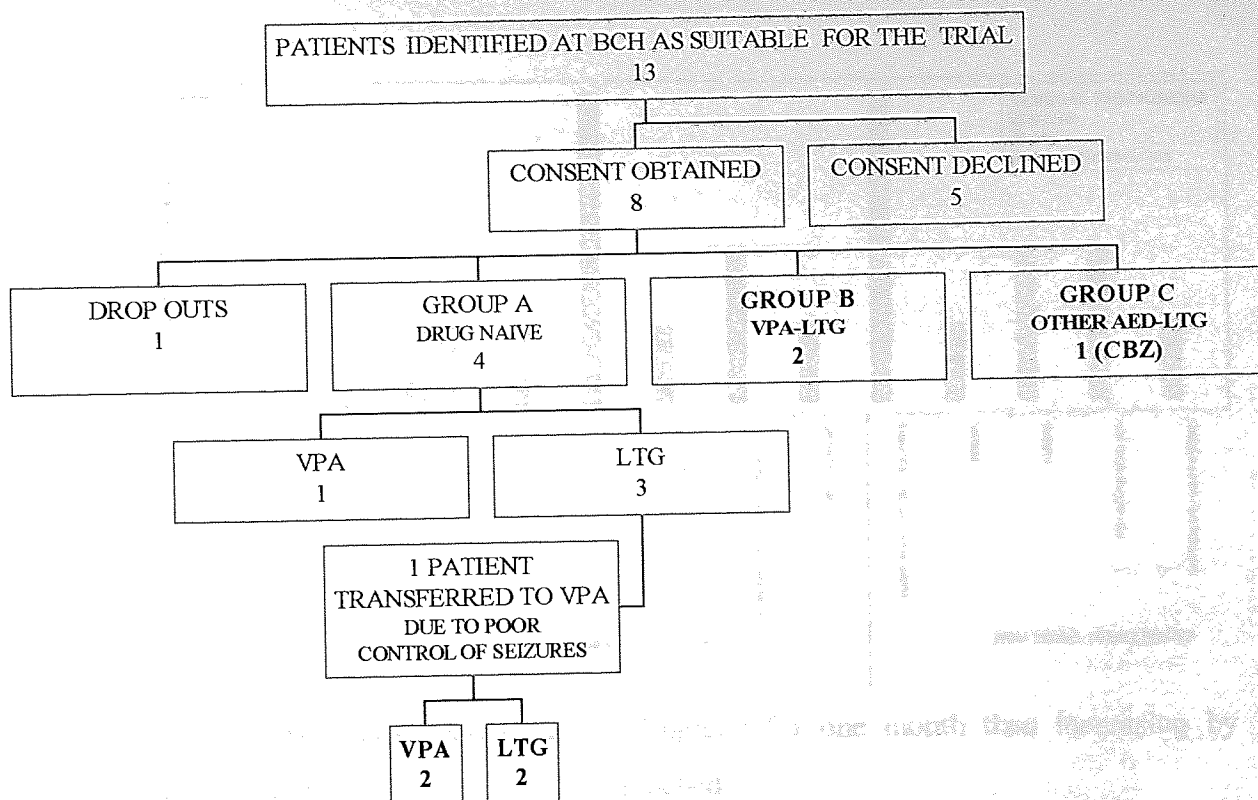
Group:	Description:
Group A	Patients who have failed treatment with VPA at a maximum tolerated dose or at a dose of 40mg/kg/day or more (To be transferred to LTG).
Group B	New onset patients requiring AED treatment (To be randomly allocated to VPA or LTG).
Group C	Patients who have failed to respond to other AEDs at the maximum tolerated dose or at a high target plasma level (To be randomly assigned to VPA or LTG).

Recruitment occurred during the period October 1999 to February 2001 and, like the adult recruitment, was very slow. Thirteen patients were originally deemed suitable for the trial but as can be seen from figure 4.6 only seven completed the trial. Four were in group A, (2 randomised to LTG and 2 randomised to VPA), and two patients were transferred from valproate in group B and one patient in group C was transferred from carbamazepine.

The mean age of the seven children who completed the trial was 12.43 years with a range of 10-14 years. One child was male and six were female and one female patient was left-handed. The mean duration of epilepsy within the group was 3.94 years with a range of 2 months to 9 years since diagnosis.

Three children had generalised tonic clonic seizures, three had absences and one had seizures which were secondary generalised. Three of the above patients had multiple seizure types (one had a combination of secondary generalised seizures and absences and the other two had a combination of absences and tonic clonic seizures).

Figure 4.6: Children's study recruitment: October 1999-February 2001



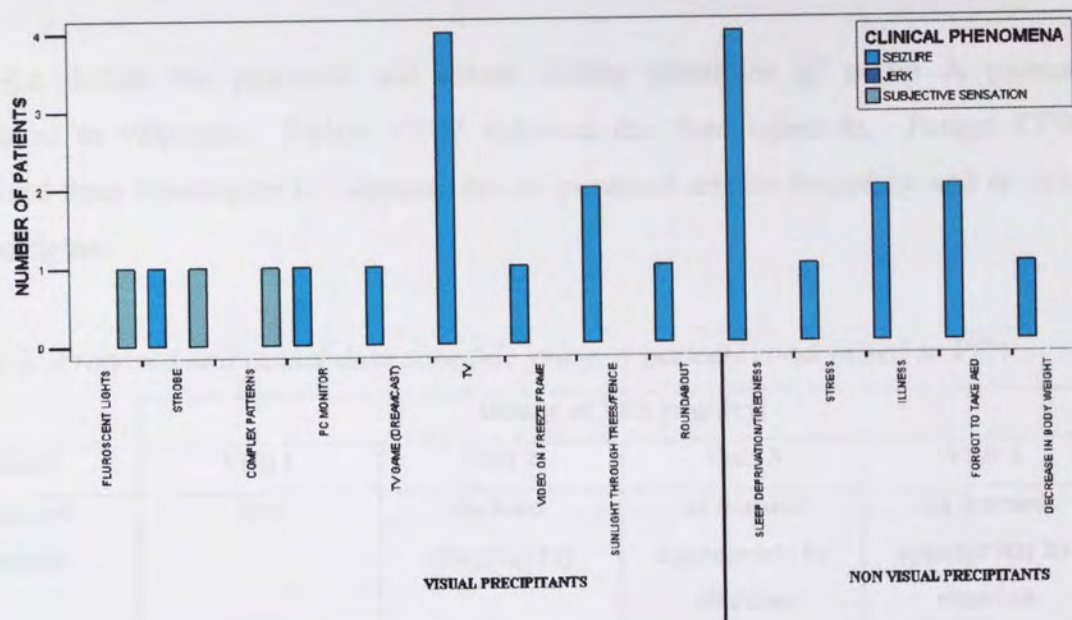
All patients displayed both pattern and photosensitivity and had identifiable seizure precipitants (as documented in figure 4.7) both visual and non-visual. The most common visual seizure precipitant was the TV with four of the patients experiencing seizures evoked by watching television. The most common non-visual seizure precipitant was sleep deprivation, similar to the adult data.

#### **4.3.2.2 Methodology**

The study was an open label trial, with a single crossover design applied to group A patients, valproate therapy being compared to lamotrigine therapy. A randomised design was applied to Groups B and C; these patients acted as their own controls.

All patients underwent baseline investigation and then commenced lamotrigine therapy. Lamotrigine was again to be titrated in a very slow manner with very small increments in dose over a period of nine months. Commencing at 5mg/day for two weeks, then

Figure 4.7: Precipitants of clinical phenomena in patients on the children's study



10mg/day for two weeks, increasing to 25mg/day for one month then increasing by 25mg/day per month until 200mg/day was reached.

Patients transferring from valproate were to gradually change medication as described in the adult protocol. Once at a dose of 200mg/day of lamotrigine if patients PSE was not clinically controlled (i.e. they were still experiencing seizures) the dosage was to be gradually increased to a maximum of 600mg/day.

In patients randomised to receive valproate, it was gradually introduced to patients over five weeks, commencing at 5mg/kg/day increasing each week by 10mg/kg/day, until the maximum dosage of 40mg/kg/day was attained.

Group C patients were to follow the same schedule as group A and B patients for the initiation of lamotrigine, the withdrawal of AED was to be carried out at the discretion of their referring clinician. Again all dosing was managed by the referring clinician and was



again subject to deviations from the proposed schedules based upon their professional discretion.

Table 4.8 details the proposed and actual dosing schedules of group A patients randomised to valproate. Patient CP07 followed the dose schedule. Patient CP02 transferred from lamotrigine to valproate due to increased seizure frequency and severity on lamotrigine.

*Table 4.8: Proposed and actual dose schedule group A patients randomised to VPA*

Patient	Dosage of VPA (mg/day)			
	Visit 1	Visit 2	Visit 3	Visit 4
<b>Proposed schedule</b>	<b>Nil</b>	<b>At least 40mg/kg/day</b>	<b>As deemed appropriate by clinician</b>	<b>As deemed appropriate by clinician</b>
CP02	Nil	LTG 25	LTG 100	VPA 800
CP07	Nil	VPA 800	VPA 800	VPA 800

Table 4.9 demonstrates the proposed and actual dosages for group A patients randomised to lamotrigine. Patient CP04's dosage was increased in accordance to the original schedule. Patient CP03 had her dose of lamotrigine initially increased in an accelerated manner and then slower than that proposed by the schedule.

*Table 4.9: Proposed and actual dose schedule group A patients randomised to LTG*

Patient	Dosage of VPA (mg/day)			
	Visit 1	Visit 2	Visit 3	Visit 4
<b>Proposed schedule</b>	<b>Nil</b>	<b>LTG 25</b>	<b>LTG 200</b>	<b>As deemed appropriate by clinician</b>
CP03	Nil (LTG 5mg for one day therefore effectively nil)	LTG 50	DNA	LTG 100
CP04	Nil	LTG 25	LTG 400	LTG 400

Note: DNA denotes that the patient did not attend for testing at that visit.

Table 4.10 details the proposed and actual dosages of group B patients. In both patients valproate was withdrawn at a much faster rate than that detailed in the original proposal. Patient CP05's lamotrigine was initiated in an accelerated manner.

*Table 4.10: Proposed and actual dose schedule group B patients transferring from VPA to LTG*

Patient	Dosage of VPA (mg/day)			
	Visit 1	Visit 2	Visit 3	Visit 4
<b>Proposed schedule</b>	<b>100% original dose of VPA</b>	<b>100% original dose of VPA LTG 25</b>	<b>75% original dose of VPA LTG 200</b>	<b>As deemed appropriate by clinician</b>
CP01	VPA 800	VPA 800 LTG 25	LTG 200	VPA 800
CP05	VPA 20	LTG 50	LTG 200	DNA

Note: DNA denotes that the patient did not attend for testing at that visit.

Patient CP06 followed the original dosing schedule as can be seen in table 4.11.

Again, as in the adult's study, there were a number of deviations from the proposed dosing schedules. Consequently for the majority of measures analysis was conducted by comparing baseline to final follow up visit.

*Table 4.11: Dosing schedule for patient CP06 transferring from LTG*

Patient	Dosage of VPA (mg/day)			
	Visit 1	Visit 2	Visit 3	Visit 4
CP06	CBZ 200	LTG 25	LTG 200	LTG 250

Patients underwent baseline investigations: EEG (with full pattern and photic stimulation); menstrual history (where appropriate); height and weight, BDI and Stroop (where appropriate); prior to alterations or commencement of treatment and were further

tested at six weeks (half way through dose incrementation), six months and 12 months. A less rigorous testing regime was decided upon for the children's protocol to reduce the amount of strain upon the child and their family and to reduce the time spent away from school.

## **Chapter 5 Adult Study**

It was originally intended that for each measure (photoparoxysmal responses, occipital spikes, normal EEG responses, background EEG, seizure control, body mass index and menstrual function) responses from visits one to six would be analysed to create dose-response curves for each individual measure. However due to retrospective recruitment, missing data and variations in dosages between patients as discussed in chapter four, section 4.3.1.2 this was not feasible. Therefore all measures were compared from baseline to last available follow up. For group A patients transferring from sodium valproate in order for the measures from their last available follow up to be included in the analysis it was necessary for the patient to have completely withdrawn from valproate at least six months previously.

The EEG responses to photic and pattern stimulation were the primary measure in this study. It was originally proposed that patients would be tested at each of the six visits with all stimulus types (photic stimulation with the grid, diffuse photic stimulation and pattern stimulation with both reversing square wave (SWR) and stationary sine wave (SS) gratings). However due to extraneous circumstances (e.g. patient fatigue and time limits) some patients were not tested with all the stimuli. In group A diffuse photic stimulation was not performed in two patients (AP11 and AP15). Pattern stimulation using stationary sine wave gratings was also not performed at follow up on one patient (AP15). In group B patients diffuse photic stimulation was not performed at baseline and/or follow up in four patients (AP04, AP07, AP13 and AP19). Pattern stimulation (SWR and SS) was not performed at follow up in one patient (AP07).

### **5.1 Photoparoxysmal responses**

Sensitivity ranges for photoparoxysmal responses were calculated and compared between baseline and final follow up visit, as detailed in the pilot study, for each stimulus type.



The patients were classified as detailed in table 5.1 based upon a study by Harding and his colleagues of the effectiveness of valproate in the treatment of photosensitive epilepsy (Harding et al, 1978).

*Table 5.1: Outcome classification*

<b>Outcome</b>	<b>Definition</b>
Abolished	PPRs seen at baseline were no longer present at follow up
Improved	The SR was reduced >78%
No change – still sensitive	The SR was reduced or increased < 78% and the patient displayed PPRs at baseline and follow up
No change – not sensitive	The patients did not display PPRs at baseline or follow up
Deteriorated	The SR had increased > 78%
New presentation	PPRs were seen at follow up but not at baseline

### **5.1.1 Results**

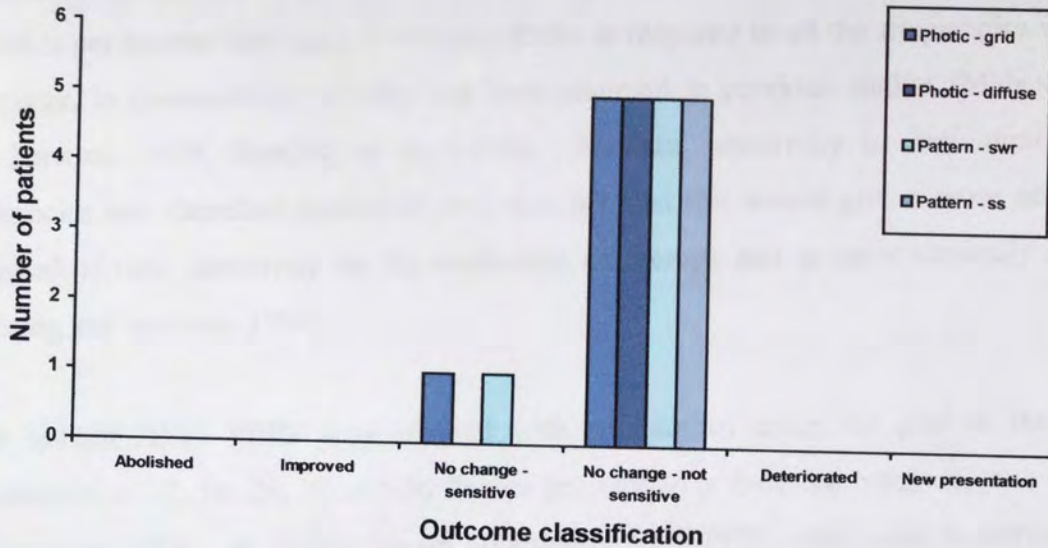
#### **Group A patients**

The outcome results from group A patients are presented in figure 5.1. Only one patient (AP15) demonstrated a change in her SR. The remaining five patients did not display photoparoxysmal responses at baseline or follow up regardless of the type of stimulation used. At follow up PPRs were still elicited with photic stimulation using the grid and with pattern stimulation using reversing square wave gratings (SWR) in patient AP15.

Due to the nature of the data statistical analysis could not be performed on outcome classification. Therefore a McNemar paired samples test of change was used to compare sensitivity (sensitive Vs non-sensitive) from baseline to follow up for each stimulus type; photic (grid and diffuse combined) and pattern (SWR and SS combined).



Figure 5.1: PPR outcome classification group A patients



The number of discordant pairs was below 20 so the exact test was used. For both photic and pattern stimulation there was no significant difference between sensitivity at baseline and follow up (McNemar  $p = 1.00$ , for both photic and pattern stimulation respectively).

The number of patients displaying PPRs at each photic and pattern stimuli frequency was examined to determine whether there was a difference between visits for each respective frequency.

As previously discussed with photic stimulation only one patient (AP15) displayed photoparoxysmal responses at baseline or follow up. Her sensitivity range was 12-30 flashes per second at baseline and 10-20 flashes per second at follow up demonstrating a shift of both the lower and upper limits to lower flash rates. This alteration did not reach the 78% level and therefore she was classified as no change – still sensitive. With pattern stimulation using the reversing square wave gratings her ranges was 2-6cpd at both baseline and follow up.

It was noted when testing with the visual stimuli that patients oftener displayed islets of non-sensitivity within their sensitivity ranges. For example if a patients range was 4-25 flashes per second they may not display PPRs in response to all the frequencies within this range, in contradiction to what has been assumed in previous studies (Maheshwari and Jeavons, 1975, Harding et al, 1978). Patients' sensitivity to individual flash frequencies was therefore examined as it was felt that this would give a more accurate portrayal of their sensitivity for the evaluation of therapy and is more clinically useful (Harding and Jeavons, 1994).

With patient AP15 PPRs were evoked with stimulation using the grid at the flash frequencies of 12, 14, 20, 25 and 30 flashes per second at baseline when she was taking 1000mg/day VPA. At follow up on 400mg/day LTG PPRs were seen in response to stimulation at 10, 12, 14, 16, 18 and 20 flashes per second. Her sensitivity range had therefore shifted slightly to lower frequencies and had also marginally expanded, although this increase did not reach the 78% level.

With pattern stimulation again only patient AP15 displayed photoparoxysmal responses. With reversing square wave gratings PPRs were evoked at 2, 3 and 6 cycles per degree at both baseline and follow up. At baseline PPRs were again elicited at 2, 3 and 6 cycles per degree with stationary sine wave gratings, unfortunately testing was not repeated at follow up.

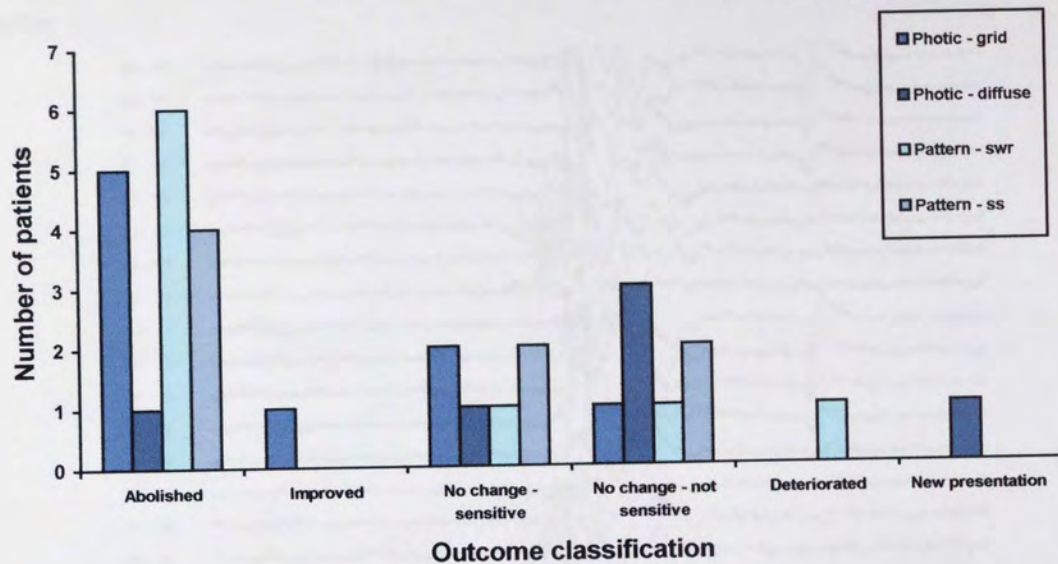
Due to the nature of the group A patient data statistical analysis regarding the number of patients displaying photoparoxysmal responses could not be executed.

### **Group B patients**

The outcome data from group B patients were analysed using the same method as group A patients and the results are presented in figure 5.2



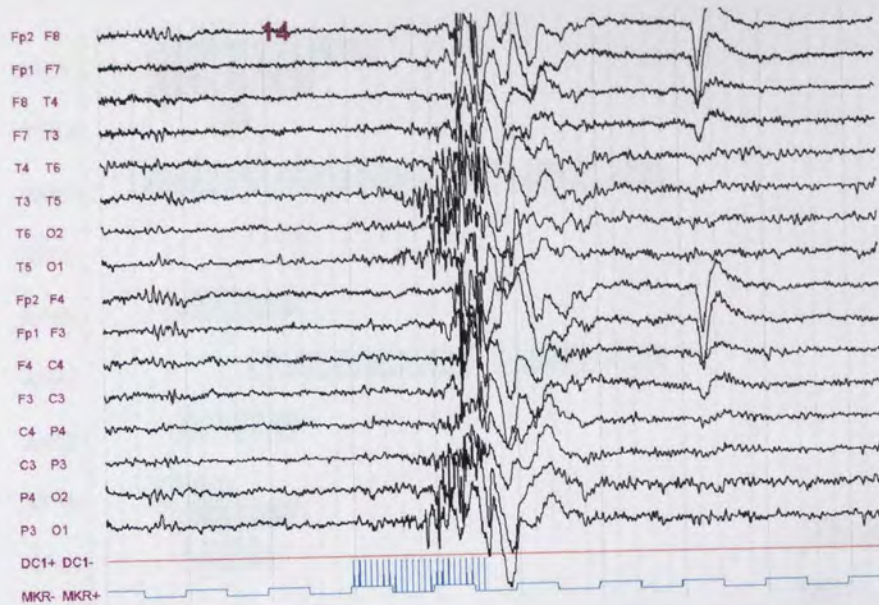
Figure 5.2: PPR outcome classification group B patients



The majority of patients who showed sensitivity at baseline experienced an abolition of PPRs or a reduction in their sensitivity range at follow up. Figure 5.3 demonstrates the abolition of a PPR. At baseline a clear grade III PPR was elicited by photic stimulation using the grid at 14 flashes per second when the patient was unmedicated. At follow up 12 months later the patient was taking 200mg/day LTG. Photic stimulation at 14 flashes per second with the grid in place evoked only a photic driving response in occipital regions.

Figure 5.3: Abolition of PPR evoked by photic stimulation following lamotrigine treatment

**Baseline**



**Follow up**



Figures 5.4-5.7 demonstrate the sensitivity ranges of sensitive patients at baseline and follow up for the four types of stimulus.



Figure 5.4: SRs of group B patients sensitive to photic stimulation with the grid at baseline and follow up

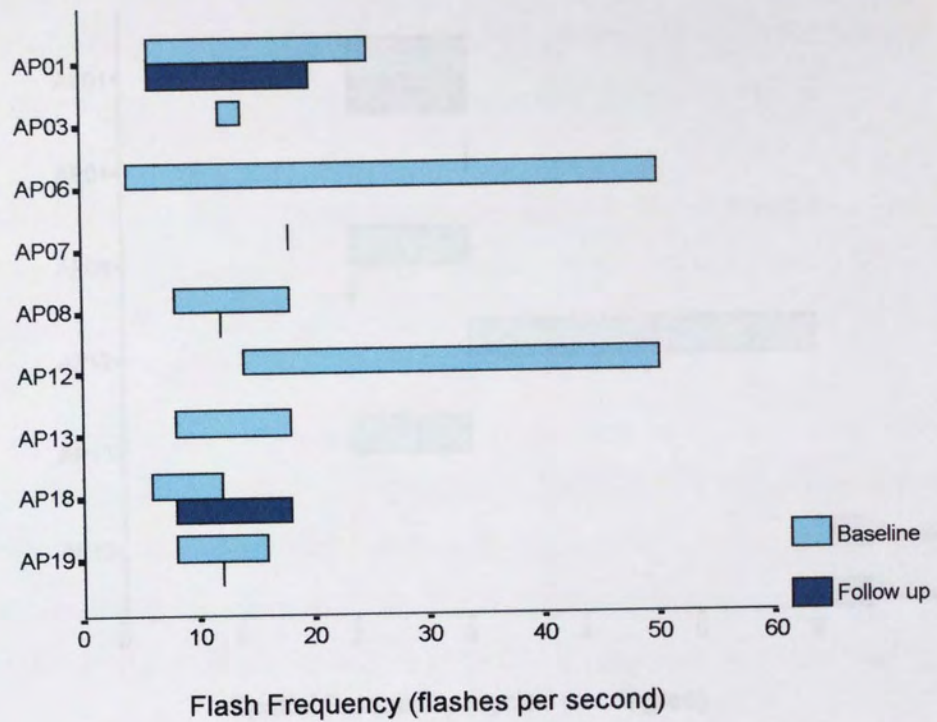


Figure 5.5: SRs of group B patients sensitive to diffuse photic stimulation at baseline and follow up

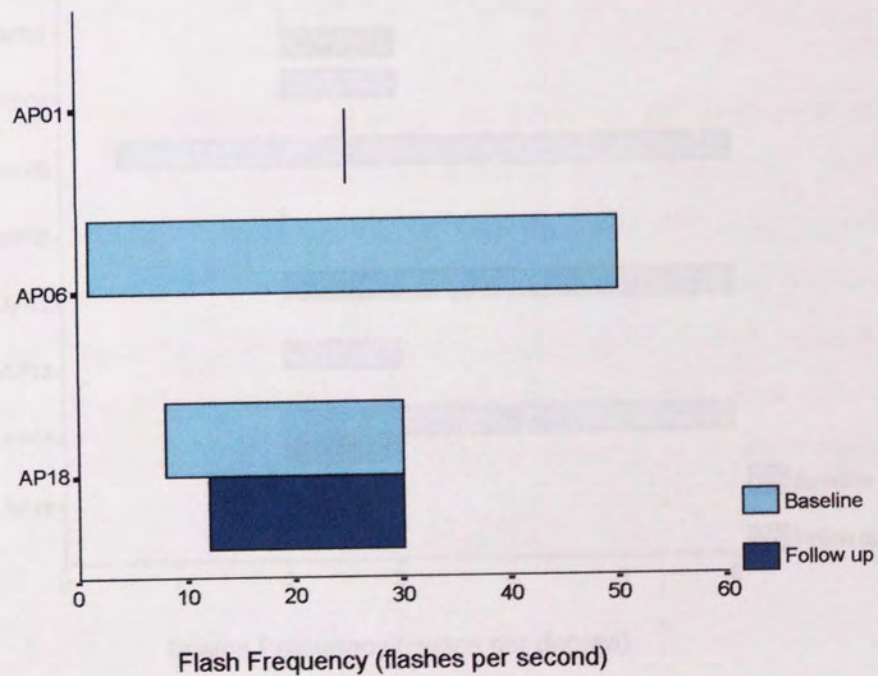


Figure 5.6: SRs of group B patients sensitive to reversing square wave gratings at baseline and follow up

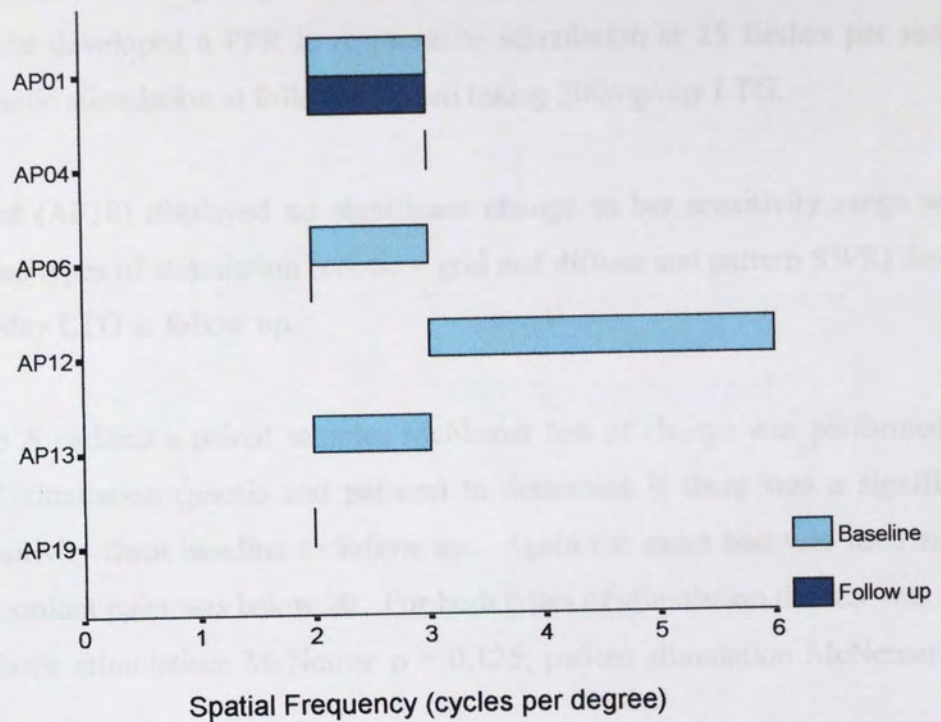
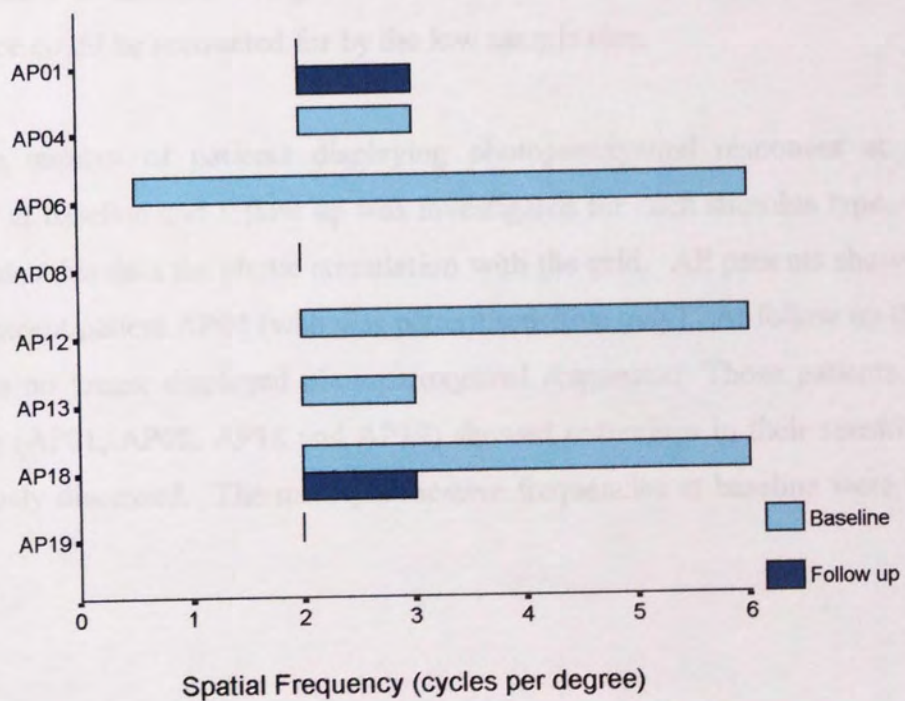


Figure 5.7: SRs of group B patients sensitive to stationary sine waves at baseline and follow up





One patient (AP01) showed no significant change in her sensitivity range and remained sensitive to photic stimulation with the grid and to pattern stimulation with stationary sine wave gratings. Her sensitivity range deteriorated when tested with reversing square wave gratings, and she developed a PPR in response to stimulation at 25 flashes per second with diffuse photic stimulation at follow up when taking 300mg/day LTG.

Another patient (AP18) displayed no significant change in her sensitivity range when tested with three types of stimulation (photic – grid and diffuse and pattern SWR) despite taking 400mg/day LTG at follow up.

As with group A patients a paired samples McNemar test of change was performed for both types of stimulation (photic and pattern) to determine if there was a significant change in sensitivity from baseline to follow up. Again the exact test was used as the number of discordant pairs was below 20. For both types of stimulation the test was non-significant (Photic stimulation: McNemar  $p = 0.125$ , pattern stimulation McNemar  $p = 0.063$ ).

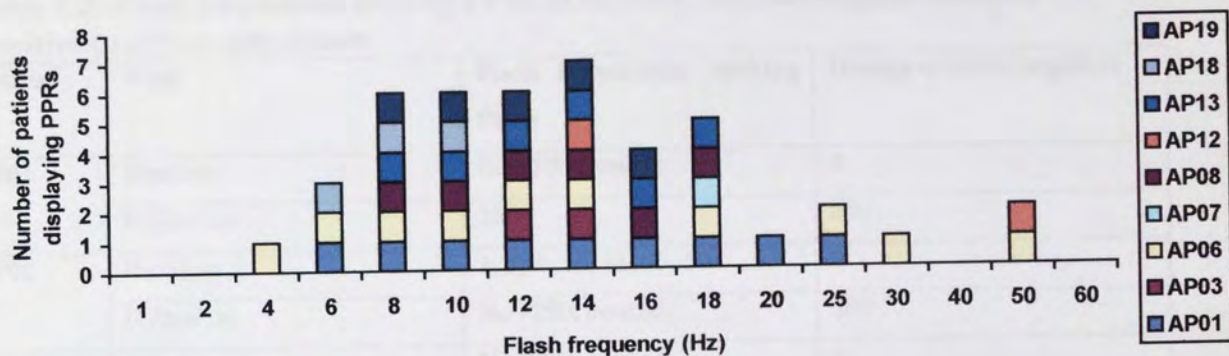
There is a trend towards significance in the pattern stimulation data with patients who were sensitive at baseline being classed as non-sensitive at follow up. The lack of significance could be accounted for by the low sample size.

Again the number of patients displaying photoparoxysmal responses at each flash frequency at baseline and follow up was investigated for each stimulus type. Figure 5.8 demonstrates this data for photic stimulation with the grid. All patients showed PPRs at baseline except patient AP04 (who was pattern sensitive only). At follow up the majority of patients no longer displayed photoparoxysmal responses. Those patients with PPRs remaining (AP01, AP08, AP18 and AP19) showed reductions in their sensitivity ranges as previously discussed. The most provocative frequencies at baseline were between 8-

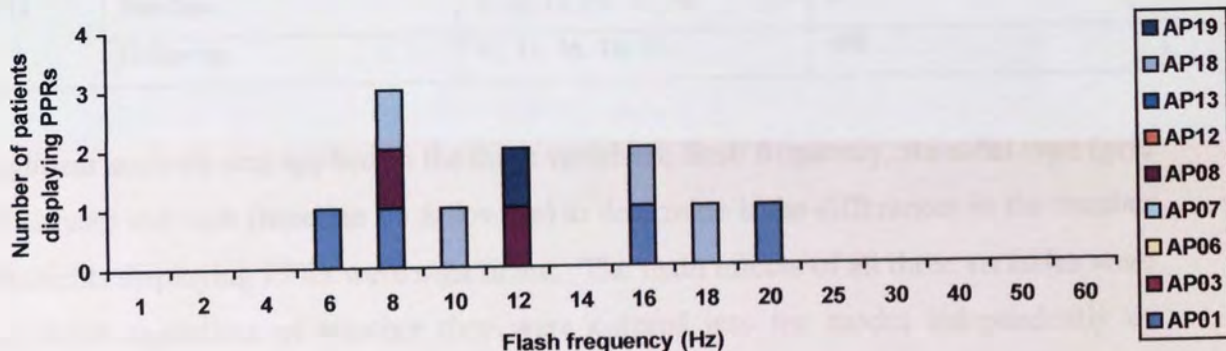
14 flashes per second, at follow up more patients displaying PPRs were seen at 8 flashes per second than at any other frequency.

Figure 5.8: Number of patients displaying PPRs at each flash frequency with photic stimulation with the grid at baseline and follow up

**Baseline**



**Follow up**



At baseline six patients were tested with diffuse photic stimulation. Two patients were sensitive, the provoking flash frequencies are detailed in table 5.2. At follow up all but one patient (AP19) were tested and three patients (AP01, AP13 and AP18) displayed PPRs, again the provocative frequencies are detailed in table 5.2. As discussed previously patient AP01 who did not show abnormality at baseline was sensitive at follow up.



The most provocative frequencies were between 8-14 flashes per second at baseline and the flash rate of 8 flashes per second evoked PPRs in the most number of patients at follow up. More patients displayed photoparoxysmal responses in response to photic stimulation with the grid than with diffuse stimulation at both baseline and follow up.

*Table 5.2: Flash frequencies evoking PPRs at baseline and follow up for patients sensitive to diffuse stimulation*

Patient	Visit	Flash frequencies evoking PPRs	Dosage of LTG (mg/day)
AP01	Baseline	No PPRs evoked	0
	Follow up	25	300
AP06	Baseline	1, 2, 4, 14, 18, 25, 50	0
	Follow up	No PPRs evoked	300
AP13	Baseline	No PPRs evoked	0
	Follow up	20	400
AP14	Baseline	8, 16, 18, 20, 25, 30	0
	Follow up	12, 14, 16, 18, 30	400

Loglinear analysis was applied to the three variables; flash frequency, stimulus type (grid Vs diffuse) and visit (baseline Vs follow up) to determine if the differences in the number of patients displaying PPRs were significant. The main effects of all three variables were significant regardless of whether they were entered into the model independently or collectively (entered independently: Pearson  $\chi^2$  (63) = 156.253;  $p = 0.001$ , entered collectively: Pearson  $\chi^2$  (17) = 121.558;  $p = 0.001$ ). However higher order effects (i.e. two and three way interactions) were non-significant. The final model generated therefore was the total independence model, including all three variables, which was also non-significant (Likelihood ratio  $\chi^2$  (46) = 38.495;  $p = 0.776$ ).

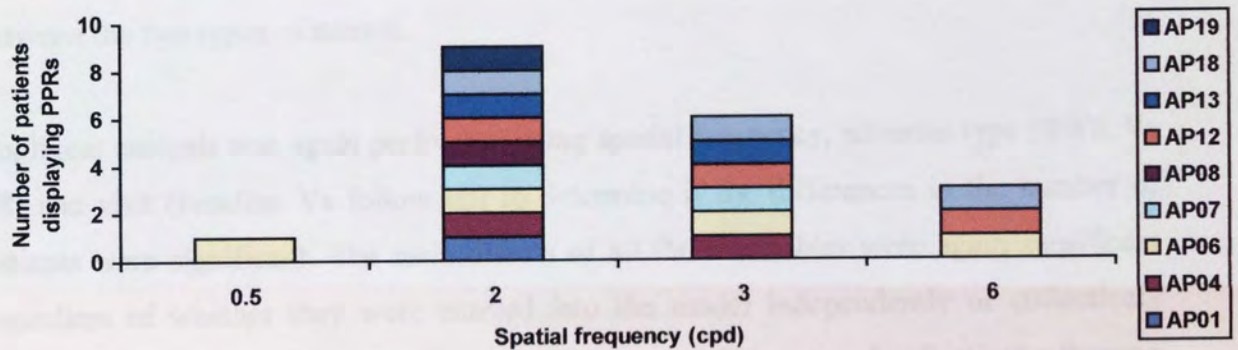
The lack of significance of interaction effects and the resulting model is probably due to the low sample size, coupled with the fact that due to the nature of the data individual cell

frequencies were often less than one and more than twenty percent of the cells contained frequencies of below five.

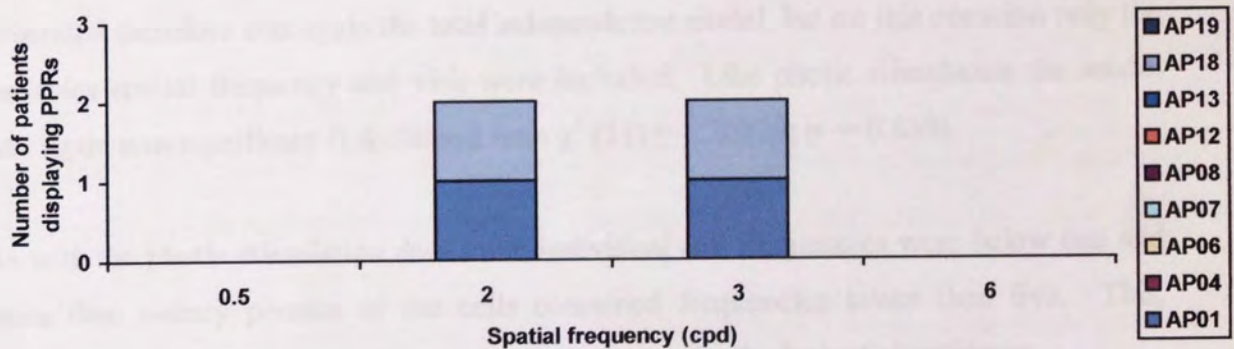
With pattern stimulation using the reversing square wave gratings all patients demonstrated photoparoxysmal responses at baseline except patient AP03 (who was photosensitive only). As can be seen from figure 5.9 only two patients (AP01 and AP08) showed PPRs at follow up.

Figure 5.9: Number of patients displaying PPRs at each spatial frequency with reversing square wave gratings at baseline and follow up

**Baseline**



**Follow up**



The most provocative spatial frequencies were 2 and 3 cycles per degree at both visits.



Figure 5.10 demonstrates the data for stationary sine wave gratings. All but two patients (AP03 and AP08) displayed sensitivity to at least one spatial frequency at baseline. At follow up photoparoxysmal responses remained in only three patients (AP01, AP06 and AP08).

As with reversing square wave gratings more patients displayed photoparoxysmal responses to the spatial frequencies of 2 and 3cpd at both baseline and follow up.

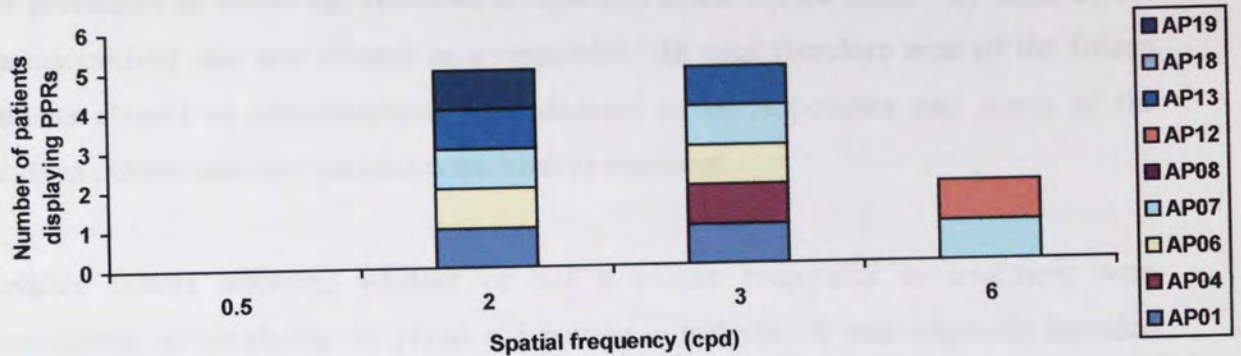
At baseline more patients demonstrated PPRs in response to reversing square wave gratings than to stationary sine wave gratings. At follow up however there was no discernible difference in the number of patients displaying photoparoxysmal responses between the two types of stimuli.

Loglinear analysis was again performed using spatial frequency, stimulus type (SWR Vs SS) and visit (baseline Vs follow up) to determine if the differences in the number of patients were significant. The main effects of all three variables were again significant regardless of whether they were entered into the model independently or collectively (entered independently: Pearson  $\chi^2$  (5) = 37.861; p = 0.001, entered collectively: Pearson  $\chi^2$  (15) = 42.122; p = 0.002). Higher order effects were non-significant. The final model generated therefore was again the total independence model, but on this occasion only the variables spatial frequency and visit were included. Like photic stimulation the model was again non-significant (Likelihood ratio  $\chi^2$  (11) = 6.20829; p = 0.859).

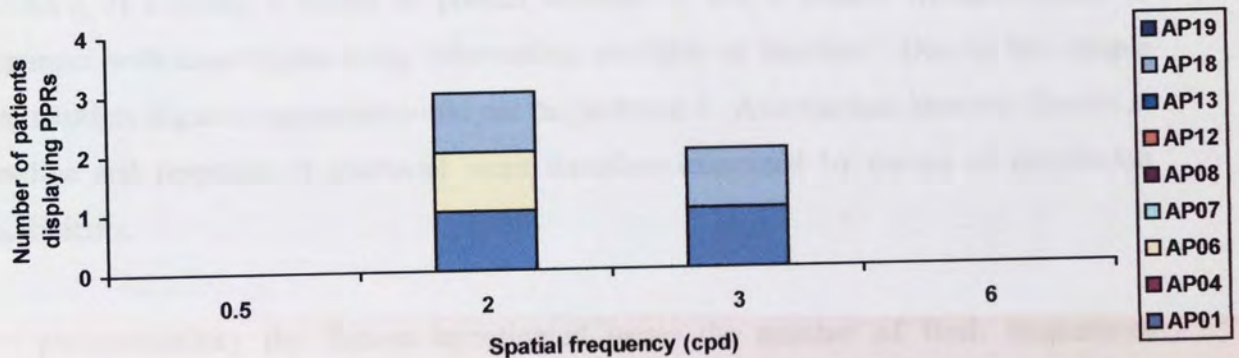
As with the photic stimulation data some individual cell frequencies were below one and more than twenty percent of the cells contained frequencies lower than five. This, coupled with the low sample size, probably accounts for the lack of significance.

Figure 5.10: Number of patients displaying PPRs at each spatial frequency with stationary sine wave gratings at baseline and follow up

**Baseline**



**Follow up**



**5.1.2 Non-responders**

Non-responders were defined as patients who did not show at least a 78% reduction in their sensitivity range (or patients in group A who did not remain non-sensitive) and/or who did not remain seizure free for one year (see section 5.5 seizure control).

Photosensitive non-responders were examined independently of pattern sensitive non-responders although later analysis demonstrated a perfect correlation between the two ( $\phi = 1.000$ ;  $p = 0.001$ ). For all patients if photosensitivity did not respond to lamotrigine treatment then pattern sensitivity did not respond also. Three patients were excluded from this analysis; patient AP01 was photosensitive only and responded to



treatment. Patient AP04 was pattern sensitive only and did not respond to treatment. Patient AP07 was photo and pattern sensitive but due to her request pattern testing was not performed at follow up, therefore comparison could not be made. In terms of her photosensitivity she was classed as a responder. In total therefore nine of the fifteen patients classed as photosensitive were deemed to be responders and seven of the fourteen pattern sensitive patients responded to treatment.

Possible factors affecting whether or not a patient responded to treatment were investigated independently for photo and pattern sensitivity. It was originally intended that this analysis would be executed by means of multiple logistic regression with the intention of creating a model to predict whether or not a patient would respond to treatment with lamotrigine using information available at baseline. Due to the sample size multiple logistic regression could not be performed. Associations between factors at baseline and response to treatment were therefore examined by means of correlation coefficients.

For photosensitivity the factors investigated were: the number of flash frequencies evoking PPRs at baseline using stimulation with the grid, the number of flash frequencies evoking PPRs at baseline using diffuse stimulation, the presence/absence of occipital spikes at baseline, the presence/absence of VEPs, lambda activity and photic driving in response to photic stimulation at baseline, the state of the resting EEG at baseline, the dose of lamotrigine at follow up, the age of the patient at the beginning of the trial, the duration of epilepsy, the diagnosis and the group the patient was in (A or B).

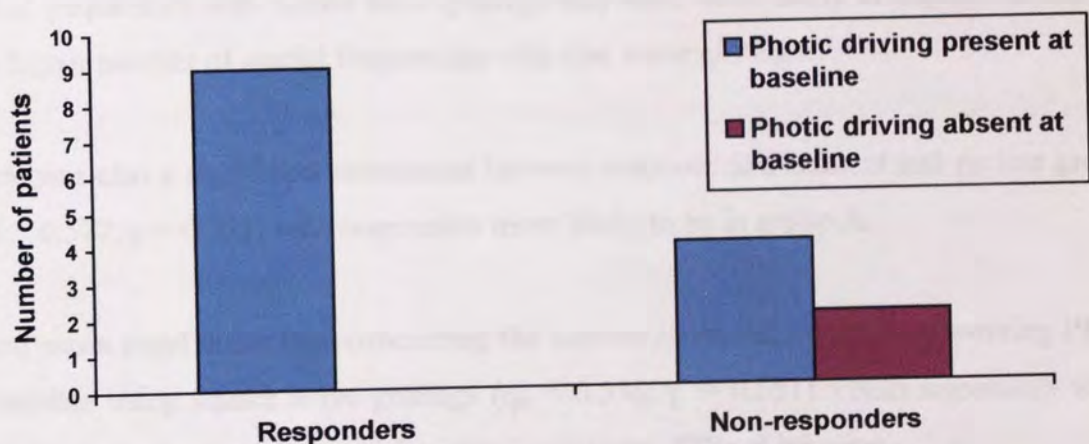
The associations between the number of flash frequencies evoking PPRs at baseline with grid and diffuse stimulation, the dose of lamotrigine at follow up, the age of the patient and the duration of epilepsy were examined by means of Pearson ( $r$ ) and Pearson point-biserial ( $r_{pb}$ ) correlations.

There was a significant correlation between response to treatment and the number of flash frequencies evoking PPRs at baseline with stimulation with the grid ( $r_{pb} = 0.764$ ;  $p = 0.001$ ). Patients who displayed PPRs to a larger number of flash frequencies at baseline were less likely to respond to lamotrigine therapy.

The only other significant correlation was between the age of the patient and the duration of their epilepsy ( $r = 0.579$ ;  $p = 0.024$ ) with older patients having a longer duration of epilepsy.

The associations between response to treatment and the presence/absence of occipital spikes, VEPs, lambda activity and photic driving and patient group were examined by means of the phi correlation coefficient. None of the correlations were significant. There was however a trend shown in the data concerning the presence of photic driving at baseline ( $\phi = 0.480$ ;  $p = 0.063$ ). Those patients who demonstrated photic driving at baseline were more likely to respond to treatment than those who did not, as is demonstrated in figure 5.11.

Figure 5.11: Presence of photic driving at baseline in photosensitive responders and non-responders





The associations between response to treatment and diagnosis of epilepsy and the state of the resting record at baseline were investigated using Cramers V correlation coefficients. Neither of these factors were significantly associated with response to lamotrigine therapy.

Possible factors affecting the response to treatment in pattern sensitive patients were investigated in the same manner. The only changes to the methodology were that instead of the number of flash frequencies evoking PPRs being used the number of spatial frequencies evoking PPRs at baseline was used for both reversing square wave gratings and stationary sine wave gratings respectively. The presence/absence of VEPs, and lambda activity at baseline was assessed again but in response to pattern stimulation rather than photic stimulation.

There was again a significant correlation between the duration of epilepsy and the patients' age ( $r = 0.692$ ;  $p = 0.006$ ) with older patients having had epilepsy for a longer period of time.

There was also a significant correlation between the number of spatial frequencies evoking PPRs at baseline with reversing square wave gratings and those evoked with sine wave gratings ( $r = 0.840$ ;  $p = 0.000$ ). If a patient was sensitive to a higher number of spatial frequencies with square wave gratings they were more likely to display sensitivity to a higher number of spatial frequencies with sine wave gratings.

There was also a significant correlation between response to treatment and patient group ( $\phi = 0.577$ ;  $p = 0.031$ ) with responders more likely to be in group A.

There was a trend in the data concerning the number of spatial frequencies evoking PPRs at baseline using square wave gratings ( $r_{pb} = 0.530$ ;  $p = 0.051$ ). Non-responders were more likely to show more spatial frequencies evoking PPRs at baseline.

It is also interesting that for both photo and pattern sensitivity the presence of occipital spikes at baseline was not associated with whether or not the patients responded to treatment ( $\phi = 0.00$ ;  $p = 1.000$ , for both photo and pattern sensitive patients respectively).

### **5.1.3 Discussion**

In group A at baseline one of the six patients demonstrated photoparoxysmal responses to photic and pattern stimulation despite valproate therapy. Sodium valproate can control pattern sensitivity (Darby et al, 1986) but not in all patients (Binnie and Wilkins, 1998) so it is not surprising that PPRs were evident in response to pattern stimulation in one patients EEG. The other patients pattern sensitivity could have been controlled by the sodium valproate or they may not have been pattern sensitive. Unfortunately measures of pattern sensitivity pre-valproate treatment were not available to substantiate this. Sodium valproate controls photosensitive epilepsy abolishing PPRs in approximately 80% of patients (Harding et al, 1978). The reported numbers of patients not displaying photoparoxysmal responses to photic stimuli are therefore expected.

There was no significant change to the sensitivity ranges in all patients following transferral from valproate to lamotrigine. This suggests that lamotrigine provides equivalent control of photoparoxysmal responses to valproate. As patients were tested at follow up at least six months post complete withdrawal of valproate it is unlikely that sodium valproate would have a remaining controlling effect of the photoparoxysmal responses (Harding and Jeavons, 1994).

It cannot be discounted that photosensitivity in some of these patients may have gone into remission, this occurs in 25% of photosensitive patients (Jeavons et al, 1986). It is impossible to test this without complete withdrawal of all medication, which because of the risk of seizures would be unethical. More than 25% of group A patients did not

display photoparoxysmal responses at follow up which suggests that in at least some of these patients lamotrigine was indeed having a controlling effect. The lack of PPRs therefore cannot be solely explained by spontaneous remission.

Photoparoxysmal responses evident at baseline were abolished in the majority of group B patients. If PPRs were not abolished patients generally displayed a reduction in their sensitivity range (beyond that of normal variation) following lamotrigine therapy. These results are as expected following Binnie and colleagues acute study of lamotrigine, where the sensitivity range of all patients was reduced and PPRs were abolished in two patients (Binnie et al, 1986).

The reduction of the sensitivity range and abolition of PPRs occurred with both photic and pattern stimuli suggesting that, like sodium valproate (Binnie and Wilkins, 1998), lamotrigine has an effect on pattern sensitivity.

There appeared to be no pattern in the reduction of the sensitivity range. For example the range did not reduce from the outer limits as has been reported in patients following treatment with sodium valproate (Harding and Jeavons, 1994).

Unfortunately the results from group B patients were non-significant, although the data concerning pattern sensitivity neared significance at the 0.05 level. The lack of significance is probably accounted for by the small sample size coupled with large intra-group variation in sensitivity ranges indicated by large standard deviations.

The sensitivity range, calculated by subtracting the lower limit from the upper limit was thought to indicate the number of flash rates to which a patient is sensitive (Maheshwari and Jeavons, 1975, Harding et al, 1978). This allowing comparison of a patients photosensitivity over time, enabling the measurement of the effectiveness of drug therapy with chronic administration (Harding and Jeavons, 1994). A fixed criterion, the 78%



level of change was developed to evaluate the effectiveness of drug treatment (Harding et al, 1978). In the original studies using the sensitivity range not all frequencies between the upper and lower limits were tested and the investigators assumed that the patient was sensitive to all the frequencies between these limits.

Patients however do demonstrate islets of non-sensitivity within the upper and lower limits of their sensitivity ranges, as has been demonstrated by the results of this study. It was previously believed that the width of sensitivity range has no clinical significance (Harding and Jeavons, 1994) and indeed when only one drug, valproate, was available for the treatment of photosensitivity it did not. This study has demonstrated that the number of frequencies to which a patient is sensitive to is of clinical significance and can aid prediction of response to lamotrigine therapy.

To evaluate outcomes in this study the 78% criterion and the original calculation of the sensitivity had to be used as there are no alternative methods to evaluate variation in photo and pattern sensitivity. It is clear from this study however that the original calculation of the sensitivity range may be flawed and further investigation of sensitivity to individual frequencies and its normal variation is required.

The most provocative flash frequencies were 8-14 flashes per second, which is lower than the range described in the literature with 15-20 flashes per second provoking PPRs in the most patients (Binnie and Jeavons, 1992).

Pattern stimulation evoked photoparoxysmal responses in the majority of patients at baseline when gratings of 2 and 3cpd were used, regardless of the type of grating. It was expected that gratings of 2 and 3cpd would be most provocative (Wilkins et al, 1980), indeed this is the reasoning behind inclusion of these frequencies in the clinical protocol. There appeared to be no difference in the provocative nature of the two types of gratings,

contrary to the literature which suggests that square wave gratings are more provocative (Binnie and Wilkins, 1998).

It was originally proposed that the sensitivity range would be examined at each dose increment of lamotrigine. Unfortunately this was not feasible due to small patient numbers and deviations from the dose schedule. With valproate treatment the duration of the photoparoxysmal response is related to dose. As the dose of valproate increases the duration of the PPR is gradually reduced until it is completely abolished (Darby et al, 1986). It is possible that lamotrigine has a similar effect on the duration of the PPR but this was impossible to determine from the current data.

Further research should also include investigation of the types of photoparoxysmal response evoked and whether this changes with lamotrigine therapy. Visual inspection of the current data suggests that the type of PPR did alter between visits as lamotrigine was gradually introduced. Again due to small patient numbers analysis of this factor cannot be adequately executed.

If the dose schedule had been adhered to in all patients the effect of lamotrigine on the latency of the photoparoxysmal response would also have been investigated. Visual inspection of the data suggests that as the dose of lamotrigine increases there is a corresponding increase in latency of the PPR. Unfortunately the aforementioned small patient numbers and deviations from the dose schedule again prevent further analysis.

A stricter classification of responder was utilised in comparison to that used in other studies. In addition to the absence of PPRs or a reduction (>78%) in the sensitivity range, patients were required to have been seizure free for at least one year in order to be classified as a responder. In the majority of studies a reduction of 50% or more is the generally accepted criteria used for clinical efficacy (Schmidt, 1991, Eriksson et al, 1998,



Jowiak and Terczynski, 2000). As data collected did not include a measure of seizure frequency the measure of one year seizure free was used.

Nine of the fifteen photosensitive patients (60%) were classified as responders. This is somewhat lower than the 80% response rate found with valproate therapy (Harding et al, 1980). This is contrary to the effect of lamotrigine in idiopathic generalised epilepsy where the literature suggests that there are no discernible differences in efficacy of the two drugs (Kerr et al, 1999, Ronga et al, 1999). Seven of the fourteen patients demonstrating pattern sensitivity (50%) were classified as responders. There are no figures in the literature detailing valproate's efficacy in the control of pattern sensitivity, therefore a direct comparison can't be made, although valproate does reduce the likelihood of PPRs being evoked by pattern stimulation under laboratory conditions (Darby et al, 1986, Binnie and Wilkins, 1998).

Patients who were both photo and pattern sensitive demonstrated a response to lamotrigine treatment for both measures suggesting that lamotrigine can be efficacious in the treatment of both disorders.

The only significant factor associated with the response to treatment was the number of frequencies evoking photoparoxysmal responses at baseline using the grid. Patients that displayed sensitivity to a higher number of flash frequencies were less likely to respond to lamotrigine therapy. This conflicts with the results of studies in the literature which suggest that diffuse photic stimulation is a more reliable predictor of clinical control (Fylan et al, 1999).

There were no other significant factors associated with response to treatment. The literature suggests that the age of patients, seizure type and state of the resting EEG may be predictors of PPR prognosis and response to therapy in juvenile myoclonic epilepsy (So et al, 1993, Wirrell et al, 1996, Gelisse et al, 2001). Again these results may be explained by the inadequate sample size, as only high correlations tend to be significant when a small population sample is utilised.

There was a trend in the photosensitive data suggesting that the presence of photic driving in the baseline EEG indicated that the patient was more likely to respond to lamotrigine therapy. Photic driving is viewed as a normal response to IPS (Harding, 1980) and is found less often in photosensitives in comparison to controls without epilepsy (Kasteleijn-Nolst Trenité, 1989). This suggests that patients who display photic driving may have a less hyperexcitable visual cortex and therefore normal responses such as photic driving are more evident and may be more likely to respond to treatment as their underlying functional abnormality within the visual system is less severe. This cannot be unequivocally concluded from the current data but warrants further investigation.

In the data concerning pattern sensitive patients there was a trend suggesting that patients who displayed PPRs to a greater number of spatial frequencies with reversing square wave gratings were less likely to respond to therapy. Again the lack of significance can be explained by inadequate sample size and this factor should be investigated in a larger population.

The only significant association with response to treatment in pattern sensitive patients was with patient group. Patients in group A were more likely to respond to lamotrigine therapy than patients in group B. It is unlikely that the effect of valproate therapy was influential in this finding. All patients were followed up post six months of complete

withdrawal of sodium valproate, indicating valproate should no longer have a controlling effect on photosensitivity (Harding and Jeavons, 1994).

Some of the patients in group A could have experienced the spontaneous remission of photosensitivity, which could explain the preponderance of responders in group A. As previously discussed this is unlikely to explain the high response rate in group A, as spontaneous remission normally only occurs in 25% of photosensitive patients (Jeavons et al, 1986).

It was previously suggested that some of the group A patients may not be pattern sensitive as they did not display photoparoxysmal responses to pattern stimulation whilst on valproate therapy. Although valproate reduces the likelihood of PPRs being evoked with pattern stimulation (Darby et al, 1986, Binnie and Wilkins, 1998) its efficacy is not well defined as no controlled studies have been conducted. It cannot be categorically stated that all group A patients were pattern sensitive as pattern testing was not performed prior to the initiation of valproate therapy, as discussed previously. It may be that patients who are photosensitive only are more likely to respond to lamotrigine than those who display sensitivity to both photic and pattern stimuli. As only one patient in this study could be classified as only photosensitive and not pattern sensitive the current data would not allow such a comparison although this warrants further investigation.

## **5.2 Occipital spikes**

In addition to lamotrigines effect on photoparoxysmal responses its effect on occipital spikes was also investigated.

### **5.2.1 Results**

#### **Group A patients**



Only two patients demonstrated occipital spikes. Patient AP09 displayed occipital spikes in response to the flash frequency of 14 flashes per second with photic stimulation with the grid in place at baseline. At follow up the occipital spikes had been abolished. Occipital spikes were also evoked with pattern stimulation with stationary sine wave gratings of 2 and 3cpd at baseline, these were again abolished at follow up after transferral from 1000mg/day VPA to 300mg/day LTG.

Patient AP15 displayed occipital spikes at 16 and 18 flashes per second with photic stimulation with the grid at baseline when taking 1000mg/day VPA. At follow up occipital spikes were seen in response to stimulation at 8, 10 and 12 flashes per second when receiving 400mg/day LTG. At two of these frequencies, 10 and 12 flashes per second, the occipital spikes preceded a PPR. With pattern stimulation using reversing square wave gratings she displayed occipital spikes at the spatial frequencies of 2, 3 and 6cpd at baseline, these were abolished at follow up.

As with the photoparoxysmal response data a McNemar paired samples test of change (exact test) was performed to compare sensitivity to each type of stimulus (photic and pattern) from baseline to follow up. Both tests were non-significant (McNemar  $p = 1.000$ , for both photic and pattern respectively).

### **Group B patients**

Only four patients in total had occipital spikes. With pattern stimulation one patient (AP13) showed occipital spikes at 2cpd with stationary sine wave gratings at baseline. These were abolished at follow up.

With photic stimulation with the grid at baseline three patients showed occipital spikes at baseline; patients AP03 (at 8, 10, 12, 14 and 20 flashes per second), AP08 (at 6 and 8 flashes per second) and AP13 (at 8, 14, 16 and 20 flashes per second). For patients AP03

and AP13 the occipital spikes evoked at the frequencies of 8, 12, 14 and 16 flashes per second, preceded PPRs. All occipital spikes were abolished for all patients at follow up.

Patient AP18 developed occipital spikes at follow up evoked by photic stimulation with the grid at 8 flashes per second and 18 flashes per second with diffuse photic stimulation, which had previously evoked a PPR at baseline.

A McNemar paired sample test (exact test) was performed on the data. There was no significant change in sensitivity from baseline to follow up for either stimulus type (photic: McNemar  $p = 0.625$ , pattern: McNemar  $p = 1.000$ ). Again due to the nature of the data no further statistical analysis was performed.

### **5.2.2 Discussion**

Occipital spikes remained with valproate therapy in two group A patients. After transferral to lamotrigine occipital spikes were abolished in one patient. In the EEG of the other patient occipital spikes were enhanced, with occipital spikes evoked at flash and spatial frequencies that had previously evoked photoparoxysmal responses at baseline.

In group B, four patients demonstrated occipital spikes. At follow up occipital spikes had been abolished in three patients and in one patient occipital spikes were present at flash frequencies that had previously evoked PPRs at baseline.

The data suggest that, unlike sodium valproate, lamotrigine therapy can abolish occipital spikes (Maheshwari and Jeavons, 1975, Binnie et al, 1980b). The literature however suggests that occipital spikes are not affected by any antiepileptic drugs in any consistent manner (Jeavons, 1982) and from such a small sample it is impossible to unequivocally conclude that lamotrigine does have an effect on occipital spikes.



Occipital spikes are frequently seen as a precursor to photoparoxysmal responses (Harding, 1996). With reports of up to 87% of patients demonstrating occipital spikes preceding PPRs (Panayiotopoulos et al, 1970). Only six of sixteen patients demonstrated occipital spikes in this study, with occipital spikes preceding PPRs in only three patients.

It has been proposed that the fact that valproate does not effect occipital spikes indicates their independence from the photoparoxysmal response (Harding and Jeavons, 1994). Indeed two separate generating systems have been suggested. PPRs are said to result from abnormalities in the parvocellular system and occipital spikes are an abnormal phenomena associated with the magnocellular system (Harding and Fylan, 1999). The fact that lamotrigine may effect both phenomena does not necessarily refute this idea. Lamotrigine may exert its action in both visual systems thereby affecting both occipital spikes and PPRs. Conversely sodium valproate may only have a discrete effect in the parvocellular system and hence only modifies photoparoxysmal responses.

The presence of occipital spikes in the EEG showed no association with response to lamotrigine therapy. This further corroborates the notion that occipital spikes are an independent phenomena from the PPR. Additionally the lack of association substantiates the opinion that occipital spikes are not clinically significant in photosensitive epilepsy and should be regarded as a normal response to IPS as suggested by other authors (Jeavons, 1982, Jeavons, 1985, Kasteleijn-Nolst Trenité, 1989).

### **5.3. Normal responses**

The effect of lamotrigine therapy on normal EEG responses evoked by photic and pattern stimulation was also investigated.

#### **5.3.1 Results**

##### **5.3.1.1 Photic driving**

###### **Group A patients**

Five patients displayed photic driving at baseline and follow up. For one patient (AP11) photic driving was only elicited at baseline with the grid. Statistical analysis to test for change in presence of photic driving between baseline and follow up was therefore redundant.

###### **Group B patients**

At baseline eight patients demonstrated photic driving. Photic driving was not evoked at baseline or follow up in one patient (AP06). Patient AP12 displayed photic driving at baseline but not at follow up and another patient (AP18) displayed photic driving at follow up but not at baseline.

A McNemar paired samples test of change demonstrated there was no significant difference in occurrence of photic driving at baseline compared to follow up (McNemar  $p = 1.000$ , exact test).

### **5.3.1.2. Visual evoked potential in the EEG**

#### **Group A patients**

Visual evoked potentials were evident in the EEGs of three patients in response to photic stimulation at baseline (AP09, AP15 and AP17). Two patients developed VEPs so that five of the six patients showed VEPs at follow up. This change was non-significant as tested by a McNemar paired samples test of change (McNemar  $p = 0.500$ , exact test).

With pattern stimulation no patients showed VEPs at baseline. At follow up however two patients (AP02 and AP09) demonstrated VEPs. This change was again non-significant (McNemar  $p = 0.500$ , exact test).

#### **Group B patients**

All but one patient (AP19) demonstrated visual evoked potentials in their EEGs in response to photic stimulation at baseline. At follow up patient AP19 now displayed VEPs and patients AP06 and AP12 no longer demonstrated VEPs in their EEGs. These changes were non-significant as tested by a paired samples McNemar test of change (McNemar  $p = 1.000$ , exact test).

With pattern stimulation visual evoked potentials were not present in the EEGs of any patients at baseline. At follow up patients AP01, AP08 AP13 and AP19 now demonstrated VEPs in their EEG. Again this change was non-significant (McNemar  $p = 0.125$ , exact test).

Both types of gratings evoked VEPs in patients AP01 and AP19, only reversing square wave gratings elicited VEPs in patient AP13 and patient AP08 only displayed VEPs in response to stationary sine wave gratings.



### **5.3.1.3 Lambda**

#### **Group A patients**

One patient (AP09) displayed lambda waves in response to photic stimulation at baseline, this activity remained at follow up. An additional four patients (AP02, AP14, AP15 and AP17) also demonstrated lambda activity at follow up. This change however was non-significant as tested by a paired samples McNemar test of change (McNemar  $p = 0.125$ , exact test).

Lambda activity was not seen in the EEG of any patient in response to pattern stimulation at baseline. At follow up three patients (AP02, AP09 and AP17) demonstrated lambda activity at follow up. Again this change was non-significant (McNemar  $p = 0.250$ , exact test).

#### **Group B patients**

With photic stimulation six patients demonstrated lambda activity at baseline (AP01, AP04, AP06, AP12, AP13 and AP18). At follow up lambda waves remained in the EEG of only patient AP13. Patient AP03 now displayed lambda activity at follow up when none was evident at baseline. This change was non-significant as tested by a paired samples McNemar test of change (McNemar  $p = 0.219$ , exact test).

Only one patient (AP13) displayed lambda wave at baseline. No patient demonstrated lambda activity at follow up. Again this change was non-significant (McNemar  $p = 1.000$ , exact test).

### 5.3.2 Discussion

Five of the six patients in group A displayed photic driving at baseline and follow up. The remaining patient only displayed photic driving in response to photic stimulation with the grid at baseline. A driving response was elicited in eight of the ten group B patients at both baseline and follow up. One patient only displayed photic driving at baseline and a further patient only demonstrated photic driving at follow up. There was no significant change in the presence of photic driving between visits in either group of patients indicating that lamotrigine does not affect this normal response to IPS. There is no available information in the literature of the effects of antiepileptic drugs on photic driving although alterations to photic driving have been reported following the administration of psychotropic drugs (Hindmarch, 1994).

As previously discussed there was a trend in the data suggesting that patients who demonstrated photic driving in their EEG at baseline were more likely to respond to lamotrigine therapy. The presence of photic driving in photosensitives may be indicative of normal function of the visual cortex as photic driving is also seen in volunteers without epilepsy or other neurological disorders. Alternatively photic driving in photosensitives may indicate a less severe abnormality of visual cortex function allowing the preservation of normal responses. Indeed the presence of harmonic responses in photic driving is a discriminatory factor in people who suffer from migraine and those who don't (Simon et al, 1983). However reports of studies in the literature suggest that photic driving is unrelated to seizure history (Jeavons, 1969) and epileptic discharges (Shih and Thompson, 1998), and that although photic driving is of scientific interest its presence rarely provides clinically useful information (Harding and Jeavons, 1994).

The visual evoked response in photosensitive epilepsy is larger in amplitude than that of control subjects without epilepsy and controls with epilepsy who are not photosensitive (Gastaut and Regis, 1964, Green, 1969, Hishikawa et al, 1967, Lucking et al, 1967,



Herrick and Harding, 1978, Guerrini et al, 1998a). It is not surprising that VEPs were evident in the EEG of the patients in this study.

Valproate decreases the abnormally high amplitude of the VEP in photosensitive patients, although the VEP tends to remain larger than that seen in individuals who are not photosensitive (Herrick and Harding, 1978). In group A patients an increase in the number of patients displaying VEPs was seen from baseline to follow up for both photic and pattern stimuli. This increase was non-significant, possibly explained by the inadequate sample size. It is possible that as valproate is withdrawn in patients its effect on the amplitude of the VEP diminishes and the VEP again increases in amplitude and is more likely to be evident in the EEG. The results also suggest that lamotrigine does not demonstrate similar control of the amplitude of the VEP.

The photosensitive data from group B patients also suggests that lamotrigine does not have an effect on the visual evoked potential. With photic stimulation nine patients displayed VEPs at baseline and eight patients continued to demonstrate VEPs at follow up, this change was non-significant. There is evidence that lamotrigine does not alter the VEP in volunteers without epilepsy (Van Wieringen et al, 1989) and in patients with epilepsy who are not photosensitive (Koehler et al, 1999).

When pattern stimulation was performed however there was an increase in the number of group B patients displaying VEPs from baseline to follow up. VEPs were not elicited in any patients at baseline whereas at follow up four patients displayed VEPs in their EEGs. This change was non-significant but could indicate that lamotrigine increases the sensitivity of the visual pathway.

The effects of lamotrigine on the visual evoked potential in photosensitive epilepsy warrants further investigation as it could illuminate the mechanism of action of the drug. Additionally Broughton and colleagues suggest subgroups of photosensitives based on

differences in their VEPs (Broughton et al, 1969). Although in the current study the presence of VEPs was not associated with response to lamotrigine treatment, responders and non-responders may be discriminated by differences in components in their VEPs.

There was an increase in the number of patients in group A showing lambda activity in response to both photic and pattern stimulation. Whereas in group B the number of patients demonstrating lambda activity in response to photic and pattern stimulation decreased. These changes were non-significant again possibly due to the inadequate sample sizes.

The differences in changes in the number of patients between visits in the two patient groups could be indicative of a suppression of lambda activity by lamotrigine, albeit to a smaller extent than the suppression occurring with valproate treatment. There are no investigations of lambda activity in photosensitive epilepsy in the literature nor any studies concerning the effect of antiepileptic drugs on this phenomenon. As lambda represents the sensory inflow of retinal afferent inputs (Billings, 1989) further investigation of the phenomena would seem appropriate in the field of photosensitive epilepsy.

The differences observed in the numbers of patients could also be accounted for by change in fixation during testing as lambda waves are adversely affected by fixation (Billings, 1989) highlighting the need for close monitoring of the patient during photic and pattern stimulation.

#### **5.4 Background EEG**

At each visit the patients resting records (including hyperventilation) were reported on by Prof. GFA Harding, Dr M Lai or Dr F Fylan. On the basis of the clinical report the record was classified as normal, non specifically abnormal or abnormal, based on a study

of the effectiveness of sodium valproate in photosensitive epilepsy (Jeavons et al, 1975). The categorisation of abnormal was given if the record contained bilateral spike (or polyspike) and wave discharges. The non-specific abnormality category was used if slow wave or non-localised sharp waves were evident in the EEG.

The state of the resting EEG was compared between baseline and follow up at 15 months for 13 of the patients. Data at 15 months follow up were not available for three patients in group B (AP04, AP08 and AP12) so baseline measures were compared with measures from visit 3, visit 5 and visit 4 respectively when patients were taking their highest dosage of lamotrigine.

### **5.4.1 Results**

#### **Group A patients**

Table 5.3 demonstrates the state of the resting record at baseline and follow up for group A patients. At baseline when patients were on valproate therapy all six patients had normal EEGs. At follow up 15 months later when patients were undergoing lamotrigine treatment one patient (AP14) had developed generalised spike and wave activity.

*Table 5.3: State of resting record group A patients*

Patient:	Visit 1: Baseline		Visit 6: 15 month follow up	
	Medication (mg/day):	State of resting record:	Medication (mg/day):	State of resting record:
AP02	VPA 1000	Normal	LTG 500	Normal
AP09	VPA 1000	Normal	LTG 300	Normal
AP11	VPA 1000	Normal	LTG 350	Normal
AP14	VPA 1000	Normal	LTG 250	Abnormal
AP15	VPA 1000	Normal	LTG 400	Normal
AP17	VPA 200	Normal	LTG 200	Normal



### Group B patients

The state of the resting record at baseline and follow up visits for group B patients is detailed in table 5.4. There was no change in the state of the background EEG after the initiation of lamotrigine therapy in four patients. Two patients (AP01 and AP09) had normal EEGs, one patient (AP03) had non-specific abnormal slow and sharp waves at baseline and follow up and one patient (AP06) showed generalised spike and wave activity at both visits.

Five patients showed an improvement in the state of their resting EEGs following lamotrigine therapy. At follow up their EEGs were normal when previously four patients (AP04, AP08, AP12 and AP18) showed non specific abnormalities and one patient (AP07) displayed generalised polyspike and wave activity.

One patient's EEG (AP13) worsened with non-specific abnormal slow at baseline and generalised spike and wave activity seen at follow up.

Table 5.4: State of resting record group B patients

Patient:	Visit 1: Baseline		Follow up visit	
	Medication (mg/day):	State of resting record:	Medication (mg/day):	State of resting record:
AP01	Nil	Normal	LTG 300	Normal
AP03	Nil	Non specifically abnormal	LTG 300	Non specifically abnormal
AP04	Nil	Non specifically abnormal	LTG 100	Normal
AP06	Nil	Abnormal	LTG 300	Abnormal
AP07	Nil	Abnormal	LTG 250	Normal
AP08	Nil	Non specifically abnormal	LTG 200	Normal
AP12	Nil	Non specifically abnormal	LTG 100	Normal
AP13	Nil	Non specifically abnormal	LTG 400	Abnormal
AP18	Nil	Non specifically abnormal	LTG 400	Normal
AP19	Nil	Normal	LTG 100	Normal

#### **5.4.2 Discussion**

Sodium valproate is effective in normalising the EEG of patients with photosensitive epilepsy (Jeavons et al, 1976, Jeavons et al, 1977, Stefan et al, 1984). All patients had normal EEGs on valproate therapy. One patient's EEG deteriorated after transferral to lamotrigine and the EEG of one drug naïve patient also deteriorated after the initiation of lamotrigine therapy. There is very little information on the effect of lamotrigine on the resting EEG in the literature, most of the studies detailing positive effects. However there are a limited number of reports of lamotrigine aggravating the EEG in specific syndromes such as severe myoclonic epilepsy (Genton, 2000) with corresponding



increases in seizures (Guerrini et al, 1998b), also documented in JME (Carranza and Wheeler, 2001).

In the remaining five group A patients their EEGs remained normal after transferral to lamotrigine. This may indicate equivalent control to valproate provided by lamotrigine. However it may be that these patients would have had normal EEGs without any AED treatment as seen in up to 60% of photosensitive patients (Aziz et al, 1989) and as was seen in two unmedicated group B patients.

Abnormal EEG activity was seen in eight of the group B patients when unmedicated at baseline. Spike/polyspike and wave activity was seen in two of these patients. The rest displayed non-specific abnormal slow/sharp wave activity. Spike/polyspike and wave activity is found in the background EEG of up to 52% of patients with photosensitive epilepsy (Quirk et al, 1995).

The non-specific abnormalities found in photosensitive patients are similar to those seen in this study i.e. sharp slow wave activity (Aziz et al, 1989, Kasteleijn-Nolst Trenité, 1989, Quirk et al, 1995).

Five of the patients displaying abnormalities at baseline showed improvement after the initiation of lamotrigine therapy. In single dose studies lamotrigine has been shown to reduce the frequency of interictal spikes (Binnie et al, 1986, Jawad et al, 1986). There is little information in the literature of its effect on the background EEG with chronic use although one study documented a reduction of secondary generalisation of focal and multifocal discharges (Dimova and Korinthenberg, 1999).

Two group B patients showed no change in their resting EEG after commencing lamotrigine therapy. Their EEGs continued to contain non-specific abnormalities and spike and wave activity respectively. Both these patients were taking 300mg/day LTG at

follow up so it is unlikely that the dosage was not sufficient as this is within the range of the normal maintenance dose for adults (Richens, 1992). The persistence of EEG abnormalities could indicate non-compliance or simply that the EEG is not responding to the lamotrigine therapy. It is not necessary for the EEG to be normal for the patient to be clinically controlled (Jeavons et al, 1977). Treatment of epilepsy should never be based on the state of the resting EEG alone, indeed many clinicians prescribe AEDs at a dose which is sufficient to prevent seizures but does not abolish all EEG abnormalities (Harding and Jeavons, 1994).

### **5.5 Seizure Control**

Patients were questioned on their seizure history at each visit. The time since last seizure was recorded and compared from baseline to last available follow up. Patients were classified as still experiencing seizures or seizure free (if they had not experienced a seizure for  $\geq 1$  year) in accordance to a study by Fylan and her colleagues of the clinical correlates of PPRs (Fylan et al, 1999).

#### **5.5.1 Results**

Eight patients presented with both visual and non-visual seizure precipitants as detailed in chapter 4, section 4.3.1. The most common visual precipitant was video games played through the television (seizures provoked in 2 patients). The most frequently reported non-visual seizure precipitants were sleep deprivation (8 patients), stress (4 patients) and alcohol (3 patients).

#### **Group A patients**

Table 5.5 details time since last seizure for group A patients. All patients were unsure at baseline of the exact date of their last seizure as they were well controlled clinically on

sodium valproate. During transferral from valproate, and in the subsequent follow up period after the initiation of lamotrigine monotherapy, no seizures were experienced by any group A patients. One patient (AP02) stated she experienced jerks during the night since changing to lamotrigine therapy but these were not diagnosed as being associated with her epilepsy.

Table 5.5: Time since last seizure group A patients

Patient	Time since last seizure	
	Baseline	Follow up
AP02	T/C approx. 10 years ago (1000mg/day VPA)	T/C 11 years ago Jerks at night (500mg/day LTG)
AP09	T/C approx. 9 years ago (1000mg/day VPA)	T/C approx. 11 years ago (300mg/day LTG)
AP11	T/C 34 months ago (1000mg/day VPA)	T/C 49 months ago (350mg/day LTG)
AP14	Absence approx. 24 months ago (1000mg/day VPA)	Absence 41 months ago (250mg/day LTG)
AP15	T/C approx. 6 years ago (1000mg/day VPA)	T/C approx. 8 years ago (400mg/day LTG)
AP17	T/C 24 months ago (200mg/day VPA)	T/C 36 months ago (200mg/day LTG)

T/C denotes tonic clonic seizure

### Group B patients

Table 5.6 demonstrates the results for group B patients. All patients experienced a reduction in seizure frequency. Six patients did not experience any seizures after the initiation of lamotrigine therapy (AP03, AP07, AP08, AP12, AP13 and AP18). A further patient (AP19) only experienced one seizure since commencing lamotrigine treatment due to omission of one dose of medication.



At baseline no group B patients were seizure free when unmedicated. At follow up after the initiation of lamotrigine treatment 5 patients were seizure free (AP03, AP07, AP12, AP13 and AP18). Again AP19 would have been classified seizure free had he not experienced a seizure due to omission of medication.

Mean dosages of lamotrigine at follow up were compared for the sub groups of group B patients (seizure free vs. still experiencing seizures) by means of a Kruskal Wallis test. There was no significant difference in mean dosage between the seizure free group (275mg/day LTG) and the group of patients still experiencing seizures (200mg/day) ( $\chi^2(1) = 0.769$ ;  $p = 0.380$ ).

Table 5.6: Time since last seizure group B patients

Patient	Time since last seizure	
	Baseline	Follow up
AP01	T/C 13 days ago	T/C 7 months ago (300mg/day LTG)
AP03	T/C 1 month ago	T/C 26 months ago (300mg/day LTG)
AP04	T/C 1 month ago	T/C 6 months ago (100mg/day LTG)
AP06	T/C 1 month ago Absence approx. 1/month	T/C 12 months ago Absence 7 months ago (300mg/day LTG)
AP07	T/C 6 months ago	T/C 29 months ago (250mg/day LTG)
AP08	T/C 2 weeks ago	T/C 11 months ago Absence 1 month ago (200mg/day LTG)
AP12	T/C 3 months ago	T/C 25 months ago (100mg/day LTG)
AP13	T/C 1 month ago	T/C 22 months ago (400mg/day LTG)
AP18	T/C 7 months ago	T/C 82 months ago (400mg/day LTG) (retrospective patient seizure free for 6 years)
AP19	T/C 3 months ago	T/C 5 months ago (one seizure in 20 months due to omission of one dose of medication) Absences 5 months ago (100mg/day LTG)

T/C denotes tonic clonic seizure

### 5.5.2 Discussion

Eight of the sixteen patients experienced spontaneous seizures in addition to seizures induced by visual stimuli. This prevalence is slightly lower than the 60% reported in the literature (Kasteleijn-Nolst Trenité, 1989). All patients presented with tonic clonic and/or absence seizures which are the most common seizure types found in photosensitive epilepsy (Jeavons et al, 1985, Kasteleijn-Nolst Trenité, 1989, Harding, 1994, Quirk et al, 1995).

The most common visual and non-visual seizure precipitants were video games and sleep deprivation respectively. This is again in accordance with the data presented in the literature (Zifkin and Kasteleijn-Nolst Trenité, 2000).

All six group A patients were seizure free on valproate and lamotrigine therapy. As discussed in chapter three sodium valproate is the drug of choice for tonic clonic seizures in the primary generalised epilepsies including photosensitive epilepsy (Shorvon, 1995). It was therefore expected that the majority of the patients would be seizure free whilst receiving valproate as it clinically controls 79-80% of patients (Harding et al, 1978, Mattson et al, 1989).

There are no studies in the literature investigating lamotrigines effect on seizures in photosensitive epilepsy. There is evidence that it controls partial and generalised tonic clonic seizures (Binnie et al, 1986, Jawad et al, 1989, Sander et al, 1990b, Loiseau et al, 1990, Messenheimer et al, 1994) being most effective in tonic clonic seizures and atypical absences (Richens and Yuen, 1991, Binnie, 1992). The results in group A demonstrate that equivalent seizure control to valproate may be achieved with lamotrigine suggesting that seizure control is comparable between the two drugs, as has been implied by the literature (Kerr et al, 1999).



All drug naïve patients demonstrated a reduction in seizure frequency after the initiation of lamotrigine therapy and 50% became seizure free at follow up. This is superior to the data reported in the literature with up to 14 % of patients becoming seizure free in pooled data of open label studies, and 32% demonstrating at least a 50% reduction in seizure frequency (Binnie, 1992). Those patients who did not become seizure free may have experienced a reduction in the severity of seizures as suggested by the literature (Betts, 1992, Smith et al, 1992) but unfortunately seizure severity was not measured in this study.

There were no significant differences in dosages between the group of patients who became seizure free and those who did not suggesting that seizure control was not entirely based on dosage of lamotrigine. It may be that those patients who were not seizure free at follow up would become seizure free if their dosages were increased as none had reached the maximum dosage of 600mg/day. These patients however may simply not be responding to lamotrigine. In order to determine this an extended follow up period would be required. It should be considered that if abolition of seizure cannot be achieved then a reduction in seizure frequency (and severity) also improves the patients' quality of life.

## **5.6 Body Mass Index**

The height and weight of each prospective patient was recorded at each visit and body mass index (BMI) scores were calculated using the formula  $BMI = \text{weight (kg)}/\text{height (m)}^2$ .

### **5.6.1 Results**

Due to the retrospective nature of recruitment for some patients baseline and/or follow up measures were not available for patients AP09, AP11, AP14, AP15 (group A), AP04,

AP12, AP13 and AP18 (group B) and therefore they were excluded from the analysis. Baseline and follow up scores were plotted for the two remaining group A patients, and for the six remaining patients in group B BMI scores were averaged then plotted. Individual scores were categorised according to the following clinical guidelines (table 5.7).

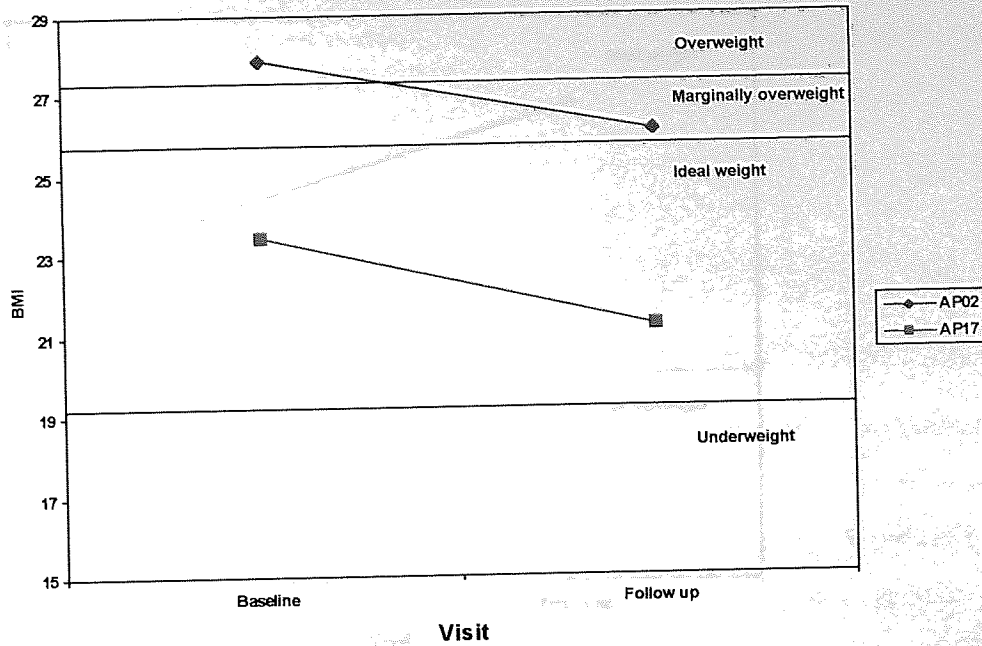
*Table 5.7: Clinical guidelines in the identification, evaluation and treatment of overweight and obesity in adults. National Heart, Lung and Blood Institute. June 17 1998.*

	Women	Men
Underweight	<19.1	<20.7
Ideal weight	19.1-25.8	20.7-26.4
Marginally overweight	25.8-27.3	26.4-27.8
Overweight	27.3-32.3	27.8-31.1
Very overweight or obese	>32.3	>31.1

### **Group A patients**

Both patients transferring from sodium valproate to lamotrigine showed a decrease in body mass index as demonstrated in figure 5.12. Patient AP02 had a BMI score of 27.88 at baseline when on 1000mg/day VPA that decreased to 26.1 at follow up when she was taking 500mg/day LTG.

Figure 5.12: BMI scores for group A patients

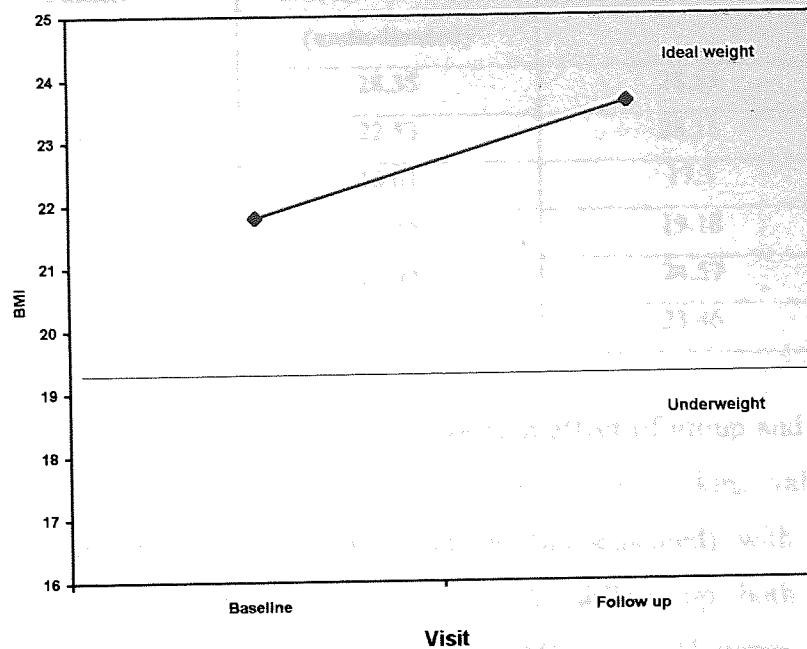


Patient AP02 was overweight on sodium valproate and became only marginally overweight after transferring to lamotrigine therapy. Patient AP17s BMI score decreased from 23.45 (200mg/day VPA) to 21.26 (200mg/day LTG). This patient remained at an ideal weight throughout the study.

**Group B patients**

Figure 5.13 displays the mean body mass index scores for group B patients, table 5.8 demonstrates individual scores and dosages of lamotrigine at follow up.

Figure 5.13: Mean BMI scores for six group B patients



All patients displayed an increase in body mass index but only one patient (AP03) displayed a clinical increase in weight changing from the ideal weight to the overweight category over the course of the study. Three patients AP07, AP08 and AP19 remained in the ideal weight classification despite minimal increases in body mass index. One patient (AP01) remained overweight and one patient (AP06) remained underweight, again both patients displaying minimal increases in BMI scores.

The data were then analysed by means of a Friedman test, to determine if there was a significant change in BMI score from baseline to follow up. There was no significant change ( $\chi^2(1) = 2.000$ ;  $p = 0.157$ ). Figure 5.12 demonstrates the mean BMI scores for both patient groups at baseline and follow up.



Table 5.8: Individual BMI scores and follow up dosages for group B patients

Patient	Baseline BMI score (unmedicated)	Follow up BMI score	Dosage of LTG (mg/day) at follow up
AP01	28.35	28.53	200
AP03	22.53	28.16	300
AP06	16.01	17.3	300
AP07	19.15	19.18	250
AP08	23.44	24.57	200
AP19	21.31	23.46	100

As can be seen in figure 5.14 an interaction effect of group and visit is suggested by the plot of the means. At baseline group A patients (taking valproate) BMI scores are considerably higher than group B patients (unmedicated), with group A patients near to the marginally overweight category. At follow up both patient groups (taking lamotrigine) show a very similar mean BMI score. However due to low sample sizes statistical tests to determine the significance of this could not be performed.

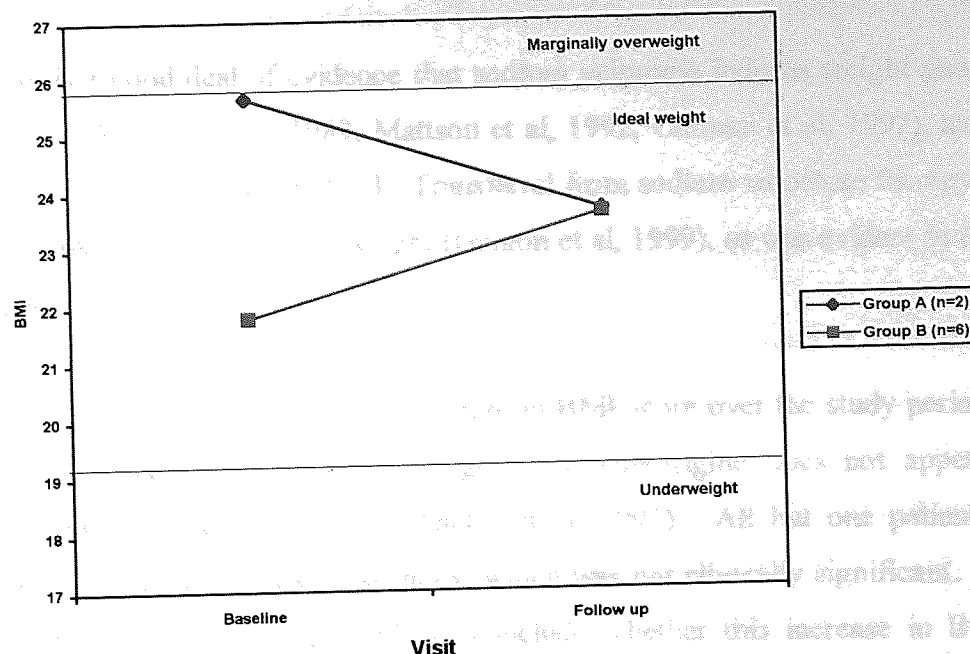
Monotherapy BMI scores were then combined and analysed by the means of a Kruskal Wallis test to investigate the effect of medication type on body mass index. Table 5.9 displays the mean BMI scores for each medication group. All means were similar with patients having a marginally higher body mass index score when taking lamotrigine than when taking sodium valproate, and finally the lowest score when unmedicated. There was no significant difference in body mass index scores between medication groups. ( $\chi^2(2) = 2.821; p = 0.244$ ).

Table 5.9: Mean BMI scores for medication groups

Medication type:	Mean BMI score:	Mean dosage (mg/day):	N:
No medication	21.798	N/A	6
LTG	23.746	260	10
VPA	23.69	800	4



Figure 5.14: Mean BMI scores for group A and group B patients at baseline and follow up



### 5.6.2 Discussion

Both group A patients transferring from sodium valproate to lamotrigine showed a decrease in body mass index. In one patient this was clinically significant, as she became marginally overweight rather than overweight according to clinical guidelines.

All drug naïve patients in group B displayed an increase in body mass index. This was only clinically significant in one patient who was previously within the ideal weight band when unmedicated and was categorised as overweight at 15 month follow up.

Due to the small participant numbers involved in this study it is difficult to generalise from these results. No real comparison can be made between medication types in this study, although it is interesting that both patient groups showed similar BMI scores whilst

taking lamotrigine and that patients displayed the highest BMI scores whilst taking sodium valproate. AP17. This patient was the only patient in the study who was taking sodium valproate at baseline and lamotrigine at follow-up.

There is a good deal of evidence that sodium valproate induces weight gain (Dinesen et al, 1984, Mattson et al, 1989, Mattson et al, 1992, Corman et al, 1997), as discussed in detail in chapter 3 section 3.2.3. Transferral from sodium valproate therapy to treatment with lamotrigine can reduce weight (Genton et al, 1999), as was evident in the two group A patients.

All group B patients showed an increase in BMI score over the study period contrary to studies in the literature which suggest that lamotrigine does not appear to have a detrimental effect on weight (Schacter et al, 1995). All but one patient displayed a minimal increase in body mass index, which was not clinically significant. Due to small patient numbers it is impossible to conclude whether this increase in BMI is due to treatment with lamotrigine. As with all medications the patient commencing lamotrigine therapy should be closely monitored and if it is deemed that weight gain is attributable to the lamotrigine, and it is clinically and/or psychologically unacceptable for the individual patient, withdrawal or alternative medication should be considered.

### **5.7 Menstrual History**

Menstrual history questionnaires were to be compared in all patients between baseline and visit 6 (15 month follow up). Due to the retrospective nature of recruitment for some patients data were not available at baseline and/or follow-up for patients AP11, AP02, AP09, AP14, AP15 (group A) and patients AP12, AP13, AP06, AP18 (group B) and therefore they were excluded from the analysis.

Three patients commenced oral or depot contraception during the course of the study (AP03, AP07 and AP17). These patients were also excluded from the analysis due to the extraneous effects of these methods of contraception on menstruation.

### **5.7.1 Results**

#### **Group A patients**

Although complete data was not available for any of the group A patients two patients mentioned they had experienced a change in their menstrual patterns. Patient AP09 stated that since transferring from sodium valproate to lamotrigine she experienced heavier bleeding on the second day of her period. Patient AP14, who had very irregular menses whilst receiving valproate therapy, stated that since withdrawing the valproate she now experienced more regular menstruation.

#### **Group B patients:**

Only three patients had complete baseline and followed up data. Patient AP01 was follow up at visit six. Patient AP04 only attended until visit three when she was clinically controlled with 100mg/day LTG. Visit five was used as a follow up measure for patient AP08 as she had commenced concomitant levetiracetam (keppra) therapy when she attended at visit six.

#### **Length of menstrual cycle**

Figure 5.15 displays data on the length of menstrual cycle. Patients AP01 and AP08 menstrual cycles were reduced after the initiation of lamotrigine therapy from 30.5 (unmedicated) to 26 days (300mg/day LTG) and 26.5 days (unmedicated) to 23 days (200mg/day LTG) respectively. Patient AP04's menstrual cycle increased from 26 days



(unmedicated) to an abnormal 38 day cycle, indicative of oligomenorrhea at 100mg/day LTG.

### Number of flow days

As can be seen from figure 5.16 the number of flow days was reduced for patients AP04 and AP08. Patient AP04's flow days were reduced from four when unmedicated to three when she was taking 100mg/day LTG. Patient AP08's flow days decreased by two days when receiving 200mg/day LTG.

*Figure 5.15: Number of days in menstrual cycle*

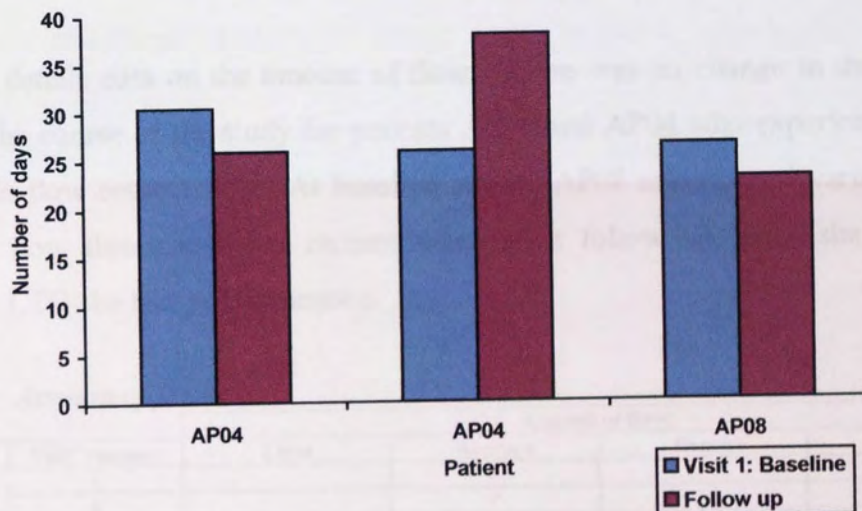
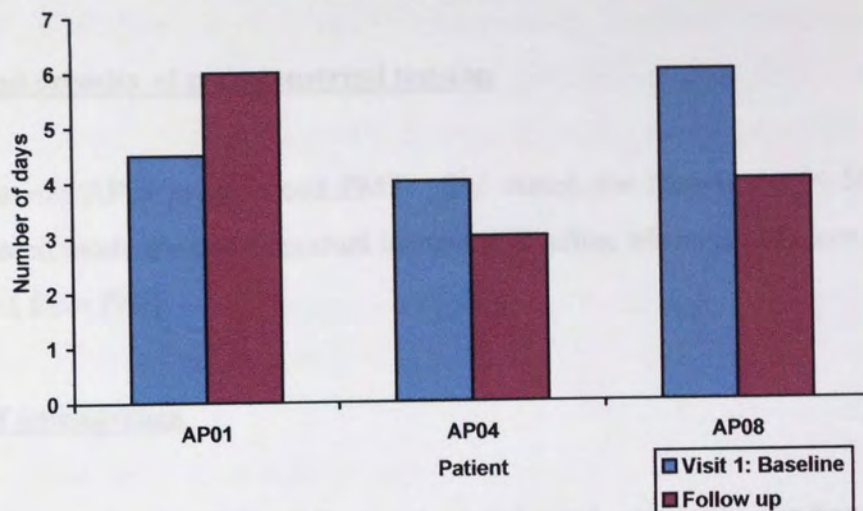


Figure 5.16: Number of flow days



### Amount of flow

Table 5.10 details data on the amount of flow. There was no change in the amount of flow over the course of the study for patients AP01 and AP04 who experienced average and variable flow respectively. At baseline patient AP08 experienced variations in the amount of flow throughout her menses whereas at follow up when she was taking 200mg/day LTG she had heavy menses.

Table 5.10: Amount of flow

Patient:	Visit Number:	Amount of flow:			
		Light	Average	Heavy	Variable
AP01	1		✓		
	6		✓		
AP04	1				✓
	3				✓
AP08	1				✓
	5			✓	

### Frequency and severity of dysmenorrhea

Only patient AP04 experienced dysmenorrhea. There was no change in the frequency, she experienced pain with menstruation often (> 50% of the time) at baseline and at



follow up, however the severity of the pain reduced from severe to mild over the course of the study.

### **Frequency and severity of pre-menstrual tension**

Again only patient AP04 experienced PMT. She stated she sometimes (< 50% of the time) experienced moderate pre menstrual tension at baseline whereas at follow up she no longer suffered from PMT.

### **Frequency of amenorrhea**

Patient AP04 sometimes (< 50% of the time) experienced amenorrhea at baseline when she was unmedicated. At follow up, when undergoing treatment with 100mg/day LTG, she no longer missed any menses for longer than a 6 month period. No other patient suffered from amenorrhea.

### **Frequency of oligomenorrhea**

Patient AP04 experienced oligomenorrhea at follow up on 100mg/day LTG.

### **Frequency of hypermenorrhea**

Patient AP08 experienced hypermenorrhea, suffering from particularly heavy menses at follow up when taking 200mg/day LTG when previously at baseline she did not.

### **Frequency of breakthrough bleeding**

Breakthrough bleeding was not experienced by any of the patients at either visit.

### **5.7.2 Discussion**

Patient AP04 showed an improvement in menstrual function after commencing lamotrigine therapy. At baseline when she was unmedicated she did not menstruate for periods of 6 months and longer (amenorrhoea) and suffered from severe dysmenorrhoea and sometimes experienced moderate PMT. At follow up when receiving 200mg/day LTG she experienced oligomenorrhoea (menses at intervals of longer than 35 days) rather than amenorrhoea. Indicating that her menses were becoming more regular. She experienced mild dysmenorrhoea and no longer suffered from pre-menstrual tension.

Amenorrhoea is seen in women with idiopathic generalised epilepsy (Murialdo et al, 1997). Amenorrhoea occurs if the hypothalamus and pituitary fail to provide appropriate gonadotrophin stimulation to the ovary leading to failure of ovulation and progesterone production or inadequate production of estradiol (Nelson et al, 2002). There is evidence that epilepsy can disrupt the menstrual cycle in this way through its effect on luteinising hormone pulsivity via its effect on the gonadotrophin releasing hormone pulse generator (Bilo et al, 1998).

Lamotrigine can reinstate menstruation after valproate induced amenorrhoea before the complete withdrawal of the sodium valproate (Isojarvi and Tapanainen, 2000) suggesting that lamotrigine may have a protective effect preventing menstrual abnormalities in women who are prone to them as a result of their epilepsy. It is possible in the case of patient AP04 that her menstrual abnormalities at baseline were as a result of her epilepsy and that the introduction of lamotrigine therapy has ameliorated these.

Patient AP08 experienced hypermenorrhoea after commencing 200mg/day LTG. There is no evidence in the literature that lamotrigine induces hypermenorrhoea. However a group A patient (AP09) stated that the bleeding on the second day of her menses was heavier

after transferring from valproate to lamotrigine, so it may be that this warrants further investigation.

Patient AP14 stated that her menses had become much more regular since transferring from valproate to lamotrigine, unfortunately there is no data to corroborate this statement. It has been well documented that sodium valproate can cause menstrual disruption (as discussed in detail in chapter 3, section 3.2.3.1) and that patients receiving valproate therapy display menstrual disturbance more frequently than patients taking other antiepileptic drugs (Murialdo et al, 1997, Isojarvi et al, 1998).

Transferral from valproate to lamotrigine can cause the cessation of menstrual irregularities (Isojarvi and Tapanainen, 2000, Stephen et al, 2001) which as discussed previously may be due to a protective effect of lamotrigine as improvements in menstruation can occur before the complete withdrawal of valproate (Isojarvi and Tapanainen, 2000).

## **5.8 Adverse effects**

At each visit patients detailed any adverse effect that they had experienced during lamotrigine therapy.

### **5.8.1 Results**

Three of the six group A patients and three of the ten group B patients experienced adverse effects whilst taking lamotrigine. No serious adverse events were reported and none resulted in discontinuation of lamotrigine therapy. Table 5.11 documents the adverse events reported.

The most frequently reported adverse effect was headache, occurring in four patients (two in group A and two in group B). In one case (AP01) the headaches commenced just prior to the initiation of lamotrigine therapy and continued throughout the 18 month follow-up period. The patient did not associate the headaches with the lamotrigine treatment. In the other three cases (AP02, AP06 and AP17) the headaches were mild and occurred after an increase in dosage. In all three patients the headaches were resolved without medical intervention within a few days to a few months.

Dizziness/"spaciness" was experienced by two patients (AP03 and AP06, both in group B), again this was transient (lasting 2 weeks in both cases) following an increase in dose of lamotrigine.

One patient (AP03, group B) reported decreased appetite, this was associated with an episode of tonsillitis and was resolved without medical intervention within 3 months.

A persistent itch in the tear duct of the right eye was experienced by one patient (AP15, group A). This occurred when the patient was taking 300mg/day LTG and was not resolved two months later when the patient was taking 400mg/day LTG. A couple of other adverse events were reported (see table 5.11) but these were not deemed to be associated with lamotrigine therapy.



Table 5.11: Adverse effects experienced by adult patients

Patient ID	Group	Medication	Adverse effect	Duration	Dose at which resolved
AP02	A	LTG 300mg	Headaches	3 months	Resolved by 500mg LTG
AP15	A	LTG 300mg	Itch in the tear duct of the right eye	2 months	Not resolved
		LTG 400mg	Swollen stomach since last period, GP suggests this may be Irritable Bowel Syndrome Couple of episodes of chest pain, difficulties in breathing, occurring in times of stress. GP suggests this is a reaction to the stress.	3 weeks	Not resolved
				Couple of episodes only	Resolved at LTG 400mg
AP17	A	LTG 200mg	A few mild headaches after increasing dose to 200mg/day. No localising features. The headaches were not severe enough to prevent daily activities or to warrant medication.	A few days	Resolved at LTG 200mg
AP01	B	LTG 50mg	Frequent headaches, sometimes associated with nausea. These have occurred ever since a virus the patient had just prior to commencing LTG therapy. The headaches are dull in nature and are mainly around the temples and the occipital areas.	18 months	Not resolved
		LTG 100mg	Still experiencing headaches although the patient does not think they are a side effect of the LTG.		
		LTG 150mg	Still experiencing headaches, occurring more frequently when the patient is tired.		
		LTG 300mg	Still experiencing headaches, approximately 2-3 per week, localised to the left hemisphere.		
AP03	B	LTG 50mg	Frequent stomach aches – associated with not eating during the day - patient does not think this is related to LTG.	3 months	Resolved by LTG 100mg, by eating during the day
		LTG 300mg	Episodes of dizziness after increasing dosage Decrease in appetite, after an episode of tonsillitis	2 weeks 6 months	Resolved on LTG 300mg Resolved on LTG 300mg
AP06	B	LTG 150mg	Headaches since increasing dose from 100 to 150mg	8 weeks	Reduced number of headaches at LTG 200mg
		LTG 200mg	Still experiencing headaches but not as frequently		
		LTG 300mg	Felt "spacey" after increasing dose.	2 weeks	Resolved at LTG 300mg



### **5.8.2 Discussion:**

Six patients reported adverse events that could have been associated with lamotrigine therapy. These were all acute dose related effects with the exception of one possible idiosyncratic reaction (patient AP15) and no chronic toxic effects were experienced.

The side effect profile in this study was similar to that reported in the literature with headache being the most frequently reported adverse effect. Many studies have documented that headaches are one of the most commonly reported adverse events occurring with lamotrigine therapy (Betts, 1992, Brodie, 1994). With the incidence ranging from 0.9% (The Lamictal-Lamotrigine Information sheet, Wellcome Trust, 1992, Schachter et al, 1995) to 12% (Betts et al, 1991). Headache is normally not severe and is a transient effect (Betts, 1992) as it was in three of the affected patients in this study. In one patient the headaches persisted for 18 months although these were not thought to be associated with lamotrigine therapy.

Dizziness was the second most frequently reported adverse event, again this is in concordance with the safety data in the literature. Schachter and colleagues reported that 50% of 446 patients experienced dizziness at some point during lamotrigine therapy but only 3% withdrew medication as a consequence (Schachter et al, 1995). More conservative reports of the incidence of dizziness are found in the literature with the Lamictal-Lamotrigine information sheet reporting 0.6% of patients experiencing dizziness (The Wellcome Trust, 1992) and Betts and colleagues reporting dizziness in 14% of their patients (Betts et al, 1991). Again dizziness tends to be mild and transient (Betts, 1992) as was the case in the patients in this study.

Conjunctivitis is mentioned in the Lamictal-Lamotrigine information sheet (The Wellcome Trust, 1992) but there is a lack of information in the literature. One patient experienced a persistent itch in the tear duct of her right eye and it may be that this was conjunctivitis occurring in reaction to the lamotrigine therapy. However at follow up this had not been diagnosed.



## **Chapter 6 Children's Study**

As in the adult study unless otherwise stated all measures were compared from baseline to visit four (12 month follow up). Patient CP05 did not attend for testing at visit four therefore for this patient measures were compared at visit three (6 month follow up).

Diffuse photic stimulation was not performed at baseline and/or follow up for patients CP05, CP06 and CP07, due to patient fatigue, therefore comparisons could not be made. Pattern stimulation was not performed for patient CP05 at six months follow up, due to a machine fault, therefore she was excluded from the analysis of pattern stimulation.

Patient CP04 did not display photoparoxysmal responses with either photic or pattern stimulation nevertheless she was included in the study as she experienced frequent seizures in response to visual precipitants (primarily the television) and displayed occipital spikes in response to visual stimulation.

### **6.1 Photoparoxysmal responses**

As detailed in the previous chapter sensitivity ranges for photoparoxysmal responses were calculated and compared between baseline and follow up for each stimulus type. Patients were categorised utilising the outcome classification described in the adult study.

#### **6.1.1 Results**

The outcome results for each stimulus type are displayed in table 6.1. Photoparoxysmal responses evoked by photic stimulation with the grid were abolished in two patients; CP05 on 200mg/day LTG and CP07 on 800mg/day VPA. With the grid and with diffuse photic stimulation one patient (CP03) improved with lamotrigine therapy (100mg/day LTG). With diffuse photic stimulation another patient (CP02) improved following treatment with 800mg/day VPA but showed no change in her sensitivity range in

response to stimulation with the grid. One patient (CP01) developed PPRs at follow up when taking 400mg/day LTG when previously at baseline when she was taking 800mg/day VPA she was not sensitive.

*Table 6.1: PPR outcome classification*

Patient	Group	Medication at follow up (mg/day)	Outcome			
			Photic: Grid	Photic: Diffuse	Pattern: SWR	Pattern: SS
CP01	B	400 LTG	No change Sensitive	New presentation	Deteriorated	No change Sensitive
CP02	A (VPA)	800 VPA	No change Sensitive	Improved	Abolished	Abolished
CP03	A (LTG)	100 LTG	Improved	Improved	No change Sensitive	Abolished
CP05	B	200 LTG	Abolished			
CP06	C	250 LTG	No change Sensitive		No change Sensitive	No change Sensitive
CP07	A (VPA)	800 LTG	Abolished		Abolished	Abolished

Photoparoxysmal responses evoked by pattern stimulation using reversing square wave gratings were abolished in two patients; CP02 and CP07, both were taking 800mg/day VPA at follow up. Patient CP01 showed an increase in her sensitivity range after switching from 800mg/day VPA to 400mg/day LTG. No other patients displayed any change in pattern sensitivity from baseline to follow up. With stationary sine wave gratings sensitivity was not altered in two patients (CP01 and CP06). Photoparoxysmal responses were however abolished at follow up in three patients (CP02, CP03 and CP07).

Due to the nature of the data statistical analysis could not be performed to determine if there was a significant change in sensitivity between the two visits.

Figures 6.1 to 6.4 demonstrate the sensitivity ranges of patients sensitive to the four stimulus types at baseline and follow up.



Figure 6.1: SRs of patients sensitive to photic stimulation with the grid at baseline and follow up

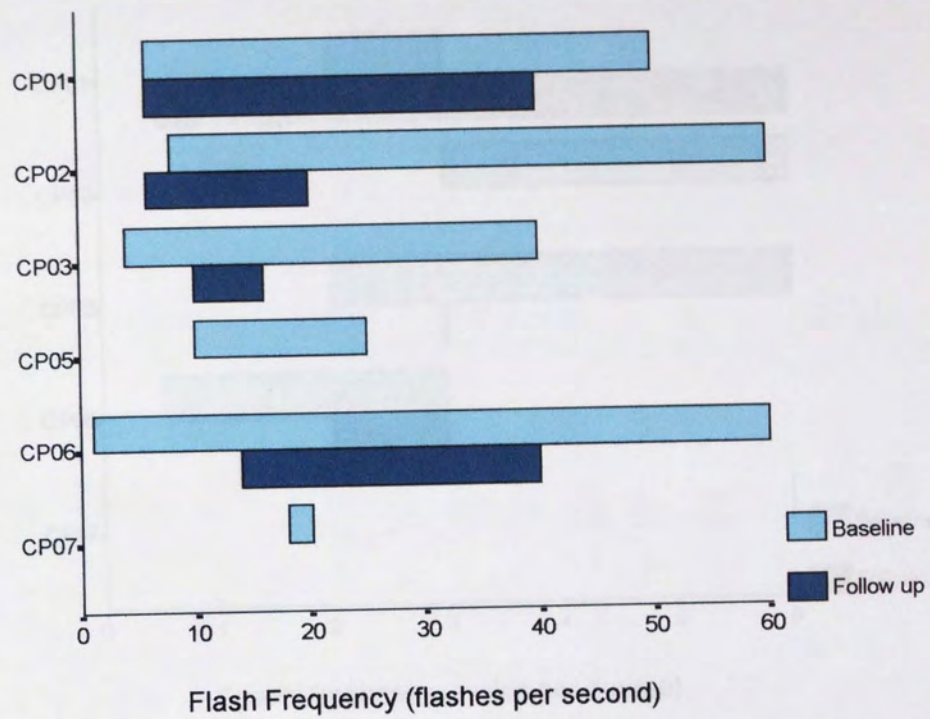


Figure 6.2: SRs of patients sensitive to diffuse stimulation at baseline and follow up

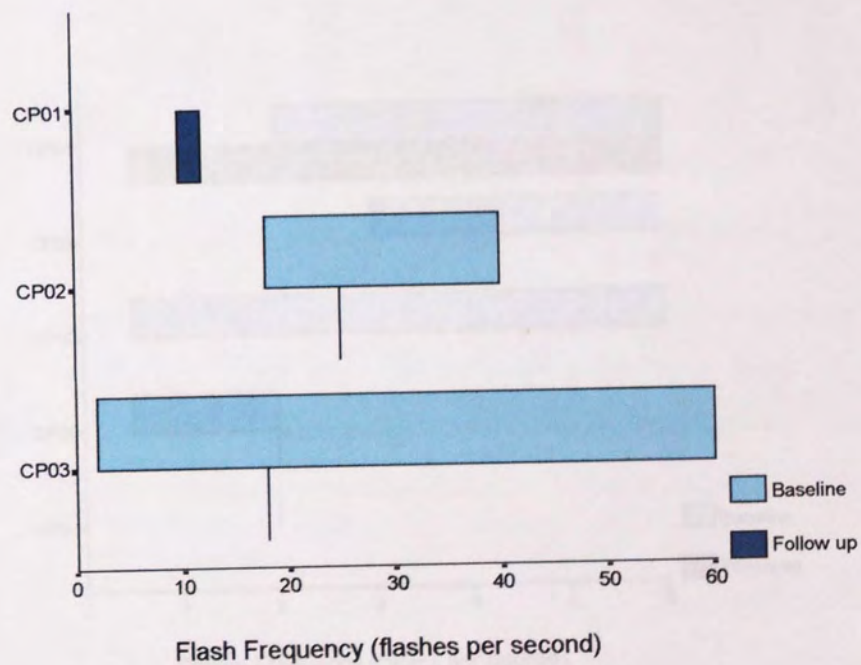




Figure 6.3: SRs of patients sensitive to reversing square wave gratings at baseline and follow up

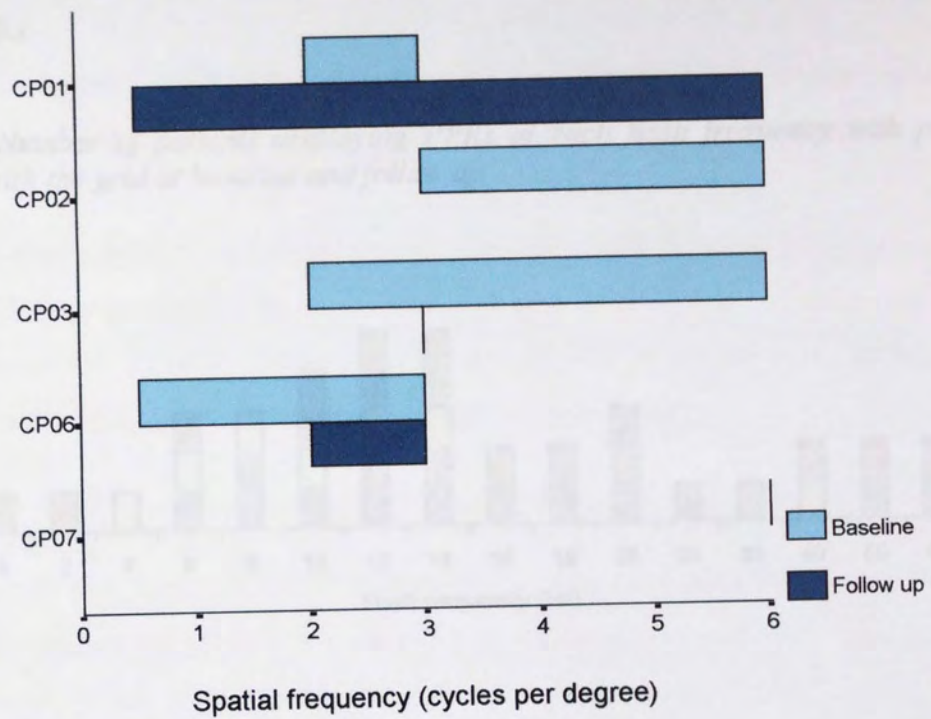
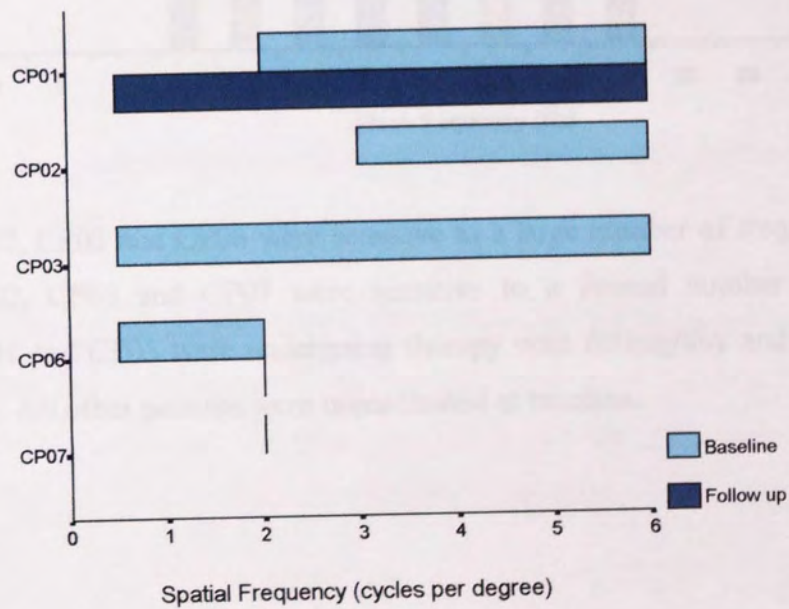


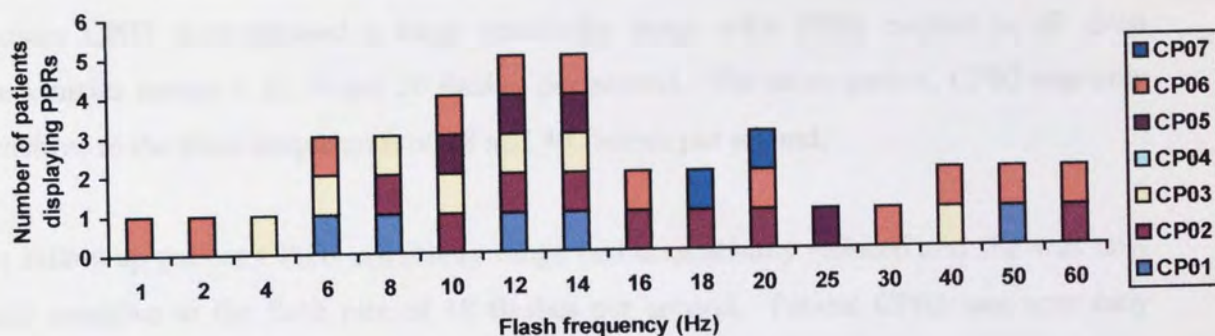
Figure 6.4: SRs of patients sensitive to stationary sine wave gratings at baseline and follow up



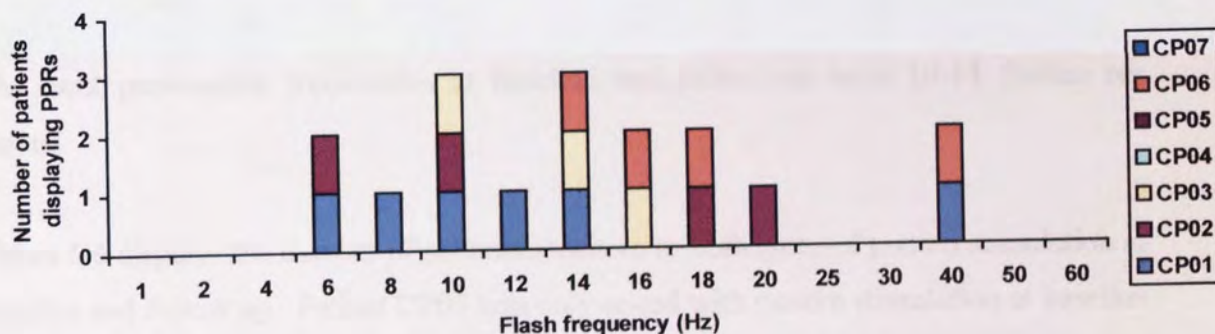
As in the adult study the number of patients displaying photoparoxysmal responses at each photic and pattern stimuli frequency was then examined. The data for photic stimulation using the grid are displayed in figure 6.5. At baseline six of the patients displayed PPRs

Figure 6.5: Number of patients displaying PPRs at each flash frequency with photic stimulation with the grid at baseline and follow up

**Baseline**



**Follow up**



Patients CP02, CP03 and CP06 were sensitive to a large number of frequencies whereas patients CP02, CP05 and CP07 were sensitive to a limited number of frequencies. Patients CP01 and CP05 were undergoing therapy with 800mg/day and 20mg/day VPA respectively. All other patients were unmedicated at baseline.

At follow up all patients ranges had been abolished or reduced except patient CP01, her range had extended since transferral to 400mg/day LTG. This extension did not however reach the 78% clinically significant level.

The most provocative flash frequencies at baseline were 10, 12 and 14 flashes per second and at follow up 10 and 14 flashes per second again evoked PPRs in more patients.

With diffuse photic stimulation two of the four patients tested displayed PPRs at baseline. Patient CP03 demonstrated a large sensitivity range with PPRs evoked at all flash frequencies except 1, 8, 14 and 50 flashes per second. The other patient, CP02 was only sensitive to the flash frequencies of 18 and 40 flashes per second.

At follow up patient CP03s sensitivity range had dramatically reduced and she was now only sensitive to the flash rate of 18 flashes per second. Patient CP02 was now only sensitive to 25 flashes per second. Patient CP01 at follow up showed PPRs in response to the flash rates of 10 and 12 flashes per second.

The most provocative frequencies at baseline and follow up were 10-14 flashes per second.

Figure 6.6 displays the number of patients sensitive to both types of pattern stimulation at baseline and follow up. Patient CP05 was only tested with pattern stimulation at baseline and although it is plotted on figure 6.6 comparison of pattern sensitivity between the two visits cannot be made.

At baseline all patients except patient CP04 displayed photoparoxysmal responses to pattern stimulation. Patient CP01s pattern sensitivity increased from baseline (800mg/day VPA) to follow up (400mg/day LTG) with both types of gratings, reaching the 78% level and leading to a classification of deteriorated.

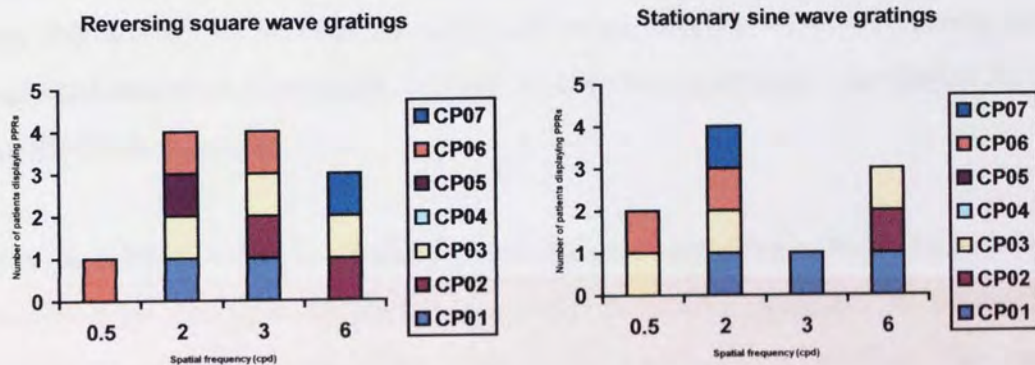


Patient CP02s pattern sensitivity was abolished as was patient CP07s. Both of these patients were taking 800mg/day VPA at follow up.

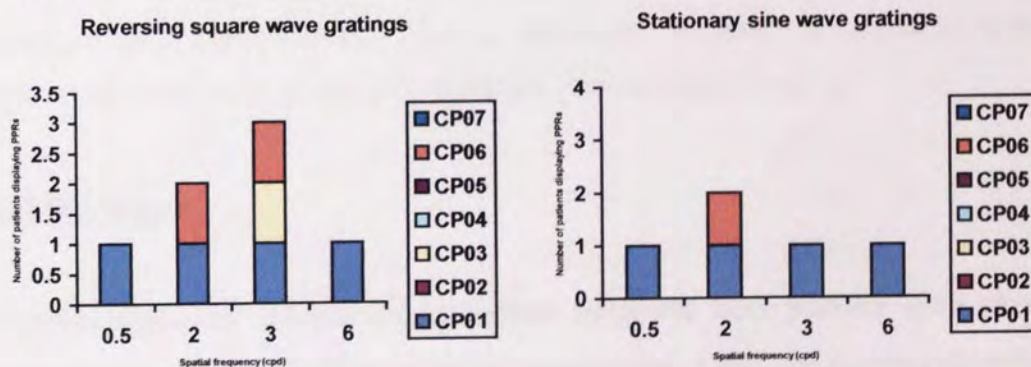
Pattern sensitivity was reduced for patient CP03 (unmedicated at baseline, 100mg/day LTG at follow up) and patient CP06 (200mg/day CBZ at baseline and 250mg/day LTG at follow up), although this reduction did not reach the clinically significant level of 78%. Photoparoxysmal responses evoked by stationary sine wave gratings in the EEG of patient CP03 were abolished at follow up.

Figure 6.6: Number of patients displaying PPRs at each spatial frequency with both types of gratings at baseline and follow up

**Baseline**



**Follow up**



The most provocative spatial frequencies for both types of grating were 2 and 3cpd. Again due to the nature of the data it was impossible to conduct statistical analysis.

### **6.1.2 Non-responders**

Non-responders were defined utilising the same criteria as described in the adult study. All patients except one were deemed to be non-responders in terms of photosensitivity. The one responder was patient CP07 who at follow up was taking 800mg/day VPA. His pattern sensitivity also responded to treatment with sodium valproate. One other patients (CP02) pattern sensitivity also responded to treatment and again she was taking 800mg/day VPA at follow up.

No further patients were classified as responders for either photosensitivity or pattern sensitivity. It should be noted that patient CP02 had been seizure free for six months but since this was the entire time she had been taking sodium valproate (having previously been randomised to lamotrigine therapy as discussed previously in chapter 4) she was classified as a responder.

As in the adult study it was originally intended that multiple logistic regression would be performed on the data to provide a model to predict response to treatment using information available at baseline. Due to the small patient numbers this method of analysis could not be performed. Unfortunately unlike the adult data the nature of the children's data prevented any further statistical analysis to determine associations between response to treatment and information available at baseline.

### **6.1.3 Discussion**

In group A patients randomised to sodium valproate both patients were classified as responders to treatment in terms of pattern sensitivity. Only one patients photosensitivity responded to treatment however. As previously discussed with the adults' results it was expected that the majority of patients randomised to sodium valproate would respond to therapy. Valproate as reported in chapter 5, section 5.1.3, controls photosensitivity in



80% of patients (Harding et al, 1978) and reduces the likelihood of PPRs evoked by pattern stimuli (Darby et al, 1986, Binnie and Wilkins, 1998).

Neither of the two drug naïve patients randomised to lamotrigine were classified as responders. One patient did show an improvement in her sensitivity range to diffuse photic stimulation and photic stimulation with the grid, and an abolition of PPRs evoked by stationary sine wave gratings. She continued to experience daily absence seizures. It is likely that these improvements in sensitivity range indicate a partial response to lamotrigine. The patient was only taking 100mg/day LTG at follow up and a further increase in dose may reduce the SR of the more provocative pattern stimuli of reversing square wave gratings (Binnie and Wilkins, 1998).

The other group A patient randomised to lamotrigine was taking 400mg/day LTG, well within the recommended daily dosing range. She was classified as a non-responder as her visually induced seizures remained. Her seizures were evoked by the television and normally occurred as she was compulsively attracted to the set. Self induced television epilepsy is notoriously difficult to treat (Binnie, 1988), which could explain the lack of response to lamotrigine therapy in this patient.

Self-induction of seizures is commonly found in the epileptic syndrome, eyelid myoclonia with absences (EMA), (Binnie and Jeavons, 1992) and indeed both of these patients were diagnosed with EMA. Patients with EMA are less likely to respond to treatment than patients with absence and other generalised epilepsies (Appleton et al, 1993) which again could explain the lack of response to lamotrigine therapy in these two patients. Valproate monotherapy is less effective in EMA than when it is combined with ethosuximide or benzodiazepines (Appleton et al, 1993). Lamotrigine has been reported as being useful in the treatment of EMA (Kent et al, 1998) although this was in the capacity of add-on therapy in patients already receiving valproate, rather than monotherapy as was the case in the two patients in this study.

All three remaining patients transferring to lamotrigine following failure to respond to valproate or carbamazepine were classified as non-responders to lamotrigine therapy.

In two patients there was no change in sensitivity ranges to either photic or pattern stimulation and the abolition of seizures was not obtained. One of these patients was diagnosed with occipital lobe epilepsy and was transferring from valproate. The other patient was transferring from carbamazepine and was diagnosed with complex partial epilepsy. Both patients were taking the appropriate first line drugs for their respective conditions (Guerrini et al 1995, Shorvon, 1995).

Between 50-80% of patients respond to the first line antiepileptic drug (Sander, 1993, Shorvon et al, 1997). If patients do not respond to the first line drug 5-10% can obtain seizure control with add-on therapy using the newer AEDs (Shorvon, 1995). Although lamotrigine therapy was unsuccessful in these patients reports in the literature suggest it is a useful drug in the treatment of refractory childhood epilepsy (Besag et al, 1998, Dimova and Korinthenberg, 1999, Frank et al, 1999). This however is again when it is used as add-on therapy with sodium valproate. This suggests that these patients may have responded to lamotrigine therapy if it had been used in conjunction with their original AEDs. Indeed a synergistic antiepileptic effect has been documented when lamotrigine and valproate are used in polytherapy (Kanner and Frey, 1999).

In the remaining group B patient PPRs evoked with photic stimulation remaining with valproate therapy were abolished after transferral to lamotrigine. She was classified as a non-responder however due to continuing absence seizures. With a diagnosis of childhood variant absence epilepsy it is likely that this particular patient would benefit from treatment with ethosuximide (Jeavons et al, 1977, Hopkins et al, 1995).

In terms of stimulus characteristics photic stimulation with the grid was more provocative than diffuse photic stimulation as expected from reviews in the literature (Harding and Jeavons, 1994). Similar to the adult data the most provocative flash frequencies were 10-

14 flashes per second, again slightly lower than the range described in the literature (Binnie and Jeavons, 1992).

With pattern stimulation the results replicated those found in the adult data with the most provocative spatial frequencies being 2 and 3cpd, in agreement with the literature (Wilkins et al, 1980). There was again no difference in the provocative nature of the gratings, contradicting the literature (Binnie and Wilkins, 1998)

Only one child was classified as a responder of both photosensitivity and pattern sensitivity following treatment with sodium valproate. Again it should be considered that the definition of a responder used in this study was stricter than that used in other studies (Schmidt, 1991, Eriksson et al, 1998, Jozwiak and Terczynski, 2000) for reasons detailed in chapter five, section 5.1.3. Nevertheless in comparison with the adult data the response rate is much lower, probably explained by the fact that childhood epilepsies are typically more difficult to treat (Besag et al, 1998)

## **6.2 Occipital spikes**

### **6.2.1 Results**

With photic stimulation using the grid five of the seven patients displayed occipital spikes at baseline (CP02, CP03, CP04, CP05 and CP07) which were abolished at follow up in four patients (CP02, CP03, CP05 and CP07). Two were taking lamotrigine at follow up (CP03 and CP05) and two were taking valproate (CP02 and CP07).

Two of the four patients tested with diffuse photic stimulation displayed occipital spikes at baseline (CP02 and CP04), these were abolished in both patients at follow up when the patients were taking valproate and lamotrigine respectively.

With pattern stimulation using the reversing square wave gratings two of the six patients tested displayed occipital spikes at baseline (CP02 and CP04) and these were abolished at

follow up. None of the six patients tested with stationary sine wave gratings displayed occipital spikes at baseline or follow up.

Figure 6.7 demonstrates the number of patients displaying occipital spikes at each flash frequency for photic stimulation with the grid at baseline and follow up.

Patient CP02 displayed occipital spikes in response to the flash rate of 50 flashes per second and preceding a PPR at 60 flashes per second. At follow up she only displayed occipital spikes in response to 8 and 12 flashes per second whereas at baseline she had previously displayed PPRs. Occipital spikes were again seen preceding PPRs at baseline in the EEG of patient CP05, in response to the flash rates of 10 and 12 flashes per second.

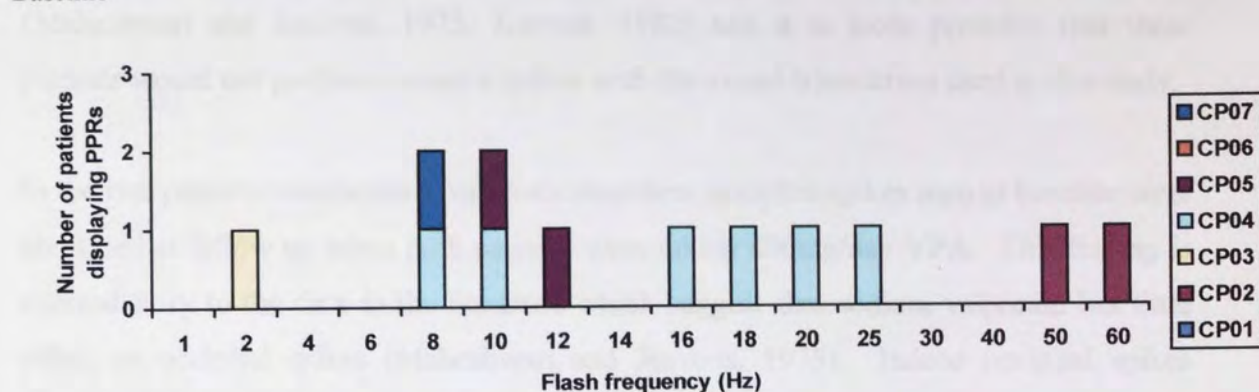
Patient CP03 displayed occipital spikes at baseline in response to 2 flashes per second, which was at the edge of her sensitivity range for PPRs with photoparoxysmal responses evoked at 4 flashes per second.

Patient CP04 only displayed occipital spikes in response to visual stimulation and the range of frequencies evoking occipital spikes increased from baseline to follow up. This increase however did not reach the clinically significant 78% level. Her sensitivity range for occipital spikes shifted to higher frequencies at follow up.

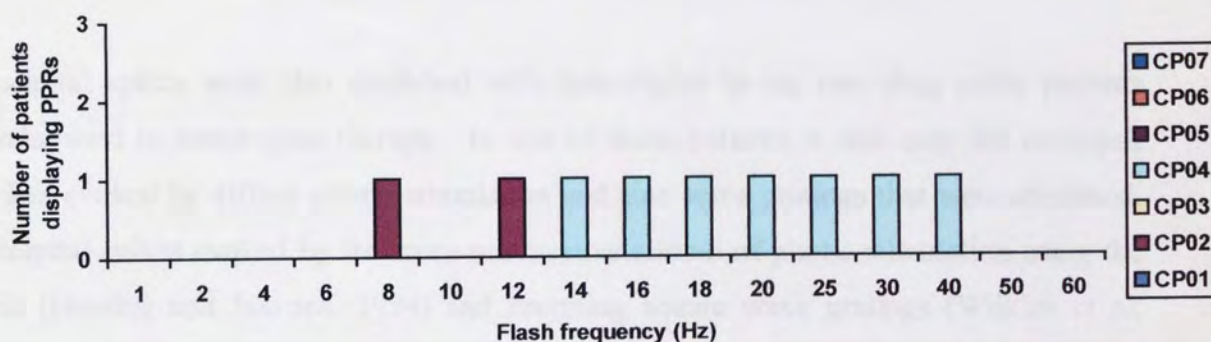
With diffuse photic stimulation patient CP02 displayed occipital spikes at baseline in response to the flash rate of 20 flashes per second, displaying a PPR at 18 flashes per second. Patient CP04 demonstrated occipital spikes at the flash rates of 14, 20 and 25 flashes per second at baseline. Occipital spikes were not evoked in the EEGs of either patient at follow up.



Figure 6.7: Number of patients displaying occipital spikes at each flash frequency with photic stimulation with the grid at baseline and follow up



**Follow up**



With pattern stimulation occipital spikes were evoked at baseline using square wave gratings of 0.5 and 2cpd in patient CP02s EEG. She displayed PPRs with gratings of 3 and 6cpd. Patient CP04 demonstrated occipital spikes with square wave gratings of 3 and 6cpd and a sine wave grating of 6cpd. At follow up neither patient displayed occipital spikes in their EEGs in response to either type of grating.

Due to the nature of the data statistical analysis could not be executed.

**6.2.2 Discussion**

Two patients did not display occipital spikes at either baseline or follow up. These patients were taking valproate and carbamazepine respectively at baseline and



lamotrigine at follow up. They were diagnosed with occipital lobe epilepsy and complex partial epilepsy. It is unlikely that either drug was controlling occipital spikes at baseline (Maheshwari and Jeavons, 1975, Jeavons, 1982) and it is more probable that these patients would not produce occipital spikes with the visual stimulation used in this study.

In the two patients commencing valproate treatment occipital spikes seen at baseline were abolished at follow up when both patients were taking 800mg/day VPA. This finding is contradictory to the data in the literature which suggest that sodium valproate has little effect on occipital spikes (Maheshwari and Jeavons, 1975). Indeed occipital spikes remained with valproate therapy with one patient; these were subsequently abolished post transferral to lamotrigine.

Occipital spikes were also abolished with lamotrigine in the two drug naïve patients randomised to lamotrigine therapy. In one of these patients it was only the occipital; spikes evoked by diffuse photic stimulation and sine wave gratings that were abolished. Occipital spikes evoked by the more provocative stimuli of photic stimulation using the grid (Harding and Jeavons, 1994) and reversing square wave gratings (Wilkins et al, 1980) remained at follow up despite a dose of 400mg/day LTG.

Lamotrigine can abolish occipital spikes (Binnie et al, 1980b) but they tend not to be affected by antiepileptic drugs in any consistent manner (Jeavons, 1982) as demonstrated by the results of this study.

The children's results like those of the adult study are difficult to generalise from and it is again impossible to conclude upon the effect of lamotrigine on occipital spikes.

### **6.3. Normal responses**

As with the adult data the effect of lamotrigine therapy on normal EEG responses evoked by photic and pattern stimulation was investigated, as was the effect of sodium valproate

in patients randomised to valproate therapy. Normal responses to pattern stimulation were not compared for patient CP05 due to missing data.

### **6.3.1 Results**

Statistical analysis could not be carried out on any of the following measures due to the low sample sizes for each treatment group.

#### **6.3.1.1 Photic driving**

All patients demonstrated photic driving at both baseline and follow up.

#### **6.3.1.2. Visual evoked potentials in the EEG**

With photic stimulation all seven patients displayed VEPs at baseline and follow up. With pattern stimulation two (CP01 and CP03) of the six patients tested demonstrated VEPs at baseline, at follow up VEPs were not seen in any of the patients EEGs.

#### **6.3.1.3 Lambda activity**

With photic stimulation two (CP01 and CP06) of the seven patients demonstrated lambda activity at baseline. At follow up lambda waves were now evoked in the EEGs of all the patients except CP04 and CP07.

At baseline only patient CP05 displayed lambda activity in response to pattern stimulation. Unfortunately she did not undergo pattern testing at follow up. Lambda waves were seen in the EEG of patient CP03 at follow up.

### 6.3.2 Discussion

All patients displayed photic driving at baseline and follow up suggesting that none of the medications involved affected this normal response to IPS.

With photic stimulation all patients demonstrated VEPs at baseline and follow up. It was expected that a number of patients would display VEPs in their EEGs in response to visual stimuli. Visual evoked potentials are reportedly abnormally large in photosensitive patients (Gastaut and Regis, 1964, Green, 1969, Hishikawa et al, 1967, Lucking et al, 1967, Herrick and Harding, 1978, Guerrini et al, 1998a), despite the reduction of amplitude provided by therapy with sodium valproate (Herrick and Harding, 1978).

With photic stimulation only two patients displayed lambda activity at baseline; taking 800mg/day VPA and 200mg/day CBZ respectively. At follow up all patients demonstrated lambda activity except two taking 400mg/day LTG and 800mg/day VPA respectively. With pattern stimulation only one patient displayed lambda waves at baseline (20mg/day VPA), but was unfortunately not tested at follow up. One previously unmedicated patient displayed lambda activity at follow up when taking 100mg/day LTG.

Unlike the adult data it is not possible to comment on these results in terms of the literature due to the small patient numbers and variations in medications and dosages the results can only be examined in terms of individual cases. It is impossible to conclude upon the affects of the medications involved in the children's study on these normal responses. The data from the adult study however would suggest that controlled studies of the affects of lamotrigine and valproate on photic driving, VEPs and lambda in photosensitive and pattern sensitive children are warranted.

## **6.4 Background EEG**

The patients resting records were reported on and categorised using the method detailed in the adult study. The resting records were compared between baseline and 12 month follow up for all patients except patient CP05. Her baseline resting record was compared to her EEG at six month follow up as she did not attend the 12 month follow up.

### **6.4.1 Results**

Table 6.2 details the state of the resting EEG for group A patients randomised to sodium valproate and table 6.3 displays data for group A patients randomised to lamotrigine therapy.

None of the group A patients demonstrated any change in the state of the resting record when baseline and follow up EEGs were compared.

*Table 6.2: State of resting record group A patients, randomised to VPA*

<b>Patient:</b>	<b>Visit 1: Baseline</b>		<b>Visit 4: 12 month follow up</b>	
	<b>Medication (mg/day):</b>	<b>State of resting record:</b>	<b>Medication (mg/day):</b>	<b>State of resting record:</b>
CP02	Nil	Abnormal	VPA 800	Abnormal
CP07	Nil	Normal	VPA 800	Normal

*Table 6.3: State of resting record group A patients, randomised to LTG*

<b>Patient:</b>	<b>Visit 1: Baseline</b>		<b>Visit 4: 12 month follow up</b>	
	<b>Medication (mg/day):</b>	<b>State of resting record:</b>	<b>Medication (mg/day):</b>	<b>State of resting record:</b>
CP03	Nil	Abnormal	LTG 100	Abnormal
CP04	Nil	Non-specific abnormality	LTG 400	Non-specific abnormality

Abnormal spike and wave activity was evident at both baseline and follow up in the resting EEGs of patients CP02 and CP03. Non-specific abnormal sharp slow wave



activity was noted in the resting record of patient CP04 at baseline and follow up. Patient CP07s EEG was categorised as normal at both visits.

Table 6.4 demonstrates the state of the resting record at baseline and follow up for group B patients.

*Table 6.4 State of resting record group B patients*

Patient:	Visit 1: Baseline		Visit 4: 12 month follow up	
	Medication (mg/day):	State of resting record:	Medication (mg/day):	State of resting record:
CP01	VPA 800	Non-specifically abnormal	LTG 400	Non-specifically abnormal
CP05	VPA 20	Abnormal	LTG 200 (visit 3, 6 months)	Non-specifically abnormal

The resting record was classified as non-specifically abnormal for both patients after transferral from sodium valproate to lamotrigine. Spike and wave activity previously seen in the background EEG of patient CP05 at baseline disappeared leaving only slow wave activity. Non-specific abnormal sharp slow activity seen in the resting record of patient CP01 at baseline was only evident during hyperventilation at follow up.

Patient CP06 transferred from carbamazepine to lamotrigine (group C), the state of her resting EEG at visits one and four is detailed in table 6.5. Spike and wave activity evident at baseline remained in the EEG at 12 months follow up.

*Table 6.5: State of resting record group C patient*

Patient:	Visit 1: Baseline		Visit 4: 12 month follow up	
	Medication (mg/day):	State of resting record:	Medication (mg/day):	State of resting record:
CP06	CBZ 200	Abnormal	LTG 250	Abnormal

Visual inspection of the data revealed that only one patient had demonstrated any change in the background EEG at follow up compared to baseline. This fact, combined with the

nature of the data and the small patient numbers, prevented any statistical analysis from being performed.

#### **6.4.2 Discussion**

Normal EEGs are found in patients with photosensitive epilepsy. The literature suggested this may be as prevalent as 60% of photosensitive patients displaying a normal EEG (Aziz et al, 1989). Only one patient in this study displayed a normal EEG, a lower figure than that expected from the literature (Quirk et al, 1995, Aziz et al, 1989). However the studies in the literature used adult patients and abnormal EEGs are more commonly found in children with epilepsy in comparison to adults with epilepsy.

In five patients the EEG remained abnormal or non-specifically abnormal regardless of treatment. Three of these patients demonstrated poly/spike and wave activity at baseline and follow up (receiving lamotrigine or valproate therapy). Spike/polyspike and wave activity in the resting EEG can be found in up to 52% of photosensitive patients (Quirk et al, 1995) and denotes patients who are more likely to experience spontaneous seizures (Gilliam and Chiappa, 1995). All three of the patients with spike/polyspike and wave activity had a history of spontaneous seizures in addition to seizure evoked by visual stimuli.

Non-specific abnormalities were seen in the EEGs of two patients at baseline (one unmedicated, one receiving sodium valproate). These abnormalities were similar to those reported in the literature, excessive sharp slow wave activity (Aziz et al, 1989, Kasteleijn-Nolst Trenité, 1989, Quirk et al, 1995). When receiving lamotrigine treatment 12 months later both patients continued to display sharp slow waves in their resting EEGs.

Only one patient demonstrated an improvement in their resting EEG. This was following transferral from sodium valproate to lamotrigine. Generally valproate is effective in normalising the EEG of photosensitive patients (Jeavons et al, 1976, Jeavons et al, 1977, Stefan et al, 1984), abolishing clinical manifestations in approximately 80% of patients (Harding et al, 1978). In this case spike and wave activity was still evident with valproate therapy. There are cases reported where valproate treatment can worsen the EEG (Jeavons et al, 1977) and patients may develop 3Hz spike and wave activity in response to valproate therapy (Myslobodsky et al, 1980). The patient in question was on a very low dose of valproate, only 20mg/day which may explain why the spike and wave activity was evident as the dosage required to normalise the EEG tends to be around 1000mg/day (Herrick and Maheshwari, 1975). With transferral to 200mg/day LTG her spike and wave activity disappeared and was replaced by non-specific slow wave activity.

As previously discussed there is little information in the literature of the effect of lamotrigine on the background EEG but it does reduce the frequency of interictal spikes in single dose studies (Binnie et al, 1986, Jawad et al, 1986). In chronic treatment a reduction of spike and wave episodes in children has been documented (Besag, 1992) as has a reduction of secondary generalisation of focal and multifocal discharges (Dimova and Korinthenberg, 1999).

Only one patient showed an improvement in the state of the resting record following treatment with lamotrigine however it should be considered that it is not necessary for the EEG to be normal for the patient to be clinically controlled (Jeavons et al, 1977). Also treatment of epilepsy is never based on the EEG but on the frequency and severity of seizures.

## **6.5 Seizure Control**

As in the adult study at each visit patients and their parents were questioned on their seizure history. The time since last seizure was recorded and compared from baseline to 12 month follow up. Patient CP05 did not attend 12 month follow up so the baseline measure was compared to follow up at six months (visit three).

### **6.5.1 Results**

Six of the patients experienced spontaneous seizures, one patient (CP07) only experienced visually induced seizures, as discussed in chapter four, section 4.3.2.1. The most common visual seizure precipitant was the television (seizures being precipitated in four patients) and the most common non-visual precipitant was sleep deprivation (again inducing seizures in four patients), similar to the adult data.

Table 6.6 details time since last seizure for group A patients randomised to sodium valproate. Both patients showed a reduction in seizure frequency since commencing valproate treatment. Patient CP07 had not experienced another seizure since commencing valproate therapy 12 months previously. Patient CP02 had not experienced a seizure since commencing valproate therapy 6 months previously.

*Table 6.6: Time since last seizure group A patients randomised to VPA*

<b>Patient</b>	<b>Time since last seizure</b>	
	<b>Baseline</b>	<b>Follow up</b>
CP02	Absences every day	T/C 7 months ago Absences 6 months ago (800mg/day VPA)
CP07	T/C 17 days ago	T/C 12 months ago (800mg/day VPA)

*T/C denotes tonic clonic seizure*

Table 6.7 demonstrates the results for group A patients randomised to lamotrigine. CP03 showed no change in seizure frequency despite taking 100mg/day LTG at follow up.



CP04 experienced a reduction in seizure frequency, not experiencing a seizure for five months at follow up on 400mg/day LTG.

Table 6.7: Time since last seizure group A patients randomised to LTG

Patient	Time since last seizure	
	Baseline	Follow up
CP03	Absences every day	Absences every day (100mg/day LTG)
CP04	T/C 10 days ago Absences every day	T/C 5 months ago Absences 5 months ago (400mg/day LTG)

T/C denotes tonic clonic seizure

Table 6.8 summarises the results of patients transferring from valproate to lamotrigine. Patient CP01 did not experience any change in seizure frequency. It is difficult to comment on the seizure frequency of patient CP05 as herself and her mother were unsure of her seizure frequency at follow up. They stated they were not aware of any absences occurring recently but could not quantify this. At baseline she had previously experienced absences every day so this could suggest a reduction in the occurrence of her seizures.

Table 6.8: Time since last seizure group B patients

Patient	Time since last seizure	
	Baseline	Follow up
CP01	T/C 4-6 weeks ago (800mg/day VPA)	T/C 4-5 weeks ago (400mg/day LTG)
CP05	Absences every day (20mg/day VPA)	Unsure, unaware of any recent absences (200mg/day LTG)

T/C denotes tonic clonic seizure

Patient CP06 had not experienced any seizures since transferring from carbamazepine to lamotrigine (table 6.9).

Table 6.9: Time since last seizure group C patient

Patient	Time since last seizure	
	Baseline	Follow up
CP06	T/C 19 days ago (200mg/day CBZ)	T/C 12 months ago (250mg/day LTG)

T/C denotes tonic clonic seizure

Patients were classified as still experiencing seizures or seizure free as documented in the adult study. At baseline all patients were still experiencing seizures. At follow up two patients were seizure free (one receiving valproate therapy, one receiving lamotrigine therapy). Due to the nature of the data and the small patient numbers statistical analysis was not performed.

### **6.5.2 Discussion**

Spontaneous seizures occur in 60% of photosensitive patients (Kasteleijn-Nolst Trenité, 1989). In this study six of the seven patients experienced spontaneous seizures. Common seizure precipitants were similar to those described in the literature (Jeavons, 1982, Kasteleijn-Nolst Trenité, 1989).

One patient (CP07) only had visually induced seizures i.e. displayed pure photosensitive epilepsy. This occurs in 40% of photosensitive patients (Kasteleijn-Nolst Trenité, 1989), they experience tonic clonic seizures and 50% have normal resting EEGs (Binnie and Jeavons, 1992), as was the case in this patient.

All patients presented with tonic clonic and/or absence seizures which are the most common seizure types found in photosensitive epilepsy (Jeavons et al, 1985, Kasteleijn-Nolst Trenité, 1989, Harding, 1994, Quirk et al, 1995).

In the two drug naïve patients randomised to valproate, one became seizure free (CP07) and the other (CP02) demonstrated a reduction in seizure frequency. As previously discussed in chapter three sodium valproate is the drug of choice for photosensitive epilepsy, with 80% of patients becoming seizure free (Harding et al, 1978), therefore these results are as expected.

Patient CP02 was originally randomised to lamotrigine but experienced an increase in frequency and severity of seizures with a dose of 400mg/day LTG. Exacerbation of

severe myoclonic epilepsy and JME has been documented in the literature (Guerrini et al, 1998b, Genton, 2000, Carrazana and Wheeler, 2001). Once transferred to valproate therapy her seizures ceased and she had remained seizure free for six months when seen at visit six. Indeed complete control of seizures with valproate is found in 64% of childhood epilepsies (Jeavons et al, 1980).

The two drug naïve patients randomised to lamotrigine continued to experience seizures suggesting they did not respond to lamotrigine therapy. There is no information in the literature of lamotrigines effect on spontaneous seizures in photosensitive epilepsy. It is efficacious in partial and generalised tonic clonic seizures (Binnie et al, 1986, Jawad et al, 1989, Sander et al, 1990b, Loiseau et al, 1990, Messenheimer et al, 1994) and generalised absences in children (Richens and Yuen, 1991). If seizure frequency is not reduced seizures do tend to become less severe (Betts, 1992, Smith et al, 1992). Unfortunately seizure severity was not measured in this study.

Seizure frequency was also unchanged in the two patients transferring from valproate to lamotrigine suggesting these patients did not respond to either of these drugs. One of the patients (CP05) experienced typical absences and may therefore respond to ethosuximide (Jeavons et al, 1977). In children lamotrigine appears to be more efficacious in partial seizures and atypical absences (Gibbs et al, 1992) which may explain the lack of response in these patients as they experienced typical absences and generalised tonic clonic seizures.

In the patient transferring from carbamazepine to lamotrigine seizures were abolished suggesting that lamotrigine is more effective in the treatment of PSE than carbamazepine which is in accordance with the literature as lamotrigine is advised for use in the primary and idiopathic generalised epilepsies (Shorvon, 1995).

Overall only two patients became seizure free, one receiving valproate therapy and one receiving lamotrigine therapy. It is impossible to conclude from these small patient

numbers but the similar results of the adult study, combined with the literature, suggests that there is no discernible difference in seizure control between the two drugs (Kerr et al, 1999).

## **6.6 Body Mass Index:**

As in the adult study the height and weight of each patient was measured at each visit and body mass index (BMI) scores were calculated using the formula  $BMI = \text{weight (kg)}/\text{height (m)}^2$ .

### **6.6.1 Results:**

Baseline and follow up BMI scores were plotted for each patient. Baseline scores were not available for patients CP03 and CP05 and therefore they were excluded from the analysis.

In both patients randomised to valproate therapy BMI scores were seen to increase, although only very slightly in the case of CP07. As can be seen from figure 6.8 at visit one he was unmedicated with a BMI score of 16.49 and when on 800mg/day VPA his BMI score increased to 16.82. Patient CP02s BMI score increased from 16.10 (unmedicated) to 18.16 (800mg/day VPA).

Patient CP04, who was randomised to LTG, also showed an increase in BMI score over the 12 months of the study. With a baseline score of 21.99 when she was not taking any medication increasing to 22.07 when on 400mg/day LTG (figure 6.8).

Figure 6.9 demonstrates a decrease in BMI score from 17.18 to 16.82 as patient CP01 transferred from 800mg/day VPA to 400mg/day LTG.

After transferring from 200mg/day CBZ to 250mg/day LTG patient CP06 demonstrated a decrease in BMI score from 24.23 to 20.84 as can be seen in figure 6.10.

All monotherapy data available was then analysed by means of a Kruskal Wallis test to investigate the effect of medication type on body mass index. Table 6.10 displays the means for each medication group. The BMI scores for no medication, lamotrigine and sodium valproate were all very similar, only carbamazepine displayed a higher BMI score, which is misleading as there was only one patient taking carbamazepine included in the analysis. There was no significant difference in body mass index scores between medication groups. ( $\chi^2 (3) = 3.108; p = 0.375$ ).

Figure 6.8: BMI scores for group A patients randomised to VPA

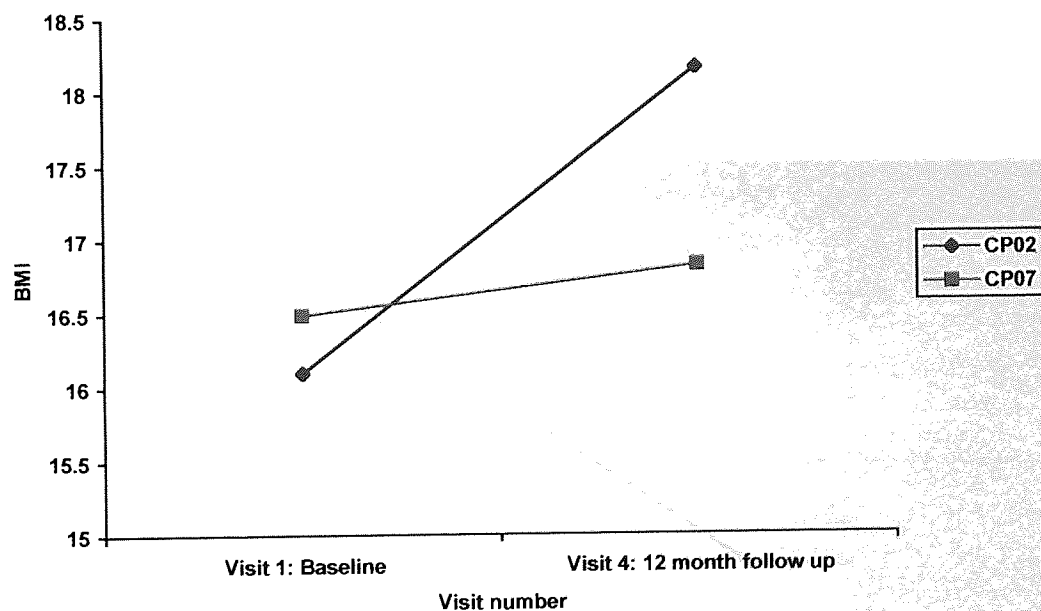




Figure 6.9: BMI scores for group A patient CP04 randomised to LTG

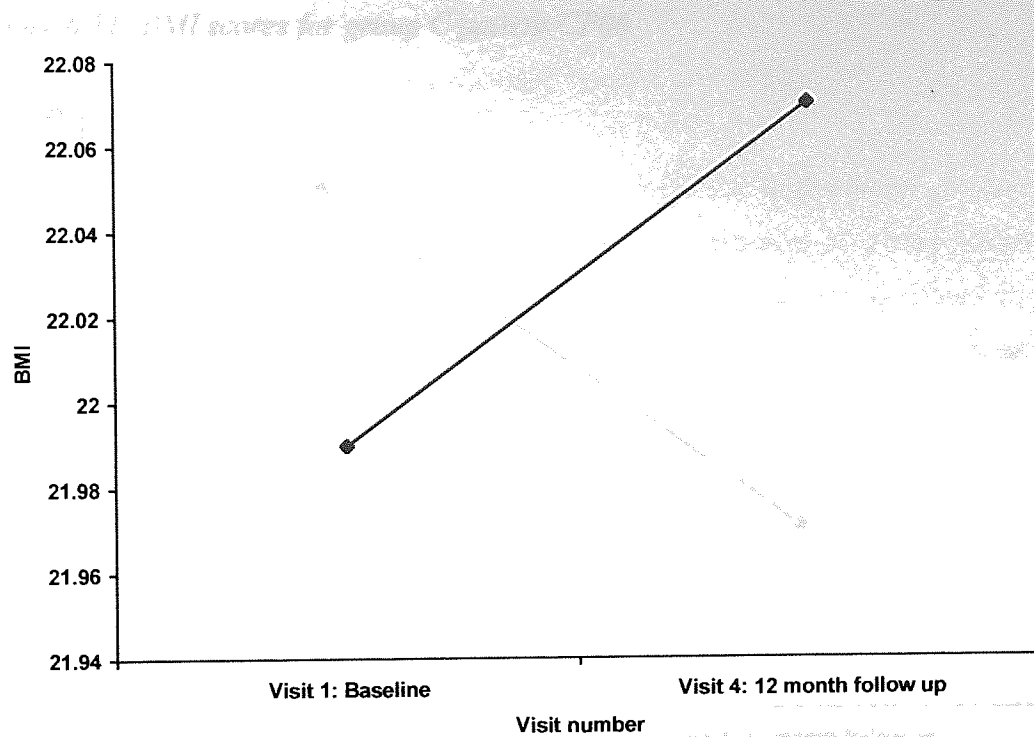


Figure 6.10: BMI scores for group B patient CP01

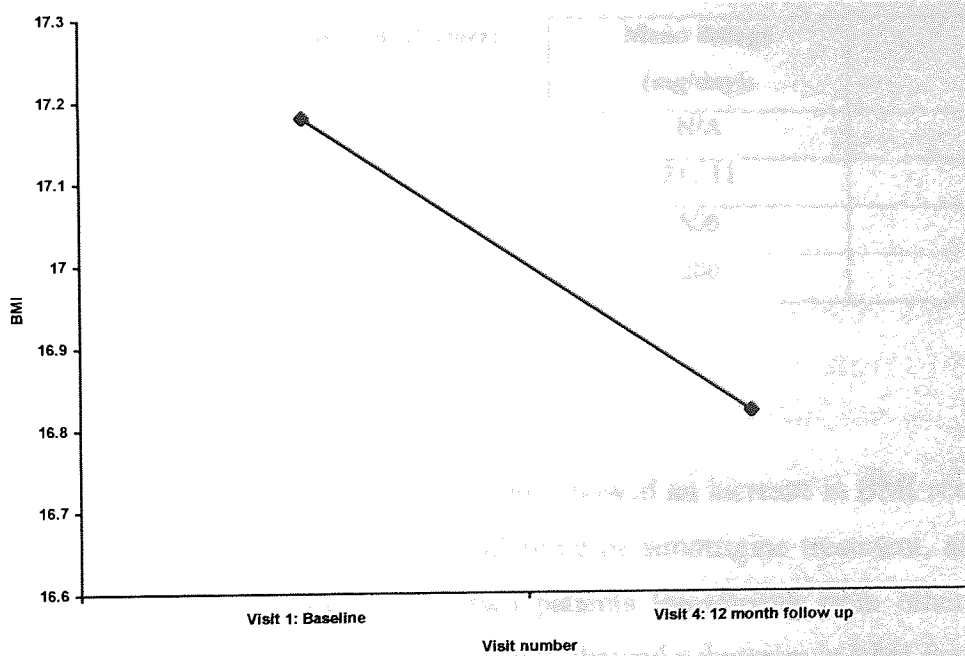


Figure 6.11: BMI scores for group C patient CP06

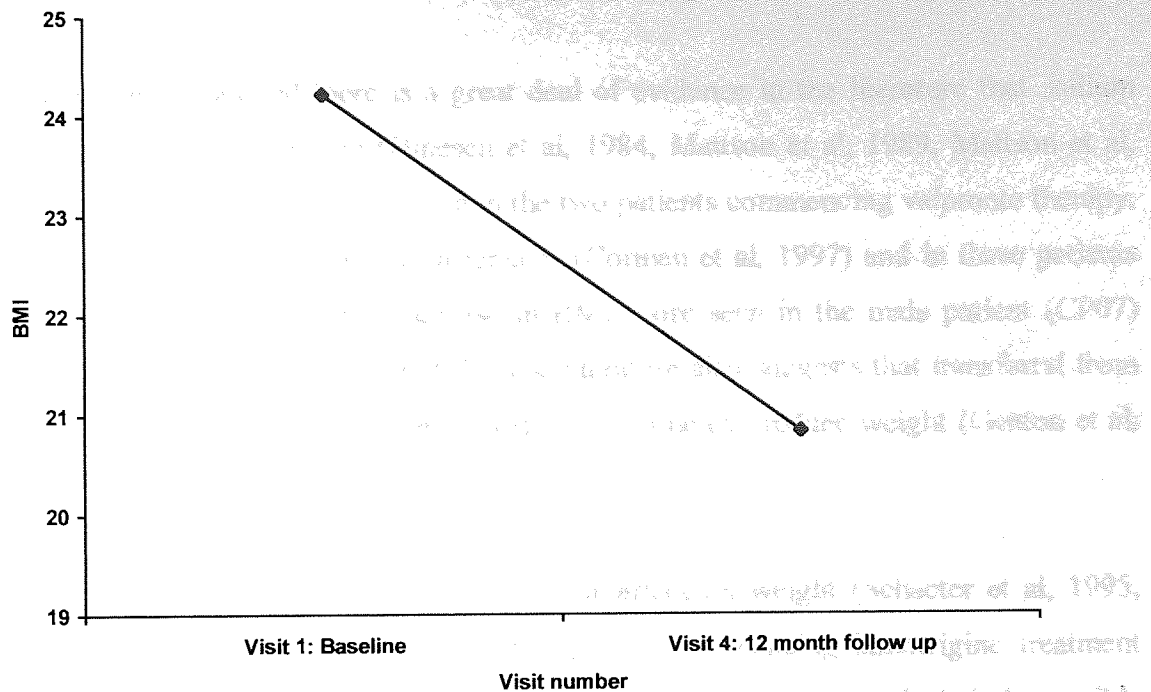


Table 6.10: Mean BMI scores for medication groups

Medication type:	Mean BMI score:	Mean dosage (mg/day):	N:
No medication	18.19	N/A	3
LTG	17.25	211.11	9
VPA	17.39	800	3
CBZ	24.23	200	1

### 6.6.2 Discussion

All drug naïve patients commencing therapy showed an increase in BMI score regardless of whether they commenced sodium valproate or lamotrigine treatment, although these increases tended to be small. The two patients transferring from other medications (valproate and carbamazepine) to lamotrigine showed a decrease in BMI score.

Again due to the small numbers involved in this study combined with a variety of medications and dosages it is difficult to generalise from these results. No real comparison can be made between medication types in this study.

As previously mentioned there is a great deal of evidence in the literature that sodium valproate induces weight gain (Dinesen et al, 1984, Mattson et al, 1989, Mattson et al, 1992, Corman et al, 1997) as was seen in the two patients commencing valproate therapy. This appears to be more common in females (Corman et al, 1997) and in these patients there was only a very minimal increase in BMI score seen in the male patient (CP07) compared to the female patient (CP02). The literature also suggests that transferral from sodium valproate therapy to treatment with lamotrigine can reduce weight (Genton et al, 1999) as was seen in patient CP01.

Lamotrigine does not appear to have a similar effect on weight (Schacter et al, 1995, Ueberall, 2001) although in this study the patient commencing lamotrigine treatment showed an increase in BMI score over the 12 months follow up period. It is impossible to conclude whether this increase in BMI is due to lamotrigine treatment or simply normal development of the child. Similar results were evident in the adult data, with all the drug naïve patients whose BMI data was available demonstrating minimal increase in BMI scores after the initiation of lamotrigine, so this may warrant further investigation.

It is difficult to make tangible conclusions from these results, all of the children should demonstrate changes in BMI associated with normal development so it is impossible to separate the effect on BMI of the medications used in the study with such small participant numbers. All patients displayed normal BMI values for age during the 12 months of the study and there was no clinical concern of the effects of any type of treatment on weight.

## **6.7 Menstrual History**

As four out of the six female patients had commenced menstruation they were given questionnaires regarding their menstrual history, which were compared between visit 1 (baseline) and visit 4 (12 month follow up).

### **6.7.1 Results**

#### **Length of menstrual cycle**

Table 6.11 displays data on the length of menstrual cycle. Data were not available for patients CP03, CP04 and CP06 at baseline as it was patient CP03's first period and both patients CP04 and CP06 were unsure of their cycle lengths. The length of menstrual cycle was reduced dramatically for patient CP01 from an abnormal 34 day cycle to a 22 day cycle.

*Table 6.11: Number of days in menstrual cycle*

<i>Patient</i>	<b>Number of days in menstrual cycle</b>	
	<b>Visit 1: Baseline</b>	<b>Visit 4: 12 month follow up</b>
CP01	34	22
CP03	N/A	28
CP04	Unsure	28
CP06	Unsure	28

#### **Number of flow days**

No data were available for patient CP03 at baseline, as she had not yet finished menstruating and this was her first period. As can be seen in figure 6.12 the number of flow days were reduced in patients CP01 and CP04, again this was rather dramatic in patient CP01 with flow days decreasing from fourteen to a more normal seven. In patient CP04 flow days were within normal limits at both visits. Flow days were increased in patient CP06 again remaining within normal limits.



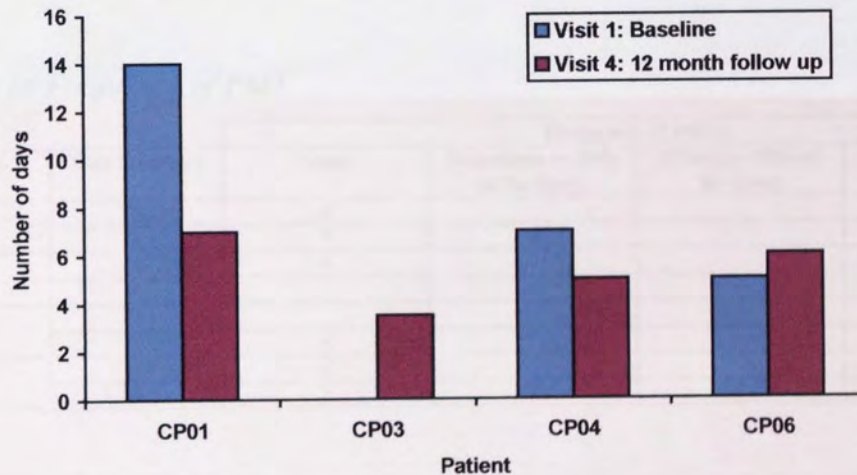
### Amount of flow

Table 6.12 details data on the amount of flow. There was no change in the amount of flow over the 12 months for patients CP01 and CP06. The amount of flow was reduced for patient CP04 from heavy to average. Again there was no information about the amount of flow for patient CP03 at baseline.

Table 6.12: Amount of flow

Patient:	Visit Number:	Amount of flow:			
		Light	Average	Heavy	Variable
CP01	1				✓
	4				✓
CP03	1				
	4				✓
CP04	1			✓	
	4		✓		
CP06	1				✓
	4				✓

Figure 6.12: Number of flow days



### Frequency of dysmenorrhea

There was no change in the frequency of dysmenorrhea for patient CP01. Patients CP03 and CP06 did not experience dysmenorrhea at baseline or follow up. Patient CP04 no longer experienced dysmenorrhea at follow up (Table 6.13).



Table 6.13: Frequency of dysmenorrhea

Patient:	Visit Number:	Frequency of dysmenorrhea:			
		Never	Sometimes (< 50% of the time)	Often (> 50% of the time)	Always
CP01	1		✓		
	4		✓		
CP03	1	✓			
	4	✓			
CP04	1				✓
	4	✓			
CP06	1	✓			
	4	✓			

**Frequency of pre-menstrual tension**

Table 6.14 displays data on the frequency of pre-menstrual tension (PMT). Patient CP01 did not experience pre-menstrual tension at either visit. Patients CP03 and CP06 did not experience PMT when questioned at visit 1 but by visit 4 both patients experienced PMT less than 50% of the time. At baseline patient CP04 stated she always suffered from PMT but at follow up 12 months later she no longer experienced PMT.

Table 6.14 Frequency of PMT

Patient:	Visit Number:	Frequency of PMT:			
		Never	Sometimes (< 50% of the time)	Often (> 50% of the time)	Always
CP01	1	✓			
	4	✓			
CP03	1	✓			
	4		✓		
CP04	1				✓
	4	✓			
CP06	1	✓			
	4		✓		

**Frequency of amenorrhea**

Patient CP01 sometimes (<50% of the time) experienced amenorrhea at baseline but no longer missed menstruation 12 months later at follow up. No other patients experienced amenorrhea.

### Frequency of oligomenorrhea

No patients experienced oligomenorrhea either at baseline or at 12 months follow up.

### Frequency of hypermenorrhea

Hypermenorrhea was not experienced by any of the patients at either visit.

### Frequency of breakthrough bleeding

Some breakthrough bleeding was experienced by patient CP01 at baseline but at follow up 12 months later this had ceased. No other patients experienced breakthrough bleeding at either baseline or follow up.

### Severity of dysmenorrhea

Table 6.15 details data on the frequency of dysmenorrhea. Over the 12 months follow up period the severity of dysmenorrhea was reduced in patient CP01 from severe to moderate. Patient CP04 no longer experienced any dysmenorrhea having previously suffered moderate pain at baseline. Patient CP06 did not experience dysmenorrhea at baseline but suffered from moderate pain at follow up. CP03 did not experience dysmenorrhea at either visit 1 or visit 4.

Table 6.15: Severity of dysmenorrhea

Patient:	Visit Number:	Severity of dysmenorrhea:			
		None	Mild	Moderate	Severe
CP01	1				✓
	4			✓	
CP03	1	✓			
	4	✓			
CP04	1			✓	
	4	✓			
CP06	1	✓			
	4			✓	

### Severity of pre menstrual tension

Patients CP01 and CP06 did not experience any pre-menstrual tension throughout the course of the study. Patient CP04 previously suffered from moderate PMT at baseline but stated she no longer experienced pre-menstrual tension at follow up. Patient CP03 suffered from mild PMT at follow up, previously not experiencing any PMT at baseline although this was her first period. (Table 6.16)

Table 6.16: Severity of PMT

Patient:	Visit Number:	Severity of PMT:			
		None	Mild	Moderate	Severe
CP01	1	✓			
	4	✓			
CP03	1	✓			
	4		✓		
CP04	1			✓	
	4	✓			
CP06	1	✓			
	4	✓			

### 6.7.2 Discussion:

At baseline an unusually long cycle length and amount of flow days coupled with some amenorrhea and breakthrough bleeding in patient CP01 suggests some dysfunction of menstruation. At 12 month follow up when the patient had ceased taking sodium valproate and was now taking 400mg of lamotrigine per day her cycle length and amount of flow days were now of a more normal length and the amenorrhea and breakthrough bleeding had ceased.

All other results suggested that patients CP03, CP04 and CP06 experienced normal menstruation at both baseline and follow up 12 months later with no discernible differences between the two visits. CP03 and CP04 were both free from medication at baseline and were taking 100mg and 400mg lamotrigine respectively at follow up. Patient CP06 was taking 200mg/day of carbamazepine at visit 1 and 250mg/day of Lamotrigine at visit 4.

There is evidence that epilepsy can disrupt the menstrual cycle through its effect on luteinising hormone pulsivity via its effect on the gonadotrophin releasing hormone pulse generator (Bilo et al, 1998). This can be independent of the type of epilepsy (Murialdo et al, 1997, Bilo et al, 1988).

There is also evidence in the literature that patients receiving valproate therapy display ovulatory dysfunction more frequently than patients taking other antiepileptic drugs (Murialdo et al, 1997). In one study all women taking valproate reported some form of menstrual disturbance (Isojarvi et al, 1998).

After transferring from valproate to lamotrigine therapy patient CP01's menstrual irregularities ceased. Studies have shown that replacement of valproate with lamotrigine can reinstate menstruation (Isojarvi and Tapanainen, 2000) and that in comparison patients on lamotrigine do not report menstrual problems as frequently as those on valproate (Stephen et al, 2001). This may be due to a protective effect of lamotrigine (and other AEDs) preventing menstrual abnormalities in women who are prone to them as a result of their epilepsy rather than valproate induced problems. Indeed in the Isojarvi and Tapanainen study the reinstatement of menstruation occurred before the complete withdrawal of sodium valproate (Isojarvi and Tapanainen, 2000).

Similar changes can also be achieved with a reduction of body weight and valproate treatment need not necessarily be stopped (Genton et al, 1999). This suggests that if valproate does disrupt the menstrual cycle it may be via its effect of weight gain. Indeed in the study by Stephen and colleagues all patients with menstrual abnormalities were obese (Stephen et al, 2001). However this is not the case in patient CP01 as she was not overweight whilst receiving valproate therapy.



## **6.8 Adverse effects**

At each visit a detailed history was taken from patients and their parents concerning any adverse effects experienced during the study.

### **6.8.1 Results**

All patients reported adverse events detailed on table 6.17. None resulted in discontinuation of medication. The most common adverse effect reported was blurred vision, occurring in three patients (CP01, CP02 and CP06). In patient CP06 only one episode of blurred vision was reported at 200mg/day LTG. Patient CP01 experienced intermittent blurred vision for 3 weeks after increasing her dose to 400mg/day LTG. This was resolved without medical intervention. Patient CP02 experienced blurred vision at 50mg/day LTG, which was resolved when she switched to valproate due to poor seizure control.

Two patients experienced decreased appetite (CP01 and CP07). CP01 was taking 250mg/day LTG and the decreased appetite was resolved within 2 weeks. Patient CP07 was taking 800mg/day VPA and his decrease in appetite was not resolved at 12 months follow up and was associated with a loss of his sense of taste.

Parents of three patients (CP01, CP02 and CP05) reported that their children appeared drowsy/unsteady/"drugged up". This was at 400mg/day LTG for patient CP01 and was not resolved at 12 months follow up. In patient CP02 this occurred at 800mg/day VPA and was resolved when the dosage was lowered to 300mg/day VPA and then again increased to 800mg/day in a slower manner. In patient CP05 the unsteadiness occurred at the initiation of LTG therapy and was resolved once the patient was taking 200mg/day LTG.

Rash was reported by one patient (CP01), occurring at 125mg/day LTG. The consultant managing this patient did not believe this was a side effect of the lamotrigine treatment and the rash disappeared at 200mg/day LTG. Other adverse effects were reported (table 6.17) but were not deemed to be associated with medication.

Table 6.17: Adverse effects experienced by patients on the children's study

Patient ID	Group	Medication	Adverse effect	Duration	Dose at which resolved
CP01	B	LTG 125mg  LTG 250mg	Rash on arms, legs and stomach. GP thought this was eczema, started on hydrocortisone. The rash was itchy and sore with no blistering, comprising of red spots. Rx dosage was increased 2 weeks ago and the rash got worse. Drowsy and tired. Dad describes her as "distant".  Decrease in appetite, nausea in the mornings. "Difficult to say if this is the LTG or not" - Dr Scherwin (BCH)	Unsure  2 weeks	Rash and drowsiness resolved by 200mg LTG  Resolved by LTG 250mg
		LTG 400mg	Intermittent blurred vision after increasing dose	3 weeks	Resolved at 400mg
CP02	A (LTG) (transferred to VPA)	LTG 400mg  LTG 500mg  VPA 800mg	Dad thinks she appears "drugged up and drowsy". Patient states she feels "alright"  Slowed speech. Seizures worse. Blurred vision. Stutter. Feels tired in the mornings. Speech slow, absences became worse. Mum thought she appeared "drugged up"	Not resolved  Unsure  When originally put onto 800mg	Not resolved  Resolved when switched to VPA  Resolved when dose lowered to 300mg then increased back to 800mg slower
CP03	A (LTG)	LTG 50mg	Aches in legs, no localisation, occasionally knees "lock up"; some aches in arms although this is not as frequent. Patient, parents and Dr don't think this is due to Rx.	2 weeks	Resolved by 100mg LTG
CP04	A (LTG)	LTG 25mg	Mood changes. Patient, parents and Dr don't think that this is due to Rx.	Unsure.	Resolved by 400m LTG
CP05	B	LTG 50mg	Mum thinks she is "unsteady" since starting on LTG	Since starting LTG	Resolved by 200mg LTG
CP06	C	LTG 200	One episode of blurred vision, pulsating circle in middle of vision	1 episode only	Resolved at 200mg LTG
CP07	A (VPA)	VPA 800mg	Losing his sense of taste, doesn't like eating a lot of things he used to. Not eating as much as he normally does.	Since starting VPA	Not resolved at 12 month follow up

### **6.8.2 Discussion:**

As in the adults study the side effect profile was similar to that reported in the literature. All patients in the children's study experienced adverse effects and indeed adverse effects are more commonly reported in children than adults, with 10% of children receiving lamotrigine therapy withdrawing due to adverse reaction (Besag, 1992). None of the adverse effects reported in this study led to withdrawal of medication.

Blurred vision was experienced by three patients and has been reported in the literature as a transient side effect of lamotrigine therapy (Schacter et al, 1995) occurring in between 0.5% (Lamotrigine Information Sheet, 1995) and 1% of patients (Schacter et al, 1995). In two patients the blurred vision was transient and in one patient it was resolved after transferral to valproate therapy. The lamotrigine was not discontinued as a result of the blurred vision but due to poor seizure control.

Decreased appetite occurred in two patients. One patient was on lamotrigine therapy and the decrease in appetite appeared to be a transient adverse effect which resolved without medical intervention as has been reported in the literature (Papacostas and Koukkoulli, 1997). The other patient was taking 800mg/day VPA and the decrease in appetite remained for 12 months. Mild transient decreases in appetite and gastrointestinal complaints have been reported associated with valproate therapy (Clark et al, 1980, Laljee and Parsonage, 1980, Dinesen et al, 1984) but not such a sustained reaction. The patients decreased appetite was associated with a loss of sense of taste, which has not previously been reported as a side effect of valproate therapy and may be in this case an idiosyncratic reaction to treatment or be purely coincidental.

Three patients experienced unsteadiness and drowsiness with parents describing their children as "drugged up". Drowsiness and ataxia are common transient side effects often occurring at the initiation of lamotrigine treatment (Betts, 1992, Brodie, 1994, Schlumberger et al, 1994, Papacostas and Koukkoulli, 1997). In one patient this was obviously a transient reaction to the commencement of lamotrigine therapy as it was resolved by 200mg/day LTG. Another patient continued to experience drowsiness and

unsteadiness at 400mg/day LTG and it is possible that this was a chronic toxic effect of the lamotrigine. The third patient experienced unsteadiness, dizziness and drowsiness at 800mg/day VPA. Such acute effects are more common if AED therapy commences rapidly at a high initial dose (Greenwood, 2000). Indeed when the dose was reduced to 300mg/day and then reinstated in small increments back to 800mg/day the adverse effects were resolved.

Rash was reported by one patient although it was not deemed to be related to lamotrigine therapy. Although rash is more commonly reported in children (Yuen, 1992) it was probably avoided in this study due to the slow nature of the dosing schedule, commencing at 25mg/day LTG with small increments over 6 months. This dosing schedule is associated with a reduction in the risk of rash (Yuen, 1992).



## Chapter 7: The Beck Depression Inventory

The Beck Depression Inventory-second edition (BDI-II) is a 21 item questionnaire designed to measure the severity of depression in adults and adolescents, 13 years and older. It may be orally administered to the patient by an interviewer or can be self administered by the patient, and requires about five to ten minutes to complete (Beck et al, 1996).

The 21 items are each concerned with a particular aspect of the symptomatology of depression (e.g. loss of pleasure, self-dislike, tiredness or fatigue, etc). Each item contains four statements graded in severity, expressing how the individual feels about that particular aspect of depression. The grading of 3 is most severe and 0 indicates the absence of problem. Figure 7.1 gives an example of one of the items. The individual is required to grade each item and the higher the overall score the more severe the depression (Deutsch Lezak, 1983).

*Figure 7.1: Item 7: Self Dislike (Beck et al, 1996)*

- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed with myself.
- 3 I dislike myself.

The suggested interpretations of the overall score are as follows (table 7.1). The BDI-II uses relatively low thresholds to decrease the probability of false negatives (Beck et al, 1996).

*Table 7.1 Interpretations of the BDI-II scores (Beck et al, 1996)*

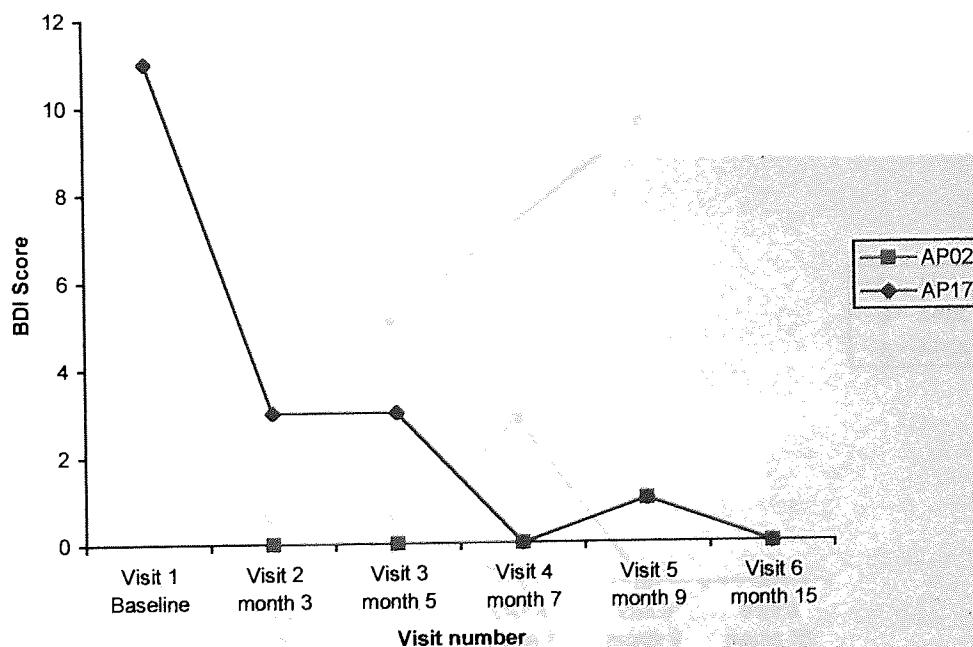
0-13	Minimal
14-19	Mild
20-28	Moderate
29-63	Severe

The BDI-II was self-administered by five adult patients and five patients from the children's study (those who were over age 13). Although it was intended that all adult patients would self administer the questionnaire at every trial visit, due to the problems with adult recruitment as described earlier and the subsequent retrospective enrolment of many of the patients, only five patients were actually tested with the BDI-II. Again due to the retrospective enrolment procedure baseline measures for three of the five adult patients were not available which obviously restricts the analysis of the results.

### **7.1 Adults study: results**

Overall scores were plotted for each adult patient over the six trial visits.

*Figure 7.2: BDI scores for adult group A patients*

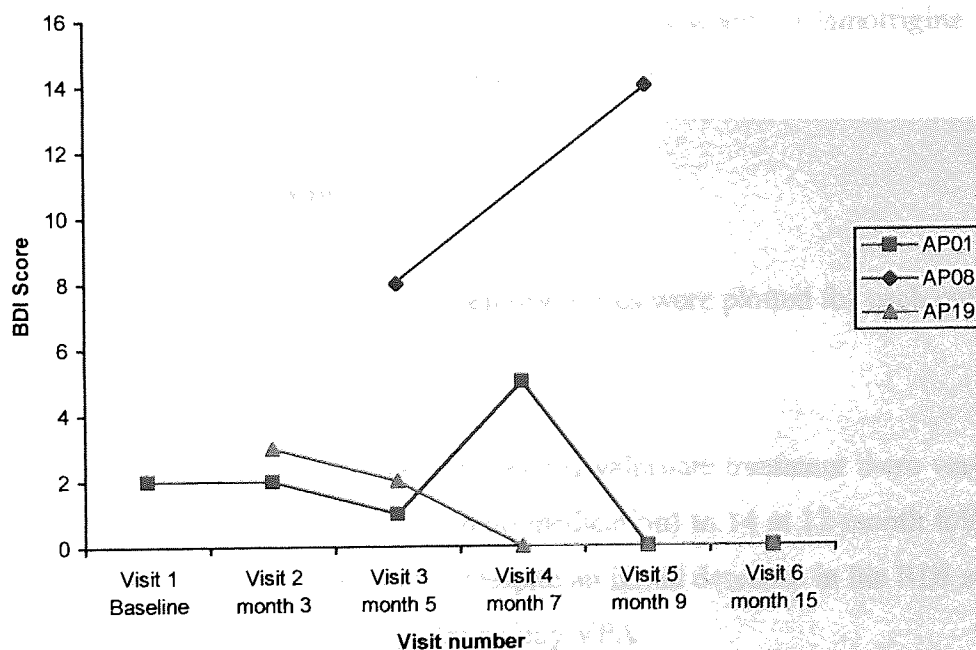


As can be seen from figure 7.2 patient AP02 showed relatively little change in BDI score throughout the 15 months. She only scored one at visit five whilst taking 300mg/day LTG, otherwise she did not score anything on the BDI-II. Unfortunately a baseline measure when she was taking 1000mg/day VPA was not conducted. Patient AP17's BDI score showed a decrease over the 15 month period. At baseline she was taking

200mg/day VPA and scored 11, whereas at follow up when she was taking 200mg/day LTG her BDI score had dropped to 0. All scores in these patients were less than 13 so only minimal depression was indicated.

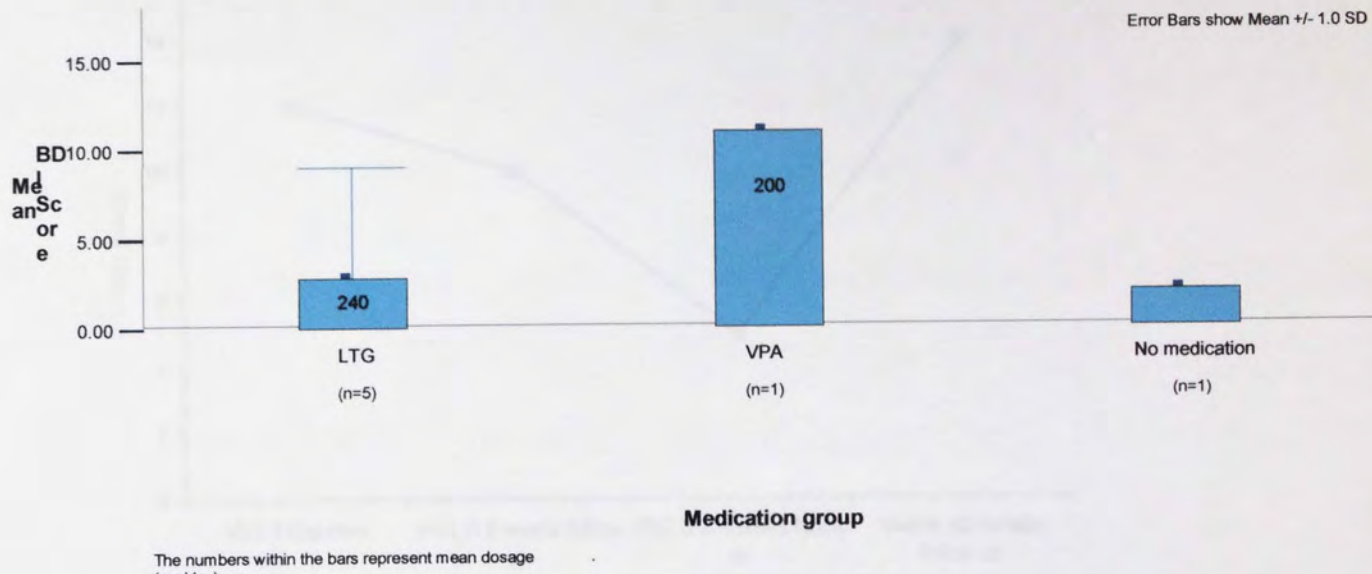
Again baseline measurements are missing for two patients in group B. As can be seen from figure 7.3 both patients AP01 and AP19 BDI scores decrease over the 15 month period when lamotrigine therapy was introduced. From 2 and 3 respectively to 0 at visit six, when they were taking 300mg/day and 100mg/day LTG respectively, although patient AP01 shows an increase in score at visit four (150mg/day LTG). BDI scores were only available for patient AP08 for visit three (100mg/day LTG) and visit five (300mg/day LTG) and as can be seen the BDI score increases dramatically from 8 (minimal depression) to 14 (mild depression).

Figure 7.3 BDI scores for adult group B patients



The data was then analysed by the means of a Kruskal Wallis test, to investigate the effect of medication type on BDI score. Figure 7.4 displays the means for each medication group. The Kruskal Wallis test showed no significant difference in BDI score between medication groups ( $\chi^2(2)=1.774;p=0.412$ ).

Figure 7.4: Mean BDI score for medication groups, adult patients



But as can be seen from figure 7.4 when patients were treated with sodium valproate they scored highest on the BDI, with much lower scores when on lamotrigine therapy and finally unmedicated patients had the lowest BDI score.

## 7.2 Children's study results

Again individual Beck Depression Inventory scores were plotted for each patient over the four visits.

In patient CP07 (figure 7.5) as he commenced valproate treatment there was an increase in BDI score from 12 at baseline (with no medication) to 14 at 12 month follow up when he was taking 800mg/day valproate. Despite an initial decrease in his BDI score at visits 1 and 2 when he was again taking 800mg/day VPA.



Figure 7.5: BDI scores for patient CP07 (Group A, randomised to VPA)

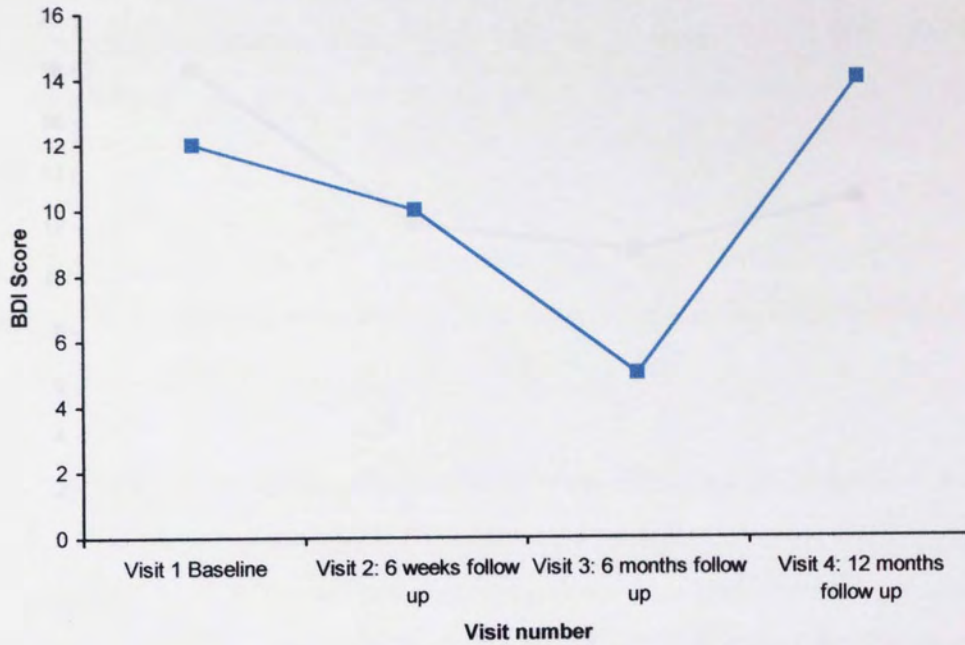


Figure 7.6: BDI scores for patient CP07 (Group B)

Figure 7.6: BDI scores group A patients, randomised to LTG

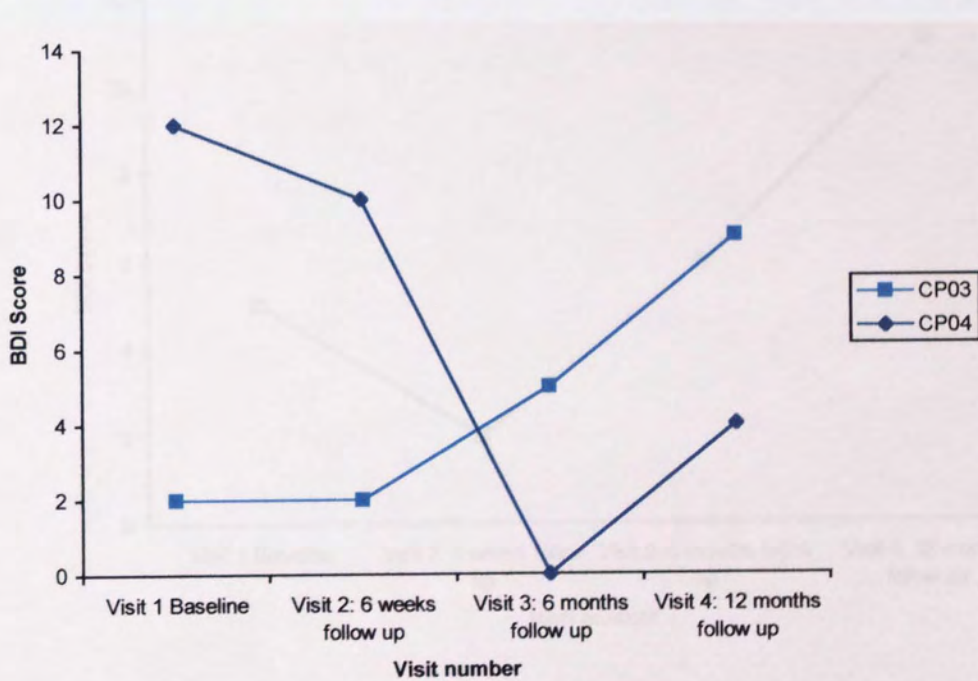


Figure 7.6 depicts the data of two drug-naïve patients randomised to lamotrigine therapy. CP03 showed an increase in BDI score as lamotrigine therapy was initiated.



Figure 7.7: BDI scores for patient CP01 (Group B)

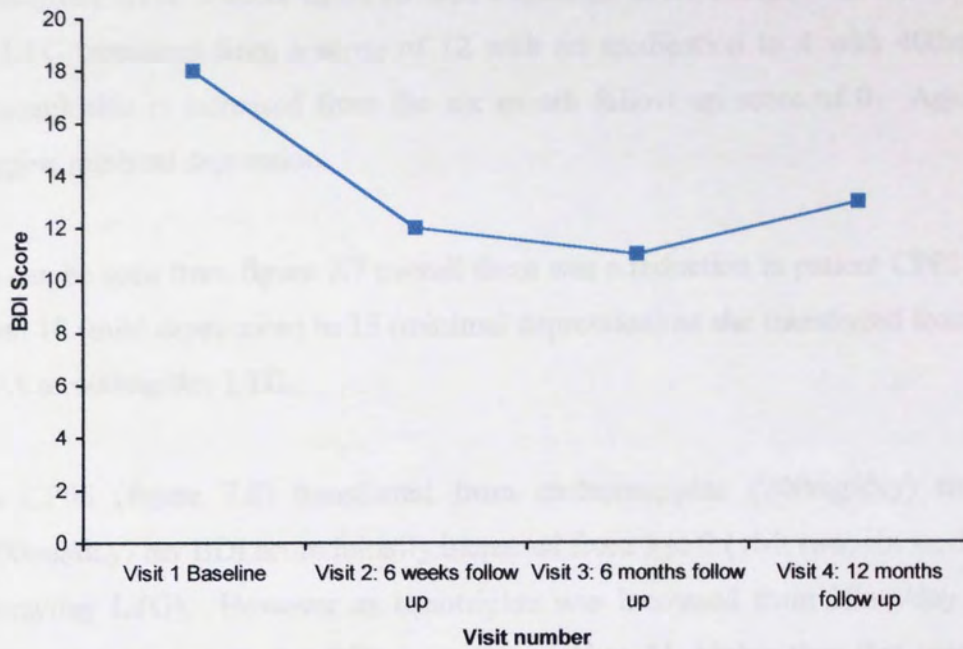


Figure 7.8: BDI scores for patient CP06 (Group C)

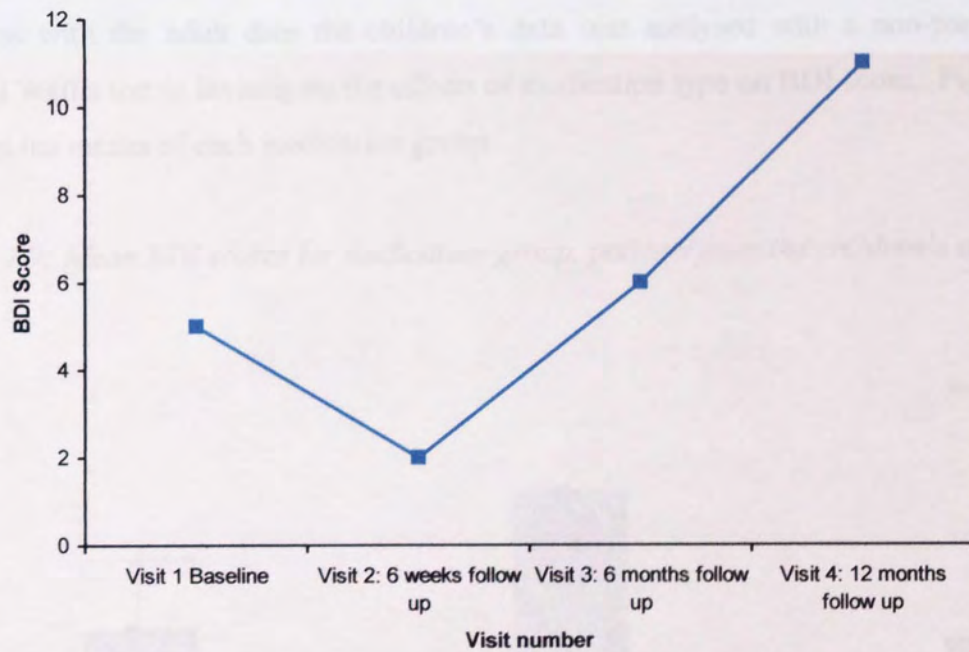


Figure 7.6 displays the data of two drug naïve patients randomised to lamotrigine therapy. CP03 showed an increase in BDI score as lamotrigine therapy was commenced

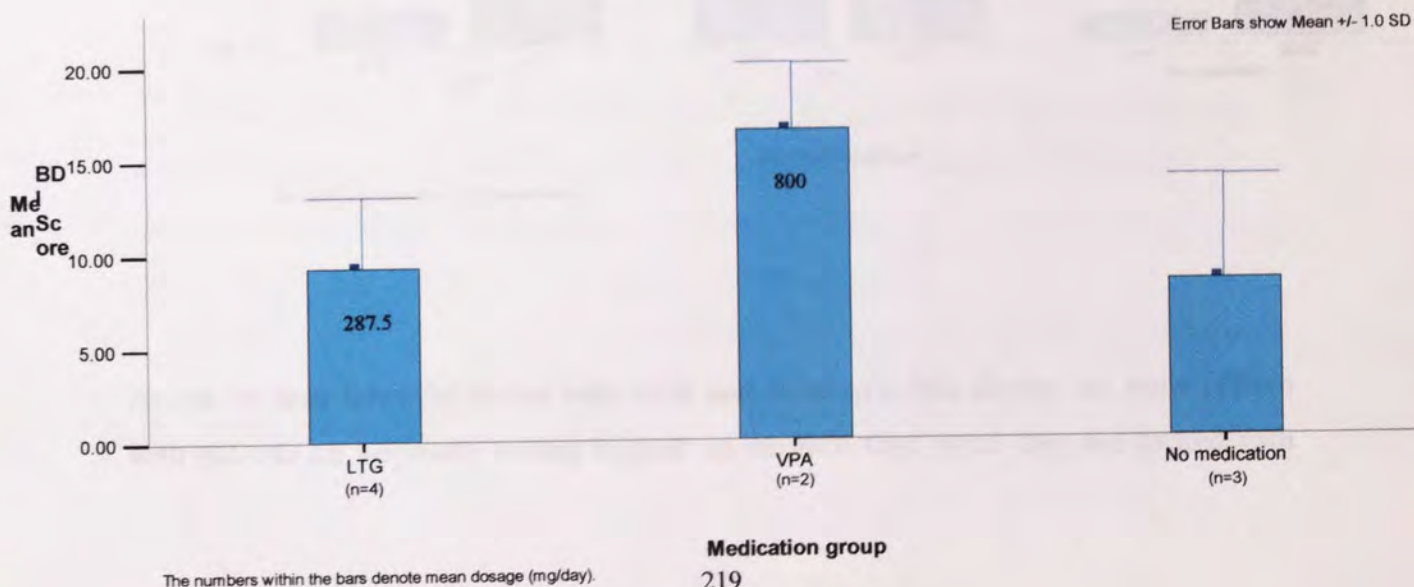
with a score of 2 with no medication at baseline and a score of 9 when she was taking 100mg/day LTG. Patient CP04 showed a decrease in BDI score with the commencement of LTG treatment from a score of 12 with no medication to 4 with 400mg/day LTG, although this is increased from the six month follow up score of 0. Again all scores suggest minimal depression.

As can be seen from figure 7.7 overall there was a reduction in patient CP01's BDI score from 18 (mild depression) to 13 (minimal depression) as she transferred from 800mg/day VPA to 400mg/day LTG.

As CP06 (figure 7.8) transferred from carbamazepine (200mg/day) to lamotrigine (200mg/day) her BDI score initially increased from 5 to 2 (visit two, six weeks follow up, 25mg/day LTG). However as lamotrigine was increased from 25mg/day at visit 2 to 250mg/day at visit six her BDI score increased to 11, higher than that seen at baseline, although still within the minimal category.

Again as with the adult data the children's data was analysed with a non-parametric Kruskal Wallis test to investigate the effects of medication type on BDI score. Figure 7.9 displays the means of each medication group.

Figure 7.9: Mean BDI scores for medication group, patients from the children's study



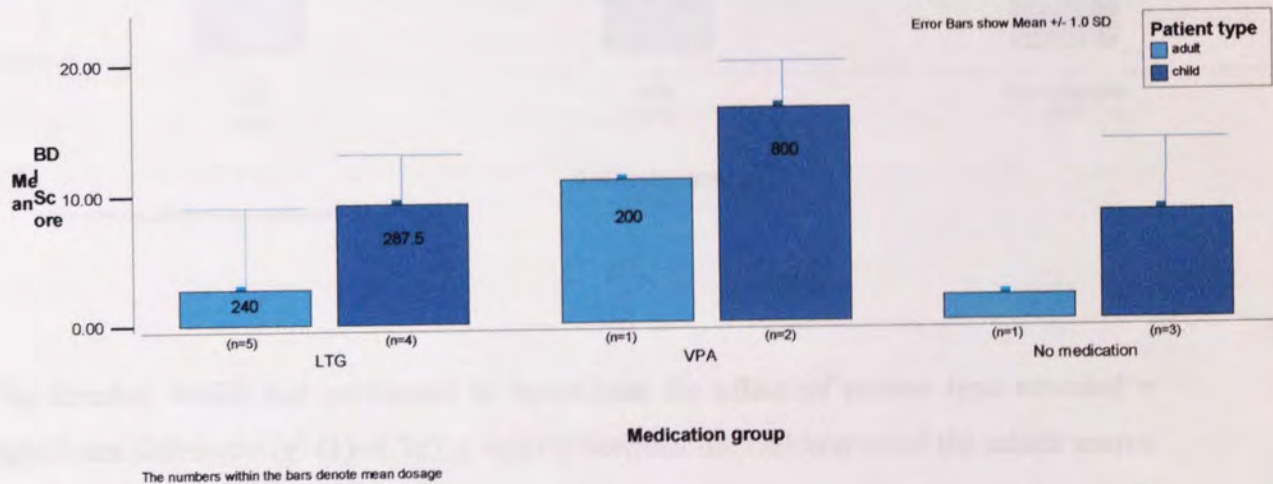


As can be seen from the standard deviations there is quite a large variability between patients' scores with each respective medication group. Again like the adult data when patients were taking valproate their BDI scores were higher than when they were taking lamotrigine or when they were unmedicated. These differences were not significant ( $\chi^2(2)=4.255;p=0.119$ ).

### 7.3 Combined results:

Due to the small patient numbers the adult and children's data were then combined and two Kruskal Wallis tests were conducted. One was again used to investigate the effect of medication type on BDI scores. The other was to examine the effect of patient type, to control for the fact that the data were from two different clinical populations; adults and children. Figure 7.10 demonstrates the means.

Figure 7.10: Mean BDI scores for both adults and children, separated into medication groups.

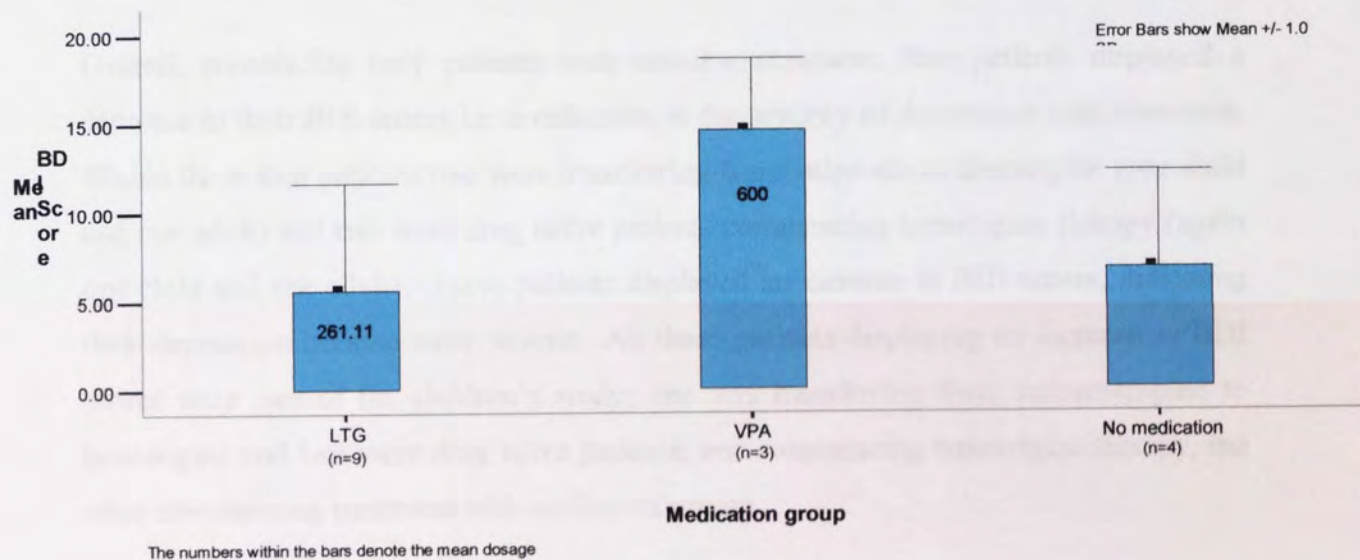


As can be seen from the means both adult and children's data display the same pattern with patients on valproate scoring highest on the BDI than when they are treated with

LTG or are unmedicated. The children's scores in all medication groups are greater than the adult's scores. Again as can be seen by the standard deviations variability of scores within each medication group is high.

Figure 7.11 demonstrates the means of BDI score for the combined data by medication group. With the data following the same pattern as described previously the Kruskal Wallis test performed on these data revealed no significant differences ( $\chi^2(2)=4.384;p=0.112$ ).

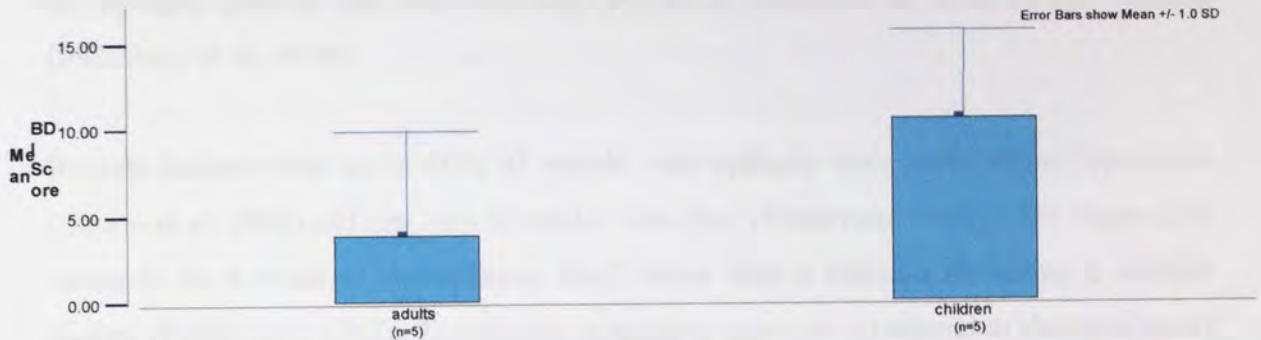
Figure 7.11: Mean BDI scores for combined data by medication group



The Kruskal Wallis test performed to investigate the effect of patient type revealed a significant difference ( $\chi^2(1)=4.363;p=0.037$ ) between the children's and the adults scores with the children scoring significantly higher on the BDI as can be seen from figure 7.12. Variability of scores within each age group was again high.



Figure 7.12: Mean BDI scores for adults and children



#### **7.4 Discussion:**

Overall, considering only patients with baseline measures, four patients displayed a decrease in their BDI scores i.e. a reduction in the severity of depression with treatment. Within these four patients two were transferring from valproate to lamotrigine (one child and one adult) and two were drug naïve patients commencing lamotrigine therapy (again one child and one adult). Three patients displayed an increase in BDI scores, indicating their depression became more severe. All these patients displaying an increase in BDI scores were part of the children's study; one was transferring from carbamazepine to lamotrigine and two were drug naïve patients; one commencing lamotrigine therapy, the other commencing treatment with sodium valproate.

Obviously with these very small patient numbers coupled with the mixture of medications and dosages it is extremely difficult to generalise from these results. It is impossible to conclude whether the addition of lamotrigine therapy has contributed to the change (in either direction) of BDI scores, and many extraneous variables (such as stress encountered at work, exams etc) could not be controlled for.

In some patients with epilepsy who are diagnosed with depression, the depression scores can improve spontaneously (Robertson, 1985) and newly diagnosed patients report more depression in comparison to normal controls but this often diminishes as they become

more adapted to their epilepsy (Smith et al, 1986). Pulliainen and colleagues compared 59 patients newly diagnosed with epilepsy to 26 normal controls and found that 24% of the epilepsy patients had mild/moderate dysphoria compared to none of the controls (Pulliainen et al, 2000).

Reports indicate that up to 50% of people with epilepsy may suffer from depression (Indaco et al, 1992) and this may be ictal or interictal (Robertson, 1985). The depression seems to be a result of the epilepsy itself rather than a reaction to having a chronic disease (Perini et al, 1986). Depression in epilepsy seems to be related to the duration of epilepsy (Robertson, 1985) with depression being more commonly found in patients who have had epilepsy for less than 10 years (Zanniello et al, 1997). It is also related to learned helplessness and attributional style (Hermann et al, 1996) and the type of epilepsy, being more common in patients with temporal lobe epilepsy (TLE) (Perini et al, 1996) although it is not related to the laterality of the epileptic focus (Hermann et al, 1996), Robertson, 1985). Nor is depression in epilepsy influenced by seizure frequency (Robertson, 1985).

Some studies have indicated that depression in epilepsy may be influenced by antiepileptic drugs. With a positive relationship being reported with phenobarbitone (Zanniello et al, 1977, Robertson, 1985) and conflicting reports as to whether patients on carbamazepine are more depressed (Zanniello et al, 1997) or less depressed (Robertson, 1985) than patients taking other AEDs.

In both patient groups (adults and children) and when the data were combined the same pattern of scores emerged when the effect of medication type was investigated. Generally when patients were taking valproate they had higher BDI scores than when there were taking lamotrigine. The lowest BDI scores were found in unmedicated patients. Again the small sample sizes and the large variability of individual scores within each medication group makes it difficult to generalise from these results.

There is little information in the literature regarding depression and specific antiepileptic drugs, although valproate has been used for many years as a mood stabiliser in manic depression (Bowden, 1998) as has lamotrigine more recently (Kotler and Matar, 1998). This would suggest there shouldn't be much difference in scores between valproate and lamotrigine treatments, although Meador and Baker have reported improvements in mood in patients with epilepsy following lamotrigine therapy (Meador and Baker, 1997). Such a mood enhancing effect could explain the difference in scores between treatment with valproate and lamotrigine. Although it would not explain why the scores of unmedicated patients were also so low compared to those on valproate. This could be linked with valproate's adverse effect profile, as most patients experienced side effects on valproate, which could have a detrimental effect on mood, although they tended to also experience side effects on lamotrigine therapy. It may be that lamotrigine's side effect profile is deemed less severe than that of valproate and although patients still experience adverse effects on lamotrigine these adverse effects do not have such a detrimental effect on mood as those experienced on sodium valproate.

There was a significant difference between the mood scores of the adult patients and the patients from the children's study, with the children scoring higher, therefore experiencing more severe depression. Mellor and colleagues have reported that children with epilepsy are particularly prone to depression (Mellor et al, 1974) and the difference between the adult group may be due to attributional styles (Hermann et al, 1996) and coping mechanisms not yet developed by the children to enable them to deal with their epilepsy (Smith et al, 1986).

To conclude it is very difficult to generalise from these results due to the problems of small sample sizes, a mixture of medications and dosages, large variability of scores within the groups, and the response bias which is present in all self-report questionnaires. However the results have shown that depression scores of an individual will vary over time and there is some indication that this may be related to the type of treatment received. Whether or not the variation was spontaneous or due to change in medication it is impossible to conclude from these data.



The results suggest that children with epilepsy may be more susceptible to depression than adults and this should be considered when managing a child's epilepsy. If lamotrigine does protect against depression in epilepsy this would be extremely fortuitous as depression in epilepsy is difficult to treat with many antidepressants lowering seizure thresholds (Betts et al, 1968).



## Chapter 8 The Stroop test

The Stroop test is a measure of focused attention and mental flexibility. The classic Stroop test consists of two parts. In the colour task the participant is asked to read aloud a list of 112 words in 120 seconds. These words are the names of four colours; red, blue, green and tan, printed in mismatched coloured ink as demonstrated in figure 8.1.

*Figure 8.1: The stroop test stimuli*

Red	Red
Blue	Tan
Green	Blue
Tan	Red
Blue	Green
Tan	Tan

In the colour word task the participant is asked to name aloud the colour of the ink each of the 112 words are printed in, and is thereby confronted with an interference situation. Reading is a highly practised skill and in most individuals is automatic so in this task the words interfere with the colour naming. The participants therefore typically take longer to complete the task and more frequently make errors (Stroop, 1935). The task measures the ease at which the participant can shift his perceptual set to conform to the changing demands of the task. The Stroop test is the most commonly used test in the investigation of cognition in epilepsy (Cochrane et al, 1998) and is a particularly sensitive and reliable measure of the cognitive effects of antiepileptic drugs (Banks and Beran, 1991).

It was originally intended that all patients would undergo testing with the Stroop at each visit. However due to the retrospective nature of recruitment in some patient this was not possible. The Stroop test was administered to five adult patients and six patients from the children's study (one child was unable to follow the instructions for the test). It was proposed that the stroop data would be examined at each dosage level. However, due to the many deviations from the proposed dosage schedule, measures were compared from

baseline to follow up. Three of the adult patients tested did not have baseline measurements and were consequently excluded from the analysis.

### **8.1 Adult study results**

The Stroop score (items completed – incorrect responses) and rate (words per minute) were plotted for the two adult patients at baseline and follow up, detailed in figures 8.2 and 8.3.

As can be seen from figure 8.2 at both baseline and follow up patient AP17 scored the maximum of 112. There was an improvement in rate with the patient performing faster at follow up (200mg/day LTG) than at baseline (200mg/day VPA).

Patient AP01 (figure 8.3) also demonstrated an improvement in colour word rate; performing faster at follow up (300mg/day LTG) than at baseline (unmedicated). She additionally demonstrated an improvement in score. At baseline she scored 79, classified as abnormal, indicative of brain damage, (Stroop manual, 1989), whereas at follow up she scored the maximum of 112.

Data from the two patients was combined with follow up data from the remaining three adult patients who underwent testing with the Stroop. The data were then analysed by means of a Kruskal Wallis test to investigate the effect of medication type on colour word score and rate. Tables 8.1 and 8.2 display the means.

It is difficult to comment on the scores or rates as only one patient was included in both the valproate group and the unmedicated group. The mean score for patients receiving lamotrigine was within normal limits and, as can be seen from the standard deviations, there were large intragroup differences in both scores and rates. The Kruskal Wallis test showed there were no significant differences in score and rate between medication groups (score:  $\chi^2 (2) = 3.052$ ;  $p = 0.217$ , rate:  $\chi^2 (2) = 0.153$ ;  $p = 0.926$ ).



Figure 8.2: Colour word score and rate group A patient AP17

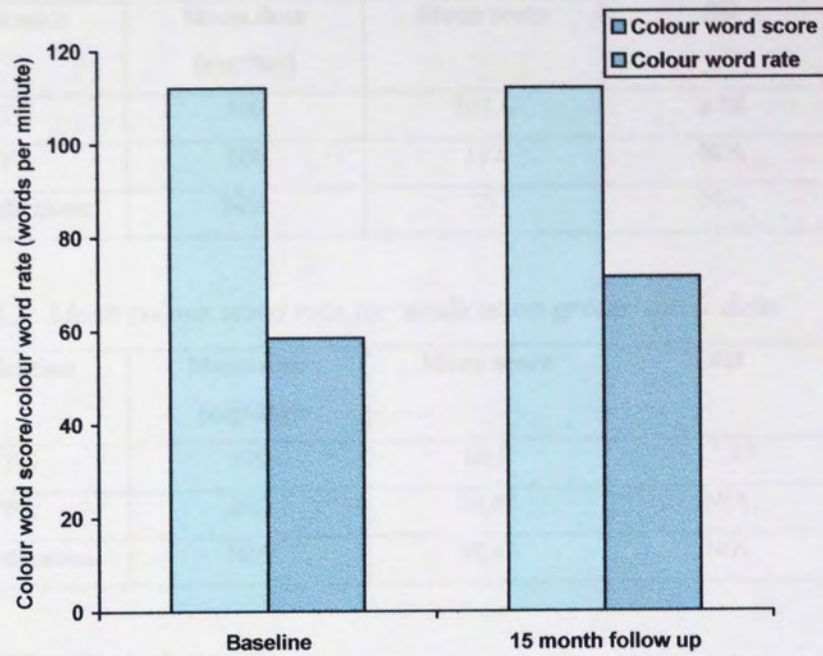


Figure 8.3: Colour word score and rate group B patient AP01

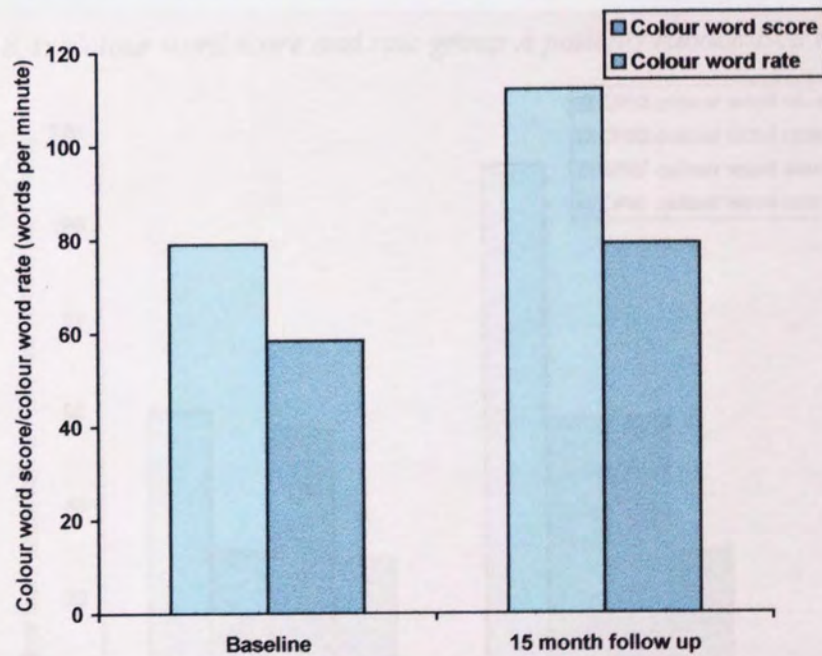


Table 8.1: Mean colour word score for medication group, adult data

Medication	Mean dose (mg/day)	Mean score	SD	N
LTG	300	107.6	6.98	5
VPA	200	112	N/A	1
No medication	N/A	79	N/A	1

Table 8.2: Mean colour word rate for medication group, adult data

Medication	Mean dose (mg/day)	Mean score	SD	N
LTG	300	66.9	15.63	5
VPA	200	58.43	N/A	1
No medication	N/A	58.43	N/A	1

## 8.2 Children's study results

Again individual patients scores and rates were plotted for baseline and follow up (figures 8.4 to 8.7).

Figure 8.4: Colour word score and rate group A patients randomised to VPA

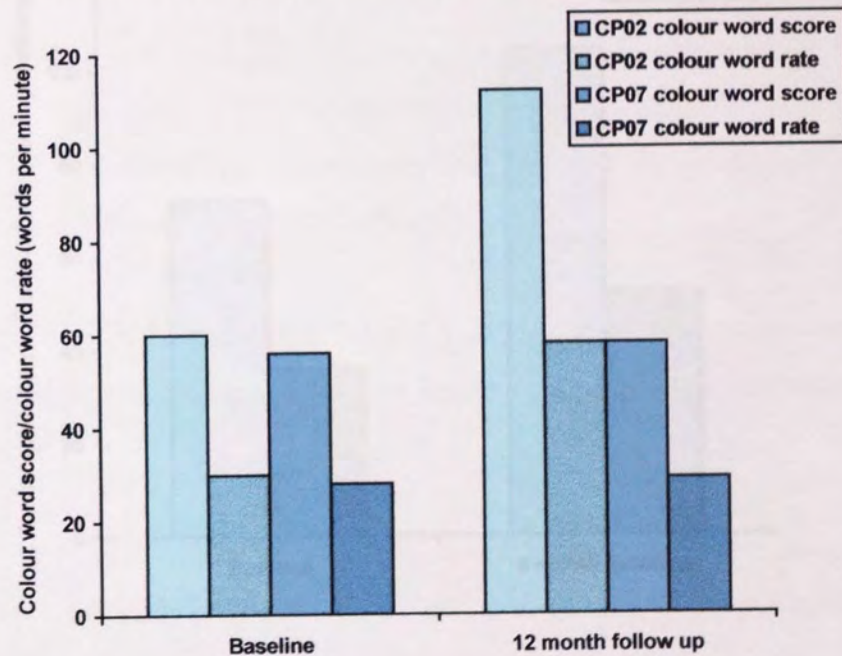




Figure 8.5: Colour word score and rate group A patients randomised to LTG

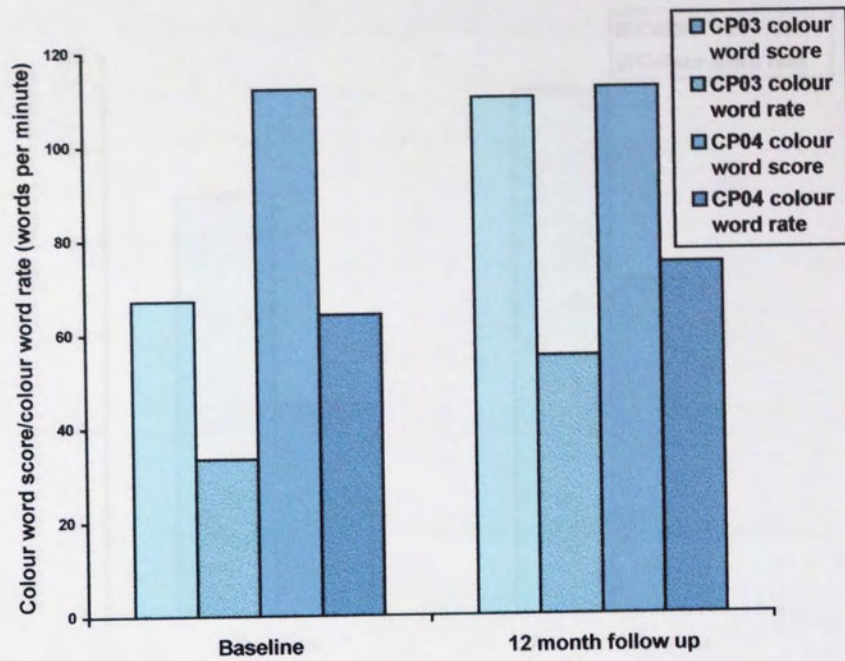


Figure 8.6: Colour word score and rate group B patient CP01

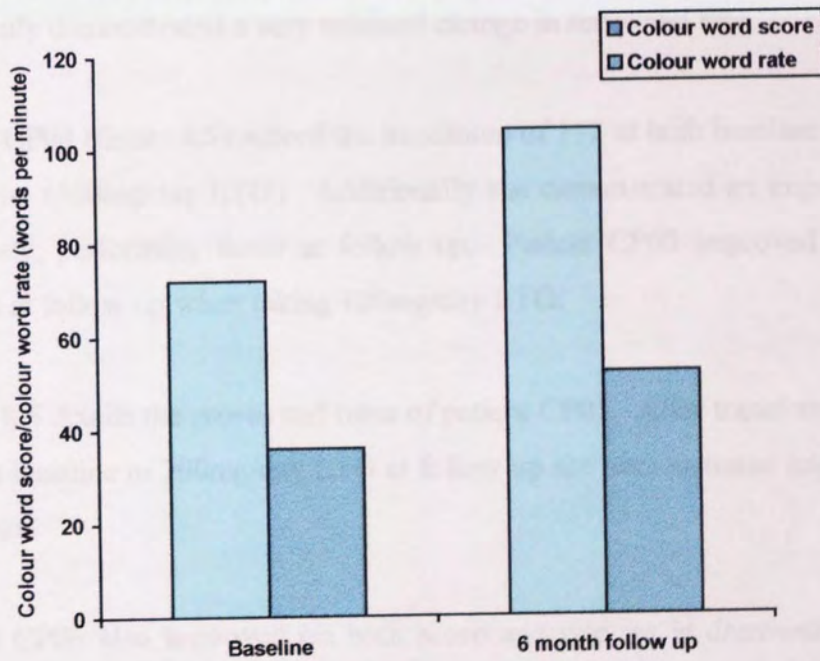
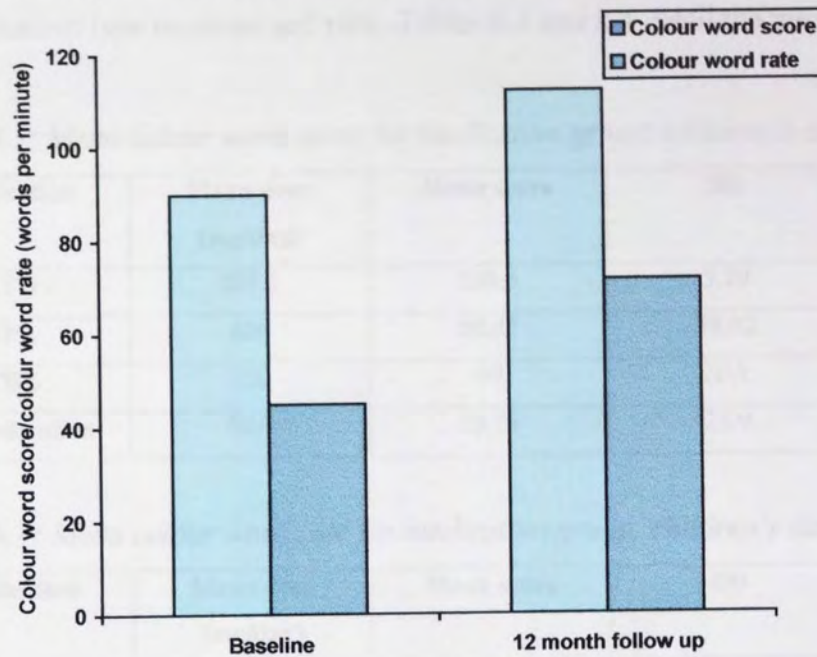


Figure 8.7: Colour word score and rate group C patient CP06



As can be seen from figure 8.4 patients CP02 and CP07 improved on both measures from baseline (unmedicated) to follow up (both taking 800mg/day VPA). However patient CP07 only demonstrated a very minimal change in score and rate.

Patient CP04 (figure 8.5) scored the maximum of 112 at both baseline (unmedicated) and follow up (400mg/day LTG). Additionally she demonstrated an improvement in colour word rate, performing faster at follow up. Patient CP03 improved in both measures, evident at follow up when taking 100mg/day LTG.

Figure 8.6 details the scores and rates of patient CP01. After transferral from 800mg/day VPA at baseline to 200mg/day LTG at follow up she demonstrated improvements in both measures.

Patient CP06 also improved on both score and rate, as is demonstrated in figure 8.7, following transferral from 200mg/day CBZ at baseline to 200mg/day LTG at follow up.



Data were again pooled and analysed using a Kruskal Wallis test to investigate the effect of medication type on score and rate. Tables 8.3 and 8.4 detail the means.

*Table 8.3: Mean colour word score for medication group, children's data*

Medication	Mean dose (mg/day)	Mean score	SD	N
LTG	287.5	109.5	3.79	4
VPA	800	80.67	28.02	3
CBZ	200	90	N/A	1
No medication	N/A	73.75	25.9	4

*Table 8.4: Mean colour word rate for medication group, children's data*

Medication	Mean dose (mg/day)	Mean score	SD	N
LTG	287.5	63.29	11.45	4
VPA	800	40.96	15.08	3
CBZ	200	45.00	N/A	1
No medication	N/A	38.87	16.9	4

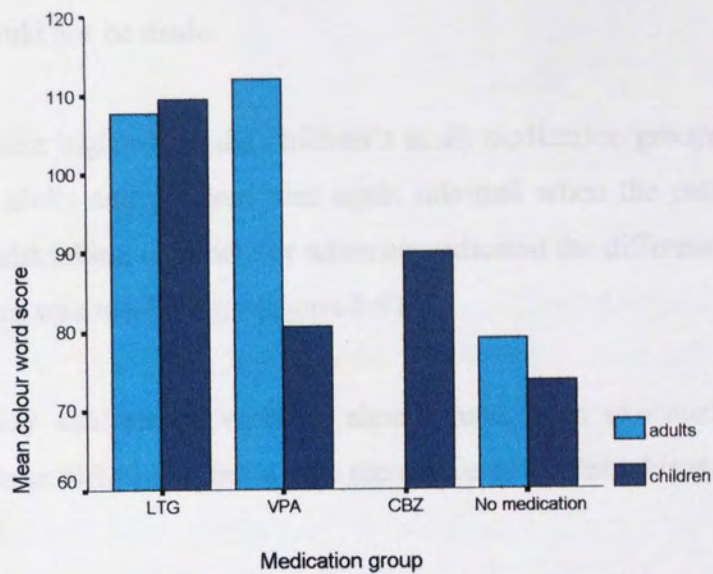
In both measures when patients were taking lamotrigine they performed better than when taking valproate or when they were unmedicated. It is difficult to comment on the effect of carbamazepine as only one patient was taking this drug. The differences in scores and rates between medication groups were again non-significant (score:  $\chi^2(3) = 3.240$ ;  $p = 0.356$ , rate:  $\chi^2(3) = 4.333$ ;  $p = 0.228$ ). Similar to the adult data the standard deviations for the lamotrigine and valproate groups were extremely large indicating high intragroup variability in both scores and rates.

### **8.3 Combined results**

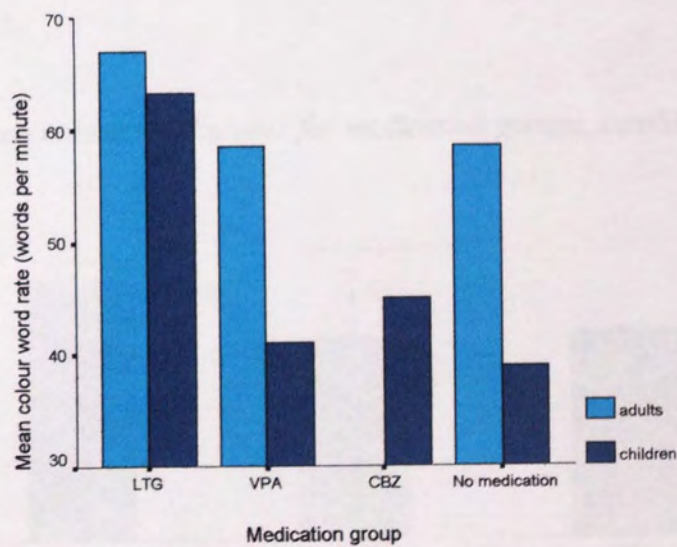
Due to the small patient numbers the adult and children's data were then combined and four Kruskal Wallis tests were conducted. Two were used to investigate the effect of medication type on score and rate and two were used to examine the effect of patient type. As with the BDI data this was to control for the fact that patients were from two

separate clinical populations, adults and children. Figures 8.8 and 8.9 detail the means for scores and rates.

*Figure 8.8: Mean colour word scores for adults and children separated into medication groups*



*Figure 8.9: Mean colour word rates for adults and children separated into medication groups*





The adults scored higher than the children (figure 8.8) when taking valproate or when unmedicated. However when taking lamotrigine the children performed better than the adults, achieving higher Stroop scores. This difference was minimal in comparison to the large differences in performance between children and adults when taking valproate or when unmedicated. No adults were taking carbamazepine during the course of the study so comparison could not be made.

The adult rates were higher than the children's in all medication groups. The difference in rate between adults and children was again minimal when the patients were taking lamotrigine. Whilst taking valproate or when unmedicated the difference in rate between adults and children was much larger (figure 8.9).

Ideally a two way analysis of variance should have been executed to examine the significance of these differences but due to the nature of the data this statistical test could not be performed.

Figures 8.10 and 8.11 detail the mean scores and rates for the combined data by medication group. When patients were taking lamotrigine they scored highest and performed fastest, and when unmedicated patients scored lowest and performed slowest. These differences were non-significant (score:  $\chi^2(3) = 5.669$ ;  $p = 0.129$ , rate:  $\chi^2(3) = 5.969$ ;  $p = 0.127$ ).

Figure 8.10: Mean colour word scores for medication groups, combined data

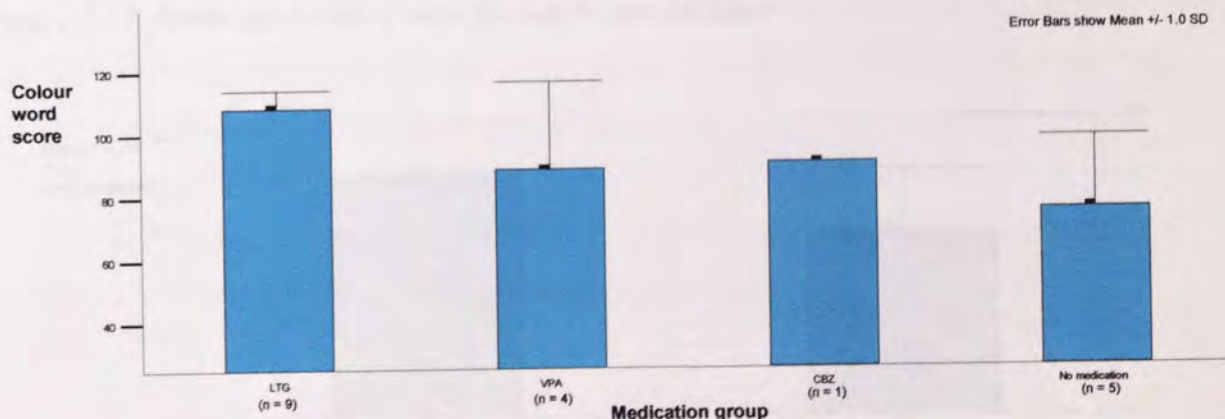
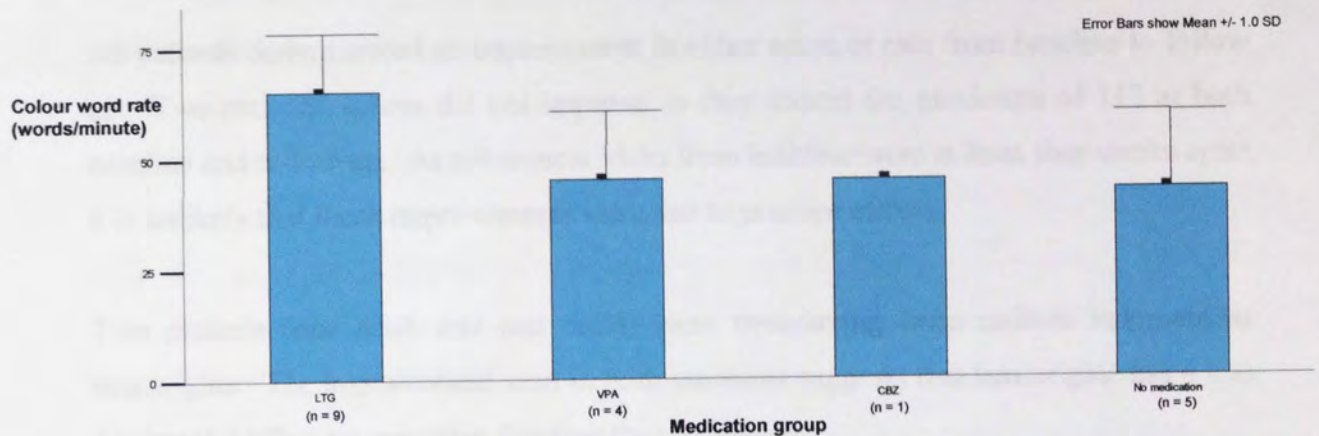


Figure 8.11: Mean colour word rates for medication groups, combined data



The adults scored higher than the children and performed faster, as demonstrated by the means in figures 8.12 and 8.13. The difference was non-significant for score ( $\chi^2(1) = 1.974$ ;  $p = 0.160$ ) but was significant for rate ( $\chi^2(1) = 3.952$ ;  $p = 0.047$ ). Again the large standard deviations indicate high intragroup variability in both score and rates.

Figure 8.12: Mean colour word scores for adults and children

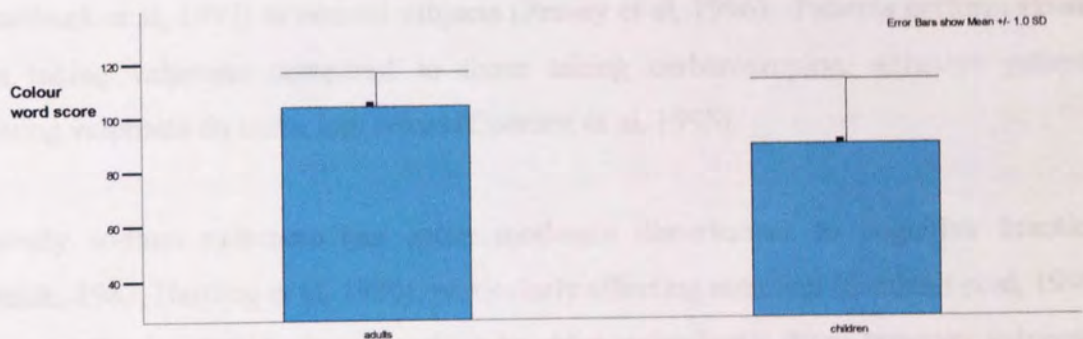
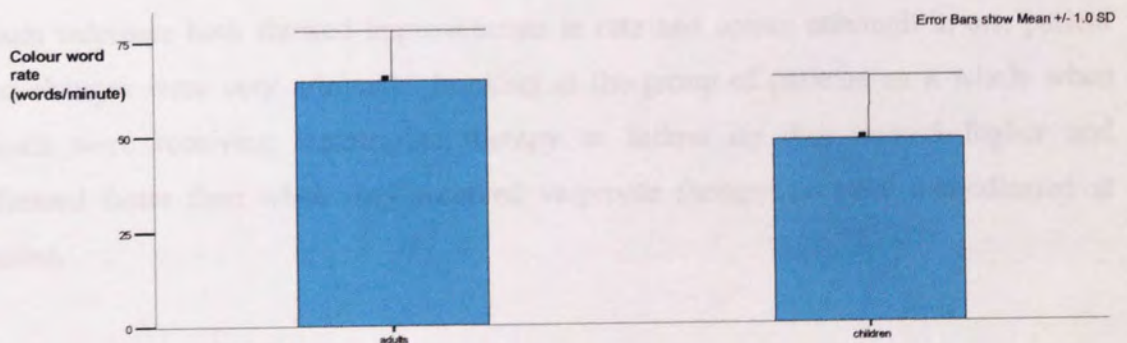


Figure 8.13: Mean colour word rates for adults and children





#### **8.4 Discussion:**

All patients demonstrated an improvement in either score or rate from baseline to follow up. Two patients' scores did not improve as they scored the maximum of 112 at both baseline and follow up. As subsequent visits from baseline were at least four weeks apart it is unlikely that these improvements were due to practice effects.

Two patients (one adult and one child) were transferring from sodium valproate to lamotrigine. The improvement seen in both measures suggests that lamotrigine has a less detrimental effect on cognitive function than valproate.

There is contradictory data in the literature concerning the effect of sodium valproate on the Stroop test. Some authors report no difference in Stroop scores when comparing valproate to a placebo in volunteers without epilepsy (Trimble and Thompson, 1984) and when comparing unmedicated scores to scores whilst receiving valproate therapy for epilepsy in newly diagnosed children (Forsythe et al, 1991). Other authors however suggest that valproate can detrimentally effect Stroop scores when compared to a placebo (Somerbeck et al, 1997) or control subjects (Prevey et al, 1996). Patients perform slower when taking valproate compared to those taking carbamazepine, although patients receiving valproate do make less errors (Coernen et al, 1995).

Generally sodium valproate can cause moderate disturbances to cognitive function (Trimble, 1987, Harding et al, 1980), particularly affecting attention (Gaulassi et al, 1990, Kwan and Brodie, 2001). In comparison to older antiepileptic drugs however valproate has a better cognitive behavioural profile (Brown, 1991, Akaho, 1996) and can improve concentration in some patients (Mattson et al, 1989). Indeed two children randomised to sodium valproate both showed improvements in rate and scores although in one patient these changes were very minimal. Looking at the group of patients as a whole when patients were receiving lamotrigine therapy at follow up they scored higher and performed faster than when they received valproate therapy or were unmedicated at baseline.

Lamotrigine also has a good cognitive behavioural profile with no detrimental affects on attention or vigilance (Marciani et al, 1999, Bonanni et al, 2001, Kwan and Brodie, 2001) and improvements on psychomotor speed, memory and recognition (Aldenkamp et al, 1997, Marciani et al, 1999, Kwan and Brodie, 2001, Meador et al, 2001).

With investigation of the effect of lamotrigine on the Stroop test reports are also contradictory. Lamotrigine therapy can impair performance (Banks and Beran, 1991) although the authors concluded that the impairment seen in this study was minimal. Lamotrigine was used as an add-on therapy in patients with refractory seizures and adverse cognitive effects are more likely to occur if the patient is prescribed polytherapy due to toxicity (Kwan and Brodie, 2001). No differences in time and error rate have been reported with lamotrigine therapy when compared to a placebo (Smith et al, 1993) and improvements in Stroop scores are also evident in patients receiving lamotrigine (Serra et al, 1996) compared to unmedicated baseline scores.

Three drug naïve patients (one adult and two children) demonstrated improvements in Stroop score and rate following the commencement of lamotrigine therapy. These results could have occurred as a result of a reduction of epileptiform activity following treatment (Bailet and Turk, 2000, Kwan and Brodie, 2001). In the two children however the EEG remained abnormal at follow up and the adult showed no epileptiform activity at either baseline or follow up. Two of the patients demonstrated a reduction in seizure frequency but none of them became seizure free. Improvement in cognitive functioning and mood have been reported with lamotrigine therapy which are not related to reductions in seizure severity or frequency (Smith et al, 1993, Meador and Baker, 1997) and it may be that lamotrigine has positive psychotropic effects.

The adults performed better on both measures than the children when patients were unmedicated or receiving valproate therapy. This may indicate that children are more sensitive to the adverse cognitive effects of valproate or uncontrolled epilepsy. Many studies have documented impairment of cognition in unmedicated children with epilepsy



(O'Leary et al, 1983, Mandelbaum and Burack, 1997, Gulgonene et al, 2000, Bailet and Turk, 2000, Aldenkamp et al, 2001, Pavone et al, 2001) and valproate (Bailet and Turk, 2000, Ronen et al, 2000) but no studies have investigated children in comparison to adults. Further studies focusing on this are obviously required.

From these results it appears that lamotrigine does not have any detrimental effects on concentration and mental flexibility as measured by the Stroop test. In fact the results indicate that lamotrigine may have an enhancing effect on cognitive processes when used to treat patients with epilepsy.

Unequivocal conclusions however cannot be drawn due to the small patient numbers and high variability within medication group, also found in other studies (Bailet and Turk, 2000). With a larger sample size and adherence to the proposed dose schedule a more detailed investigation of lamotrigines effect on the Stroop could have been carried out resulting in dose response curves for the magnitude of the Stroop effect and association with other factors such as seizure control, epileptiform activity in the EEG and diagnosis.

## Chapter 9: Summary and conclusions

The results of the measures of photoparoxysmal response outcome, seizure control, background EEG and occipital spikes are summarised for both adults and children in table 9.1 to 9.3.

Adult patients in group A did not demonstrate any significant changes in their photo and pattern sensitivity ranges after transferral from valproate to lamotrigine, with five patients remaining non-sensitive. This suggests that, like valproate, lamotrigine can control photo and pattern sensitivity. Some of these patients could have experienced spontaneous remission but it is unlikely that this could explain the data from all the patients in this group. The results from group B also suggest lamotrigine is efficacious in the abolition and reduction of the sensitivity range in both photo and pattern sensitivity. The children's results were not as impressive with only two children demonstrating an improvement or abolition in their sensitivity range to photic stimulation after the initiation of lamotrigine therapy. Following treatment with valproate one child showed an abolition of PPRs in response to both photic and pattern stimulation and another to pattern stimulation only. These results indicate that valproate therapy is more effective in reducing the SR of photo and pattern sensitive children.

Both the adult and the children's data indicated that the most provocative flash frequencies were 8-14 flashes per second and that photic stimulation with the grid was more provocative than diffuse photic stimulation. In terms of pattern stimulation there was no difference in the provocative nature of the two types of grating and the spatial frequencies which evoked PPRs in the most number of patients were 2 and 3cpd.

All of the group A patients remained seizure free after transferral to lamotrigine therapy, suggesting lamotrigine can also control seizures in photosensitive patients. Fifty percent of the group B patients became seizure free following treatment with lamotrigine and all the remaining patients demonstrated a decrease in seizure frequency. Again the

Table 9.1: Summary of adult patients group A data

Patient	Diagnosis	Medication at follow up (mg/day)	Responder		Outcome			Occipital spikes			Seizure free for $\geq 1$ year	Background EEG at follow up
			Photic	Pattern	Photic: Grid	Photic: Diffuse	Pattern: SWR	Pattern: SS	Photic	Pattern		
AP02	JME	500 LTG	Yes	Yes	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Yes	Normal
AP09	Pure photosensitive	300 LTG	Yes	Yes	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Abolished	Yes	Normal
AP11	None given	350 LTG	Yes	Yes	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Yes	Normal
AP14	Pure photosensitive	250 LTG	Yes	Yes	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Yes	Normal
AP15	Pure photo and pattern sensitive	400 LTG	No	No	No change sensitive	No change sensitive	No change sensitive	No change sensitive	No change sensitive	Abolished	Yes	Abnormal
AP17	PGE	200 LTG	Yes	Yes	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Yes	Normal

PGE = primary generalised epilepsy

Table 9.2: Summary of adult patients group B data

Patient	Diagnosis	Medication at follow up (mg/day)	Responder			Outcome				Occipital spikes			Seizure free for ≥1 year	Background EEG at follow up
			Photic	Pattern	Photic: Grid	Photic: Diffuse	Pattern: SWR	Pattern: SS	Photic	Photic	Pattern			
AP01	Pure photosensitive	300 LTG	No	No	No change sensitive	New presentation	Deteriorated	No change sensitive	Not sensitive	Not sensitive	Not sensitive	No	Normal	
AP03	JME	300 LTG	Yes	N/A	Abolished	Not sensitive	Not sensitive	Not sensitive	Abolished	Not sensitive	Abolished	Yes	NSA	
AP04	None given	100 LTG	N/A	No	Not sensitive	Not sensitive	Abolished	Abolished	Abolished	Not sensitive	Not sensitive	No	Normal	
AP06	PGE	300 LTG	No	No	Abolished	Abolished	Abolished	Abolished	Abolished	Not sensitive	Not sensitive	No	Abnormal	
AP07	JME	250 LTG	Yes		Abolished						Not sensitive	Yes	Normal	
AP08	JME	200 LTG	No	No	Improved	Not sensitive	Abolished	Not sensitive	Not sensitive	Not sensitive	Abolished	NO	Normal	
AP12	None given	100 LTG	Yes	Yes	Abolished	Not sensitive	Abolished	Abolished	Abolished	Not sensitive	Not sensitive	Yes	Normal	
AP13	None given	400 LTG	Yes	Yes	Abolished		Abolished	Abolished	Abolished	Abolished	Abolished	Yes	Abnormal	
AP18	None given	400 LTG	No	No	No change sensitive	No change sensitive	No change sensitive	No change sensitive		New presentation	Not sensitive	Yes	Normal	
AP19	OLE	100 LTG	No	No	Improved		Abolished	Abolished	Abolished	Not sensitive	Not sensitive	No	Normal	

NSA = non specifically abnormal



Table 9.3: Summary of children's data

Patient	Group	Diagnosis	Medication at follow up (mg/day)	Responder		Outcome				Occipital spikes			
				Photic	Pattern	Photic: Grid	Photic: Diffuse	Pattern: SWR	Pattern: SS	Photic	Pattern	Seizure free for $\geq 1$ year	Background EEG at follow up
CP01	B	OLE	400 LTG	No	No	No change sensitive	New presentation	Deteriorated	No change sensitive	Not sensitive	Not sensitive	No	NSA
CP02	A (VPA)	None given	800 VPA	No	Yes	No change sensitive	Improved	Abolished	Abolished	Abolished	Abolished	No	Abnormal
CP03	A (LTG)	EMA	100 LTG	No	No	Improved	Improved	No change sensitive	Abolished	Abolished	Not sensitive	No	Abnormal
CP04	A (LTG)	EMA	400LTG	No	No	Not sensitive	Not sensitive	Not sensitive	Not sensitive	Still has OS	Abolished	No	NSA
CP05	B	CVAE	200 LTG	No	No	Abolished			No change Sensitive	Abolished	Not sensitive	No	NSA
CP06	C	CPE	250 LTG	No	No	No change sensitive		No change sensitive	Abolished	Not sensitive	Not sensitive	Yes	Abnormal
CP07	A (VPA)	None given	800 LTG	Yes	Yes	Abolished		Abolished	Abolished	Abolished	Not sensitive	Yes	Abnormal

NSA = non-specifically abnormal  
 CVAE = childhood variant absence epilepsy  
 CPE = complex partial epilepsy

children's data were somewhat disappointing with only two patients becoming seizure free. One patient was receiving valproate therapy and the other had transferred to lamotrigine from carbamazepine. The combined results indicate that seizure control with lamotrigine can be achieved in some adult patients and it is more difficult to achieve in children.

Based on measurements of PPR outcome (determined by changes in sensitivity range, and seizure control all patients were classified as responders or non-responders. In the adult patients 60% (9/15) of photosensitive patients and 50% (7/14) of pattern sensitive patients were classified as responders. If patients were sensitive to both photic and pattern testing and they responded to therapy sensitivity was reduced in both disorders. This suggests that lamotrigine is efficacious in the treatment of both photo and pattern sensitivity in adults, although not as efficacious as sodium valproate with its 80% response rate in photosensitivity (Harding et al, 1978). Only two children were classified as responders, one in terms of photo and pattern sensitivity, the other child's pattern sensitivity responded to therapy but her photosensitivity did not. Both children were taking sodium valproate. These results again imply that photo and pattern sensitive children are more difficult to treat than adults and that valproate is much superior to lamotrigine in the treatment of children.

In the adults the number of flash frequencies evoking photoparoxysmal responses at baseline was significantly related to response to lamotrigine therapy, with patients who initially displayed PPRs to more flash frequencies being less likely to respond to treatment. A similar trend was seen in the pattern sensitive data, with patients demonstrating PPRs to a larger number of spatial frequencies (with reversing square wave gratings) at baseline again less likely to respond to lamotrigine therapy. This association however was not significant.

Occipital spikes were abolished after the commencement of lamotrigine therapy in six adult patients suggesting that unlike sodium valproate lamotrigine has an effect on occipital spikes. In two patients occipital spikes were seen at follow up at the flash rates

which had previously evoked PPRs. Two drug naïve children commencing lamotrigine therapy and one child transferring from valproate to lamotrigine demonstrated an abolition of occipital spikes. This again suggests lamotrigine has an effect on occipital spikes, implying that it affects both magnocellular and parvocellular visual systems. There was no association with the presence of occipital spikes and response to lamotrigine therapy providing further evidence that occipital spikes are independent from photoparoxysmal responses and that occipital spikes are not a clinically significant finding in the EEGs of photo and pattern sensitive patients.

There was no significant change in the presence of photic driving or lambda activity from baseline to follow up in the EEGs of any of the patients involved in both studies. The number of group B adult patients displaying lambda activity decreased at follow up, whereas the number of group A adult patients increased. This could indicate a suppression of lambda by lamotrigine, although to a lesser extent to that resulting from sodium valproate, but with the small patient numbers it is impossible to categorically state this. There was a non-significant increase in the number of group A adult patients displaying VEPs in their EEGs in response to photic stimulation following transferral to lamotrigine, indicating lamotrigine does not have similar control of the amplitude of the VEP in photosensitive patients to valproate. There was no change in the number of group B adult patients demonstrating VEPs in response to photic stimulation at baseline and follow up, although with pattern stimulation there was a non-significant increase of patients displaying VEPs. All children displayed VEPs in their EEGs at baseline and follow up with both photic and pattern stimulation regardless of medication. These results indicate that none of the medications involved in the study exerted a significant effect on photic driving, visual evoked potential or lambda activity, although the effects of lamotrigine on these normal response to IPS deserves further investigation.

All of the group A adult patients had normal resting EEGs when taking sodium valproate, one patient's EEG deteriorated following transferral to lamotrigine. Two of the group B adult patients had normal EEGs when unmedicated. Five of the eight group B patients displaying abnormal EEGs at baseline improved following initiation of lamotrigine

therapy, and one patient's EEG deteriorated. One child displayed a normal resting EEG at baseline. One of the six children displaying abnormalities in their EEG at baseline showed an improvement after transferral from valproate to lamotrigine. These results suggest lamotrigine can improve the resting EEG in some photo and pattern sensitive patients, although it appears not to be as effective as sodium valproate and in some cases may aggravate the abnormal activity seen in the resting EEG. Improvements in the state of the resting EEG are again more difficult to achieve in children in comparison to adults.

The two group A adult patients whose data were available showed a decrease in body mass index following transferral from valproate to lamotrigine. All drug naïve adult patients demonstrated an increase in BMI after initiation of lamotrigine therapy, as did all drug naïve patients in the children's study commencing lamotrigine or valproate therapy. One child transferring from valproate to lamotrigine also displayed an increase in BMI, whereas another demonstrated a decrease of BMI, as did a further child transferring from carbamazepine to lamotrigine. It is difficult to conclude upon the effect of the medications used in this study upon body mass index. There were no clinical concerns regarding the body mass index scores of any patient following therapy initiated during this study although the unexpected increase in BMI seen in drug naïve patients commencing lamotrigine therapy warrants further investigation.

Due to the small patient numbers it is very difficult to conclude upon the effects of lamotrigine on menstrual function. It is possible that menstrual abnormalities seen in two patients (one adult and one child) ceased as a result of a protective effect of lamotrigine. There were no clinical concerns regarding the menstrual function of any patients following lamotrigine therapy although reports from two adult patients suggest lamotrigine may increase the amount of menstrual flow.

Six of the sixteen adult patients reported adverse effects, which could have been associated with lamotrigine treatment. All children reported adverse effects. The side effect profile was similar to that reported in the literature with the most common adverse effects reported with lamotrigine therapy being headaches, dizziness and blurred vision.



Decreased appetite and unsteadiness were reported with both lamotrigine and valproate therapy. All adverse effects were acute and dose related with one possible idiosyncratic reaction. They were mild and transient and no patient needed to discontinue treatment.

A decrease in depression as measured by the Beck depression inventory was seen in four patients (two children and two adults) following the initiation of lamotrigine therapy. Two patients (one adult and one child) were drug naïve and two patients were transferring from sodium valproate. Three patients, all children, demonstrated an increase in the severity of depression following the commencement of lamotrigine and valproate therapy respectively and following the transferral from carbamazepine to lamotrigine. It is difficult to conclude if treatment with lamotrigine contributed to any of these changes. There was a significant difference in BDI scores between the adults and the children suggesting that children with epilepsy may be more prone to depression than adults with epilepsy.

All patients tested demonstrated an improvement in Stroop scores or rate unless they had achieved the maximum score at baseline. Two patients (one child and one adult) transferred from valproate, data from these patients and pooled scores demonstrate superior performance when patients were taking lamotrigine at follow up in comparison to when they were on valproate or were unmedicated. These results suggest that lamotrigine may have a less detrimental effect on cognitive function than valproate. Examination of the data indicates that improvements in performance were not related to a reduction of epileptic activity, implying that lamotrigine possibly has an enhancing effect on cognition in patients with epilepsy. Adults performed better than the children in both measures when unmedicated or when taking valproate, however the children performed better when taking lamotrigine, suggesting children may be more susceptible to the adverse cognitive effects of valproate or uncontrolled epilepsy.

There are a number of limitations to this study, primarily the low patient numbers as a consequence of difficulties with recruitment (as described in chapter 4). It is difficult to unequivocally conclude from such small population data, especially when examining the

measures of body mass index, menstrual history, BDI and the Stroop. The limited sample size prevented more in-depth statistical analysis from being performed and this, coupled with widespread intragroup variability of many of the measures, could account for the lack of significance of many of the statistical tests that were performed.

The primary measure of this study was the sensitivity range to photo and pattern stimulation. It is theoretically possible, as discussed in chapter 5, section 5.3.1 that this measure of sensitivity could be flawed. When the sensitivity range was originally devised there was no internationally standardised approach to testing photo and pattern sensitivity. Upper and lower sensitivity limits (i.e. the highest and lowest frequencies which consistently evoked a PPR) were determined and it was assumed that a patient was sensitive to all the frequencies within these limits. The sensitivity range is therefore determined by subtracting the lower limit from the upper limit. Using the sensitivity range a fixed criterion of 78% was implemented to evaluate drug therapy, based upon studies of the natural variation over time of the SR (Harding et al, 1978). The problem with this method is that patients often display islets of non-sensitivity within their SR limits. This is more noticeable now that standardised measures of testing have been implemented (Kasteleijn-Nolste Treinté et al, 1999). The standardised screening method tests at fixed frequencies and therefore gives a more detailed description of the patient's sensitivity to individual frequencies, which can be more useful clinically when advising the patient of potentially hazardous environmental stimuli. Using the sensitivity range to define a patient's sensitivity can be misleading, for example if a patient's upper limit is 40 flashes per second and their lower limit is 10 flashes per second, the SR implies that they are sensitive to the 30 flash frequencies in between (40-10), however when individual flash frequencies are tested it could transpire that the patient is only sensitive to some of the flash frequencies e.g. 10, 15 and 40 flashes per second. This can cause confusion when using the 78% criterion to evaluate response to drug therapy.

In this study the SR and the 78% criterion level were used as unfortunately it is the only standardised measure allowing the evaluation of the effects of drugs on photo and pattern sensitivity. However the number of fixed frequencies of the standardised protocol a

patient was sensitive to was also calculated at each visit. The percentage change of this measure was calculated for patients and it did not correspond with the percentage change of the SR. For example at baseline one patient's upper limit was 50 flashes per second and her lower limit was 6 flashes per second, giving an SR of 44. At follow up her upper limit was now 40 flashes per second but her lower limit remained at 6 flashes per second giving an SR of 34. Her SR therefore decreased by 22.7 % after treatment. However, if the individual frequencies she was sensitive to are examined she was sensitive to 6, 8, 12, 14 and 50 flashes per second at baseline, a total of five frequencies. At follow up she was sensitive to six frequencies, 6, 8, 10, 12, 14 and 40 flashes per second. If using the number of fixed frequencies in the standardised protocol as a denominator this is a 20% increase in sensitivity following treatment.

Bearing in mind that the results of this study indicate that response to treatment is related to the number of fixed frequencies a patient is sensitive to at baseline it suggests that further investigation of the sum of fixed frequencies (SFF) method of evaluating photo and pattern sensitivity is required. A similar study to Harding et al, 1978 examining the SFF at regular intervals in unmedicated patients and in patients whose medication remains constant would be useful in determining the normal variation of the SFF over time and to develop a similar criterion to the 78% level used with the SR to evaluate the effects of drug therapy.

There were frequent deviations from the original dose schedule preventing the calculation of dose response curves for each measure as originally proposed. Deviations generally occurred as a result of clinical decisions. For the purpose of the study it was necessary to devise a standardised dosing schedule but in the treatment of individual patients this schedule was often inappropriate. Deviations from the schedule also occurred due to delayed appointments with clinicians and as a consequence of patients' confusion.

There was no formal measure of compliance incorporated into the study. At each visit patients were questioned regarding compliance. Some patients stated they occasionally forgot to take their medication and a couple of patients admitted they deliberately omitted

medication as they did not like it (when medicated with valproate and carbamazepine). A measure of compliance would therefore have been useful, particularly when analysing response to treatment.

This study was designed to provide a comprehensive evaluation of the effect of lamotrigine on photo and pattern sensitivity. However the primary concern was the well being of the patients involved and consequently on some occasions photic and/or pattern testing was reduced or omitted if patients were uncomfortable or suffering from fatigue. Additionally it was desired that the study have as minimal an impact as possible on patients' lives. All extraneous variables could therefore not be controlled. For example when examining the data from the menstrual histories data from patients who had commenced using the contraceptive pill during the course of the study were excluded from analysis. Consequently adequate conclusions could not be drawn from the data due to low patient numbers, however to prevent the patients from using the contraceptive pill would have been unethical.

Despite the inadequacies described above it can be concluded that lamotrigine is efficacious in the treatment of photo and pattern sensitive adults, although it appears that it is less effective than valproate and less effective in the treatment of children. Lamotrigine has a good side effect profile, although weight should be closely monitored after the commencement of therapy, as should the amount of menstrual flow. Treatment with lamotrigine does not have any detrimental effects on concentration and mental flexibility and may actually enhance cognitive function in photo and pattern sensitive patients.

It is clear from the results that lamotrigine should not be used for the treatment of photo and pattern sensitivity in children. In male patients it is advisable to treat photo and pattern sensitivity with sodium valproate unless they do not tolerate it in which case lamotrigine should be considered as an alternative. With the preponderance of photosensitive epilepsy in females and the concerns over the risks of valproate therapy in this population an alternative treatment is required. Lamotrigine can be used to



effectively treat women of a child-bearing age unless they display sensitivity to a high number of flash frequencies in which case they will probably not respond to lamotrigine therapy and treatment with valproate should be considered. Female patients who do not present with sensitivity to a high number of flash frequencies and who are experiencing adverse effects with sodium valproate, particularly those with disturbances to menstrual function, should be transferred to lamotrigine.

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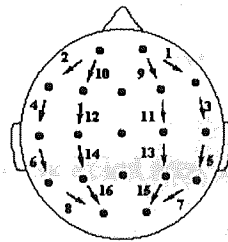
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## Appendix A: Protocol for photic stimulation

1. Room light was standardised.
2. The patient was briefed on the test procedure and was asked to tell the investigator (after the stimulus had been switched off) if they experienced any subjective sensations during the investigation.
3. The lamp with grid was placed 30cm in front of the patient's eyes and the patient was asked to fixate in the encircled area in the centre.
4. The patient was asked to wear their prescription spectacles if normally worn to improve close vision. The patient was asked if they could see the grid more clearly with or without their spectacles. The best option for the individual patient was used.
5. The patient was asked to relax their facial muscles to reduce EMG artefact.
6. An anterior/posterior montage (figure A1) was used.

*Figure A1: Photic montage*



7. The Grass PS22 photic stimulator was used at intensity 2 ( $1,363 \text{ cd/m}^2$ ).
8. Testing commenced with the patient's eyes open. The lamp was flashed for 5 seconds then the patient was asked to close their eyes, the flash continued for a further 5 seconds then the lamp was switched off. The patient was then asked to reopen their eyes.
9. At least 7 seconds rest was allowed between flash frequencies.
10. The routine flash frequency range was tested in the following order; 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 50, 40, 30, 25f/sec.
11. If an abnormality was evoked the flash was terminated immediately, and then testing was resumed at the next flash frequency.
12. If at any point the patient became distressed testing was halted and if the patient did not want to continue testing the investigation was abandoned.

## **Appendix B: Protocol for pattern stimulation**

1. The patient was seated 150cm from the 50Hz TV screen, so that the screen subtended 18° horizontally and 14° vertically of the visual arc, and was asked to fixate on the encircled area in the centre.
2. The patient was asked to wear their prescription spectacles if required to do so for that distance.
3. When the stimulus grating was not present the screen displayed a uniform grey background, mean luminance 190cd/m<sup>2</sup>.
4. A full explanation of the procedure was given to the patient and they were asked to relax their facial muscles to reduce EMG artefact.
5. The SC Electronics T22 grating generator was set to square wave reversing mode, reversing at 1 Hz, contrast of 900 (86%) testing was carried out on the patient commencing with a grating of 0.5cpd, followed by gratings of 2, 3 and 6cpd.
6. The stimulus commenced with the patient's eyes open, after 5 seconds the patient was asked to close their eyes. After a further 5 seconds the patient was asked to again open their eyes and focus on the encircled area on the screen, following 5 seconds the stimulus was switched off.
7. At least 7 seconds was allowed between stimulus presentations.
8. A stationary sine wave grating was then used at the same contrast and spatial frequencies as the square wave grating.
9. If an abnormality was evoked the flash was terminated immediately, and then testing was resumed at the next flash frequency.
10. If at any point the patient became distressed testing was halted and if the patient did not want to continue testing the investigation was abandoned.

**Appendix C: Menstrual history**

Age at menarche:

Number of days in cycle:

Number of flow days

Amount of flow:

- Light (1-2 pads/day)
- Average (3-4 pads/day)
- Heavy (5+ pads/day)
- Variable

Menstrual problems - frequency:

	Never	Sometimes (<50% of the time)	Often (> 50% of the time)	Always
Dysmenorrhea				
Pre-menstrual tension				
Amenorrhea				
Oligomenorrhea				
Hypermenorrhea				
Breakthrough bleeding				

Menstrual problems – severity:

	None	Mild	Moderate	Severe
Dysmenorrhea				
Pre-menstrual tension				

Date of last menstrual period:

Comments (e.g. differences from LMP):



## Appendix D: Children's study protocol

### Visit 1: Baseline

- I) Medical histories and patients' height and weight were taken by Dr W Whitehouse or Dr E Wassmer from the Birmingham Children's Hospital.
- II) Menstrual histories were taken where appropriate
- III) Full EEG investigations with intermittent photic stimulation and pattern stimulation were performed at Aston University.
- IV) The Beck Depression Inventory was performed where appropriate
- V) The Stroop test was performed where appropriate.
- VI) Patients were asked to complete a patient diary in order to record seizures or subjective sensations, these were consulted when subsequent medical histories were taken at each follow up visit.

### Further assessments:

Investigations I-V were carried out at 6 weeks, 6 months and 12 months post commencement of drug therapy.



**Burrow CE, Harding GFA, Betts T, Fylan F and Lai M 2001**  
**Preliminary findings of a trial to determine the effect of lamotrigine on photoparoxysmal responses in photosensitive and pattern sensitive patients.**  
**Clinical Neurophysiology 112: (Suppl. 1) S23**

Photoparoxysmal responses (PPRs) are the epileptiform phenomena seen in the electroencephalograph in response to provocative visual stimuli. We investigated the effects of lamotrigine on PPRs in patients diagnosed as being photosensitive and/or pattern sensitive. Fifteen patients were followed up for 15 months whilst they commenced lamotrigine monotherapy or transferred from sodium valproate to lamotrigine therapy, due to concerns over valproate's adverse effects. Preliminary results show that patients changing from sodium valproate, can achieve equal control with lamotrigine. In addition, lamotrigine appears to reduce occipital spikes remaining in the EEG with valproate therapy. Generally in patients commencing lamotrigine monotherapy, PPRs elicited by photic stimulation are initially abolished at lower dosages than those evoked by pattern stimulation, although in one case, PPRs had returned at 15 months. It appears that abnormal occipital/posterior temporal activity replaces the abolished PPRs, suggesting that lamotrigine may prevent the generalisation of abnormalities evoked with photic and pattern stimulation. At higher doses of lamotrigine this abnormal posterior activity can also be seen to disappear.

**Burrow CE, Betts T, Harding G, Fylan F and Yarrow H 2001**  
**The effect of lamotrigine on photoparoxysmal responses in the EEG**  
**Seizure 10: 397**

Photosensitive epilepsy (PSE) which predominately affects females, is usually treated with sodium valproate. However, sodium valproate has been shown to have an adverse side-effect profile, including teratogenicity, and may be associated with the expression of the polycystic ovary syndrome. It is clear, therefore, that an alternative treatment for PSE would be valuable. We have investigated the effect of lamotrigine on photoparoxysmal responses (PPRs) elicited by photic or pattern stimulation in the EEGs of patients with photosensitive epilepsy. Patients were followed up for 12 months whilst they transferred from sodium valproate to lamotrigine, or commenced lamotrigine monotherapy. Results show that patients changing from sodium valproate can achieve equal control with lamotrigine, as indicated by the EEG. In patients commencing lamotrigine monotherapy PPRs elicited by photic stimulation are more responsive to lamotrigine than those evoked by pattern stimulation. In a sub-group of patients commencing lamotrigine, abnormal occipital-posterior temporal activity replaces the PPRs suggesting that lamotrigine may prevent the generalisation of abnormalities evoked by photic and pattern stimulation. The results suggest that lamotrigine may be an appropriate substitute for sodium valproate in the treatment of photosensitive epilepsy.