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Psychiatric co morbidity in epilepsy, psychiatric and psychosocial morbidity before and after surgical treatment.

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I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree Doctor of Medicine is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed 

Student Number _____

Date 16/10/13

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Summary

Introduction

Epilepsy is a common disease with an incidence of 20-70 per 100 000 annually and prevalence of 0.5-1% of the population. Data to date assessing psychopathology in refractory epilepsy patients is conflicting.

In a subgroup of medically refractory epilepsy patients, surgical intervention is considered. Studies of outcome after neurosurgical resection of epileptogenic tissue or temporal lobectomy focus on frequency of seizures as their primary outcome measure. Neurosurgical intervention for epilepsy is associated with significant undesired psychiatric consequences including psychosis, major depression, obsessive compulsive disorder and suicide.

Methods

This study is prospective cohort study which examined a group of patients with medically refractory epilepsy, and also examined a cohort who proceeded to surgery before and after surgery. This study used the Hospital Anxiety and Depression Scale (HADS) and the Structured Clinical Interview for DSM IV (SCID I), to examine for an axis-1 psychiatric diagnosis. In addition, the study assessed the presence of personality disorder using the SCID-II. The Quality of life in Epilepsy (QOLIE-89) assessed social outcome. All patients admitted to the Epilepsy Monitoring Unit or who attended the Neurology OPD in Beaumont Hospital with treatment resistant epilepsy are considered a candidate for inclusion.

All participants were assessed using the same instruments as those unwilling to participate. Those that proceeded to surgery were reassessed three to six-months after surgery using the same structured interview and standardised self rating questionnaires.

Conclusions

The findings of this study demonstrated the high prevalence of psychiatric comorbidity (49%) in patients with medically refractory epilepsy.

In addition, the presence of a psychiatric disorder and the severity of the symptoms of psychiatric illness were correlated strongly with quality of life.

Overall, this study has demonstrated that undergoing surgery for medically refractory epilepsy had an overall positive impact on mental health with a significant reduction in the severity and prevalence of psychiatric symptoms and an improved quality of life.

Chapter 1 Introduction

Overview

This chapter provides an overview of the clinical features of epilepsy and its association with psychiatric disorders, considers its prevalence based on epidemiological studies and examines aetiological theories for the associated psychiatric disorders. In order to provide a framework to relate the findings of this study, several questions need to be addressed by discussing the current literature findings and its limitations. The primary question relates to current understanding of the association between epilepsy and psychopathology with a particular focus on depression, psychosis and personality disorders in the medication refractory population.

1.1 Introduction

According to consensus by the International League Against Epilepsy (ILAE) and International Bureau for epilepsy (IBE) 'an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition'. The lifetime prevalence of epilepsy is approximately 0.5% [1] The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is not one sole condition but more an umbrella term for a variety of conditions in which seizures occur. In 2010 the ILAE published new guidelines on classification, which have long been complicated by the advances in aetiology, seizure types and foci. Seizures broadly are divided into generalised encompassing tonic-clonic, absence, myoclonic, clonic, tonic,and atonic and into focal seizures with additional descriptors- with or without

impairment of consciousness or awareness. Further classification can be used based on the underlying aetiology- genetic, structural/metabolic or unknown cause.

Epilepsy, as the historical 'sacred disease' has had a long association with psychiatric disorders, with possession in the Middle Ages thought to be causal of both. The development of the EEG (Electroencephalogram) by Hans Berger allowed a modern understanding of epilepsy with localisation and the link to lesions. However, in addition to improved understanding of the organic aetiology of epilepsy, there was early recognition by Morel, for example, of psychological disturbance as part of or consequence of seizure[2].Localisation of seizures to the temporal lobe and limbic system with its involvement in emotional processing led to further understanding of mental disorders with epileptic seizures. More recent developments in the field of neurology and psychiatry have allowed incorporation of biological factors related to epilepsy, medication effects etc. with an understanding of the implications of psychological and social factors in more comprehensive models of psychopathology in epilepsy.

Examination of epilepsy and co morbidity with psychiatric disorders has been complicated by a lack of clarity of the phenomenology in both fields. The most useful classification which has emerged is to link psychopathology according to its temporal relationship with seizures i.e. pre (hours before seizure), post (hours or days following seizure), peri(during seizure) and inter ictal (phase between seizures when EEG is returned to baseline). Psychopathology for the purpose of this chapter will be discussed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) categories of Mood, Anxiety and Psychotic disorders diagnostic classifications[3]

1.2 Epilepsy and psychopathology

Studies examining the relationship between psychopathology and epilepsy to date have tended to be small, use non representative samples and fail to use standardised instruments. Specific studies looking at psychiatric outcomes of epilepsy surgery have been further limited by short follow-up periods. Population based studies estimating rates of overall psychiatric co-morbidity are few, with studies estimating rates of between 11-35.5%.[4, 5] Tellez et al estimated population based prevalence rates of various psychiatric conditions associated with epilepsy using a Canadian national population health survey and found an overall lifetime prevalence of 35.5%, with lifetime rates of major depression of 17.4%, anxiety disorder 22.8% and prevalence of suicidal ideation of 25%[6]. Smaller studies also consistently show higher rates of psychopathology in epilepsy although there is also consistent evidence indicating that psychiatric illness continues to remain under diagnosed or undertreated in patients with epilepsy.[7, 8]

1.3 Mood disorders in epilepsy

1.3.1 Mood disorders: prevalence in epilepsy

In a review, Herman and colleagues summarised the published prevalence rates of major depression in epilepsy and reported estimates ranging from 8-48% [9] Comparison of these studies was complicated by heterogeneity of assessment tools used, the lack of standardised assessments and the lack of operational criteria used to diagnose psychiatric disorder.

In one of the few multicentre studies which used operational diagnostic criteria, Jones and colleagues reported that, in people with epilepsy, high rates of depressive disorder (21.1%), 15.5% agoraphobia (15.5%), 13.2% generalised anxiety disorder (13.2%) and social phobia (10.3%) were identified. They also identified that fewer than half of those with a depressive disorder were being treated with an antidepressant and, of those being treated, 43% still met the criteria for MDD (Major Depressive disorder) suggesting either inadequate treatment, refractory illness or poor adherence to medication.[10]

Reported incidence of suicide and DSH(deliberate self harm) varies but may be as high as 4-5 times that of general population [11, 12] Rates of an increase of up to 25 fold have been reported in patients with temporal lobe epilepsy (TLE) [13]

Examination of mood symptoms in epilepsy must also consider the relationship with seizure events. In a study of prodromal affective symptoms in patients with epilepsy, a decline in mood pre ictally in a period of up to 72 hours was noted, with a subsequent return to baseline taking up to 3 days after seizure occurrence.[14] Fear is generally more recognised than depression in the pre ictal phase and up to 25% of auras have an emotional component with 15% having an affective element.[15]

1.3.2 Mood disorders: Aetiology in epilepsy

The potential aetiology of depression in this population remains unclear and a multifactorial model is most likely. Various causative factors have been proposed:

(i) Epilepsy related factors.

Many studies report that people with TLE (temporal lobe epilepsy) have higher rates of depression [10, 16] and in addition, the importance of limbic structures in regulating mood is well described [17, 18] . However other studies have showed no increased rate compared with extra temporal epilepsy [19] and the fact that patients with TLE tend to have more than one type of seizure may be a more important factor. The association between seizure type e.g. complex partial seizures also remains controversial as does side of focus with both right and left sided foci found to be associated with depression in epilepsy.[20] Depression has been linked with possible left sided hypo metabolism. [21] Recent studies have examined the connectivity of mesial temporal lobes and report that chronic active TLE may be associated with hypoactivity and dysfunction in anatomically connected regions distant from the epileptic focus. Left sided TLE may lead to decreased activity in frontal lobes and hypoactivity in these regions has been linked to depression.[22] [21] Brain imaging studies [23] and neuropsychological tests [20] provide additional evidence for a link between frontal lobe dysfunction, depression and TLE.

Disturbances of various neurotransmitters, in particular serotonin, noradrenaline, dopamine, Gamma-amino butyric acid (GABA) and glutamate have been identified in both depression and epilepsy with structural and functional alterations from one disease probably increasing risk of developing the other. [24] [25, 26] Several PET (Positron emission tomography) reverse studies of serotonin transmission have been performed in TLE patients with and without depression. Decreased binding to the 5-HT 1A receptor have been found in the amygdala, hippocampus, temporal cortex, insula, anterior cingulate and the raphe nucleus ipsilateral to seizure origin and in the contra lateral hippocampus.[24, 25, 27] SSRIs (serotonin reuptake inhibitors) reverse have been shown to abolish or reduce seizures in animal models of epilepsy[28] and serotoninergic mechanisms are presumed to be directly involved in these anti convulsant effects. [29] However higher doses of SSRI's may have a proconvulsant effect due to emergent GABA ergic and glutamergic disturbance.[30]

In addition to direct epilepsy related factors other neurological factors- must be considered i.e. that depression is related to the condition causing the epilepsy e.g. cerebrovascular disease, dementia, Multiple Sclerosis.

(ii) Patient factors

The majority of studies find male preponderance of epilepsy patients with co-morbid mood disorder, but others show more females or no gender association in those with epilepsy and mood disorders.[31, 32] Lund reports twice the percentage of epilepsy patients with learning disability had psychiatric disorder compared with those with learning disability alone but others have shown no association[33, 34].

The area of genetic loading or family history is again conflicting with Robertson et al showing a positive association and Mendez et al finding none.[16, 35]Early age of onset of seizures has been shown to be both a predisposing and protective factor.

(iii) Medication factors

Many anti epileptic drugs (AEDs) are associated with mood sequelae, both positive and negative. Those that produce a negative effect appear to be those which act on BDZ-GABA (benzodiazapine gamma amino butyric acid) reverse receptor complex and include barbiturates, topiramate, vigabatrin[36] Drugs with potential positive mood effects included carbemazepine and valproate while tiagabine, levetiractam and felbamate have intermediate risk of mood effects. There is limited data to date on the effect of zonisamide. Other mechanisms of effect postulated include the effect of these drugs on free tryptophan and AED induced folate deficiency.

The concept of forced normalisation whereby psychiatric symptoms worsen with improvement in seizures is more usually associated with psychosis but seizure improvement associated with worsening psychosis has also been noted with depression in epilepsy. Mula and colleagues hypothesed that the negative effect of AEDs on mood may be related to this concept.[36] Interestingly, while complete resolution of seizures is associated with worsening psychosis, worsening mood in depression can be more associated with a reduction in seizures. In 2006 the FDA added an alert to AEDs based on an increased odds ratio (OR) of suicidal ideas in people taking AEDs for epilepsy but not significantly so for those taking AEDs for other indications.

(iv) Psychological factors

Psychological factors must also be considered in depression with epilepsy. The unpredictability and uncontrollability of seizures have been likened to the 'learned helplessness' model of Seligman [37] thus predisposing to depression with a pessimistic attributional style to attributing global difficulties to epilepsy, increasing the risk of developing depression. In a study of inpatients with epilepsy, Herman and colleagues identified social support, perceived stigma, external locus of control and poor vocational adjustment as significant predictors of depression scores. Following multiple regression analysis four key factors were identified: increased stressful life events, female gender, poor adjustment to epilepsy and less adequate financial status.[38]

The Hermann Whitman model for psychiatric comorbidity in epilepsy attempts to encapsulate the multitude of potential risk variables into 1. Brain related 2. Non brain related and 3. Treatment related.[38] They note that these variables may be interrelated and should not be seen as independent. Also they may reflect a more general factor e.g. severity is influenced by other factors including age of onset, seizure types etc. They also hypothesise that each factor loading may explain the variance for different disorders, e.g. brain related factors (seizure frequency, age onset) which may explain variance in psychosis while non brain factors may explain depression variance where social and psychological factors may be more relevant.

Recent studies have focused on the interesting finding of a bidirectional relationship between epilepsy and depression[39, 40] Patients with epilepsy have a higher risk of developing depression and patients with depression are more likely to develop epilepsy. Hitiris and colleagues found a 2.2 times higher probability of treatment refractory epilepsy in patients with a history of psychiatric disorder and most interestingly a history of depression preceding the first seizure in these refractory patients.[41]

1.3.3 Interictal Dysphoric Disorder in epilepsy

Although not defined by the DSM IV, a distinct syndrome of interictal dysphoric disorder (IDD) has been identified [42] based on findings of increased interictal dysphoria, irritability and emotionality. Blumer reports that between a third and a half of patients with epilepsy seeking medical care suffer IDD of sufficient severity to require intervention. [42] As not recognised under current DSM criteria, patients presenting with these symptoms which are milder than those required to diagnose major depressive disorder may have to be classified under atypical depressive disorder. The intermittent nature of the symptoms excludes a diagnosis of dysthymic disorder.

1.3.4 Mood disorders: Treatment in epilepsy

As already noted, mood symptoms are poorly diagnosed and treated despite recognition of increased rates and a link to pharmaco-resistance of epilepsy. The lack of recognition and treatment of mood disorders in people with epilepsy can have serious consequences resulting in increased morbidity and mortality. In addition patients with depression and epilepsy utilise more health resources than those with epilepsy alone[43] . The influence of mood disorders on the quality of life of people with epilepsy is another vital factor to consider. Studies have demonstrated that depression is the single most important factor in predicting health related quality of life [44, 45] . This has also been identified in treatment refractory patients who undergo temporal lobe surgery.[46]

Clearly there should be a high index of suspicion for existence of a comorbid mood disorder in patient with epilepsy. Specific enquiry regarding suicidality should occur as well as questioning for relationship of symptoms to seizure occurrence. As with the general population, recognition of a mood disorder does not necessarily translate to adequate treatment. Specifically in epilepsy, concern regarding side effects of antidepressant medication may result in reluctance of clinicians to prescribe.

Due to the likely multifactorial aetiology of mood disorders in epilepsy, treatment must address several components. In mood symptoms precipitated or exacerbated by seizure events, adequate management of seizure disorder is necessary. A medication history is essential to evaluate possible positive or negative mood effects of AEDs.

As discussed above, psychosocial factors play an important role in the development of depression. However limited studies have been conducted to date evaluating efficacy of non pharmacological interventions in people with epilepsy. One small study examined the impact of cognitive behavioural therapy in epilepsy and found significantly greater reductions in rates of dysphoria and depression when compared with pharmacotherapy treated controls.[47] Interventions such as cognitive behavioural therapy have long established efficacy in the general population.[48]

In patients with co morbid mood disorder, use of AEDs with known positive mood effects should be considered. Caution however is advised with switching AEDs as withdrawal reactions have been noted and in approx. 40% of people with epilepsy, affective symptoms have been noted in withdrawal phase.[49]

Antidepressant therapy is the mainstay of treatment of depressive disorders. Many studies report that 60-70% of acute major depressive episodes will respond to ADT and early treatment will reduce duration of episode by 50%[50, 51] . However, there are limited double blind trials of antidepressants in patients with epilepsy. Kanner et al found that of 100 patients treated with sertraline (an SSRI), only one had an increase in seizure frequency due to the drug but more than half had complete resolution of depressive symptoms [7].

Serotonin abnormalities have been linked to both epilepsy with co-morbid depression and epilepsy alone with an improvement in seizures in animal models of epilepsy in the absence of depression[28]. Alper et al used FDA data to examine 75,000 patients and noted an increased rate of seizures with some neuroleptics especially clozapine and the tricyclic antidepressant clomipramine but all new generation ADT (antidepressants) except bupropion were associated with lower seizure incidence than placebo. Seizure incidence in the placebo group was found to be higher, perhaps indicating a lower seizure threshold in depressed patients due to depression itself.[40]

Drug interactions are another important consideration in epilepsy. Effects on cytochrome P450 enzyme system of both AED and ADT must be considered. ADT can alter serum levels of AEDS esp. the enzyme inducing AEDs, Phenobarbital, carbamazepine (CBZ) and phenytoin (PHT). The SSRI fluoxetine inhibits cytochrome P450 enzymes thus increasing level of CBZ and PHT.

Electroconvulsant therapy usage is not contraindicated in epilepsy although, similar to general population use, it is reserved for treatment refractory patients and where patient safety is at risk.

1.4 Psychosis in epilepsy

1.4.1 Psychosis: Prevalence in epilepsy

As in depression, studies that have examined the phenomenology of psychosis in epilepsy have been conflicting. Temporal divisions based on relationship to seizure events are generally used to divide psychotic symptoms- pre, post, inter and peri-ictal psychosis. However, as the epileptic brain between seizures is not normal, the focus purely on psychosis in the context of seizures may be a mistake. In addition, the similarity of epilepsy related phenomena to psychotic disorders may not necessarily imply a common underlying aetiology. Further confusion has developed as application of DSM IV criteria can lead to a diagnosis of psychotic symptoms as 'psychosis secondary to a general medical condition' or 'primary psychotic disorder not otherwise specified' depending on a subjective judgement of epilepsy as a causative factor of psychotic symptoms.[52]

Nonetheless, for ease of comparison of the literature, this chapter will focus on psychosis divided into the most commonly described peri ictal, post ictal and interictal which can be further subdivided into brief interictal psychosis and the more chronic schizophrenia-like psychosis. Population level studies have shown prevalence of psychosis in epilepsy in the range of 0.7-7%[4, 53, 54]

(i) Peri-ictal

The most common association of psychotic symptoms in the peri ictal phase is when patients with complex partial seizures present with a range of perceptual, behavioural and cognitive symptoms. Simple partial seizures may cause affective disturbance, hallucinations and thought disorder but insight is usually maintained. However, symptoms may be misinterpreted with resulting behavioural disturbance.[55]

(ii) Post ictal psychosis

This phenomena usually follows seizure clusters or recent exacerbation in seizure frequency[56]. It can also be related to AED withdrawal. Kanner and colleagues reported post ictal psychosis rates of 6.4% in an epilepsy monitoring unit. [57] Between the last seizure and psychosis onset there is usually a non psychotic period lasting a few hours to a few days.[56, 57] Psychotic symptoms can be delusions, hallucinations and while Sneiderian first rank symptoms do occur, they are less common. The mean duration of psychotic symptoms is approximately 79 hours while Savard et al note that all post ictal symptoms in their studied group resolved within 1 month.[58] Brief psychosis may reoccur

frequently with 2-3 episodes per year in Kanner's study. Conversion to chronic psychosis has been reported to occur in up to 15%[56]

(iii) Brief interictal psychosis (alternating psychosis)

In this disorder, an antagonistic relationship between epilepsy and psychosis is presumed. Periods of increased seizures alternate with episodes of seizure freedom during which the patient becomes psychotic. This phenomenon has been labelled 'forced normalisation' as during these phases the EEG becomes more normal but psychotic symptoms worsen.

(iv) Schizophrenia like psychosis

Slater et al were among the first to investigate the relationship between epilepsy and chronic psychosis.[59] Overall evidence shows that schizophrenia like psychosis is 6-12 times more likely in a patient with epilepsy than in the general population.[60] However this rate may be overestimated given the highly selective populations examined. In the absence of epilepsy this condition would meet criteria for a diagnosis of schizophrenia but some atypical features have been identified; reduced negative symptoms, relatively well preserved personality and ability to maintain interpersonal relationships. In his early work, Slater noted a high rate of religious experiences and delusions where onset tends to be 10-20 years after onset of epilepsy[59].

1.4.2 Psychosis: Aetiology in epilepsy

As with mood disorders, multifactorial models of aetiology are most likely. A strong association with temporal lobe epilepsy (TLE) has been noted but this remains controversial. The increase reported by other authors may simply reflect the fact that TLE is the most common form of epilepsy.[61]

Chronic sub ictal activity in the temporal lobe with possible changes in monoamines especially post synaptic dopamine receptor sensitivity has been proposed as a potential mechanism for TLE psychosis.[58, 62] SPECT (single photon emission computed tomography) studies showing low level of striatal dopamine D2 receptors in patients with peri-ictal psychosis supports this hypothesis.[63] Other potential mechanisms proposed include increased GABA turnover, reduction in cerebral aspartate and glutamate, changes in endorphins, peptides, brain adenosine and the second messenger system.[64]

The majority of studies do find an excess of left temporal foci although there have also been negative laterality studies[65, 66] Laterality findings are complicated by the use of surface electrodes, the fact that foci on one side does not imply normal opposite side and the fact that left sided foci are generally more common in epilepsy.

Various seizure related factors have also been considered. In particular, complex partial seizures that are secondarily generalised are more associated with psychosis, and duration of epilepsy of greater than 10 years has been reported.[56, 57, 67] Savard et al found increased rates of ictal fear, bilateral independent discharges and gross structural lesions but all of these findings have not been replicated in other studies[58] . Kanemoto and colleagues showed that psychosis was associated with frequent psychic auras and increased rates of mesial temporal sclerosis (MTS) especially in the left side.[67]

Neuropathological studies using post lobectomy tissues have been conflicting. Taylor et al found that patients with psychosis are less likely to have MTS and more alien tissue lesions while Roberts found that 40% had MTS, 20% alien tissue and 20% no lesions.[68, 69] Larger ventricles, more periventricular gliosis, more focal damage, more periventricular white matter softening have been reported in patients with psychosis in epilepsy.[70]

Various patient related factors have also been examined. Early onset of epilepsy [69] and a female bias have been reported but not replicated.[59, 71] No association with a family history of schizophreniform disorders, birth injuries, head injuries or febrile convulsions have been found. De novo schizophrenia like psychosis may develop post operatively after temporal lobectomy and rates of 3-38% have been reported.[68, 72]

Sachdev explores possible pathophysiological mechanisms under two broad possible mechanisms: 1. Psychosis due to electrical discharges 2. A shared common neuropathology between epilepsy and psychosis. [60]

(i) Psychosis due to electrical discharges

While psychosis as a consequence of epileptiform disturbance may account to some degree for ictal, post ictal and brief interictal psychosis, it is more difficult to attribute schizophrenia like psychosis to this explanation. Sachdev discusses kindling as a possible mechanism. Animal studies demonstrate the potential for repeated epileptiform discharges to facilitate subsequent propagation along specific pathways which may result in interictal disturbances leading to psychotic symptoms. [73] Another mechanism proposed is that plastic regenerative changes may affect the medial temporal lobes following seizures resulting in psychosis. It has been demonstrated that stimulation of the hippocampus leads to axonal sprouting from dentate granule cells before the development of seizures.[74] The dysfunctional regeneration and mis wiring may therefore explain development of schizophrenia like psychosis.

(ii) Psychosis due to a common underlying dysfunction with epilepsy

In a neuroimaging study patients with epilepsy and psychosis compared with a group of patients with epilepsy alone, significant grey and white matter deficits were found in patients with temporal lobe epilepsy with psychosis. Some of these deficits overlap with those found in schizophrenia.[75]

Neurodevelopmental abnormalities leading to cortical dysgenesis have been hypothesised as the common factor. Studies show hippocampal cell loss and sclerosis in TLE, patients have been found to have alien tissue lesions implying defective neuroembyrogenesis. Patients with MTS commonly have heterotopias, hippocampal neuronal loss and synaptic reorganisation in the hippocampus.[76] Schizophrenia has also been associated with cortical maldevelopment, reorganisation of the pyramidal cell layer and there is evidence also for synaptic reorganisation.[77-79] These abnormalities all suggest dysfunctional development in both epilepsy and in schizophrenia which may encompass the whole brain rather than psychosis in epilepsy being directly and solely related to the specific epilepsy pathology focus. Sachdev discussed a composite model i.e. patients with epilepsy who develop psychosis have a brain lesion which makes them vulnerable to psychosis.[60] This lesion may be neurodevelopmental or secondary to trauma/hypoxia of infection. The abnormality may be widespread but may focus on limbic structures leading to dysfunctional connectively. This abnormality causes electrical storms in limbic structures with resulting seizures which themselves may exacerbate the abnormally due to kindling effects.

After a period of time the further disruption of systems may lead to psychosis. The seizures themselves, either via subictal activity or effects on catecholamines and pre and post synaptic glutamergic and GABA ergic activity, modulate the expression of psychotic symptoms.[60]

1.5 Personality disorders in epilepsy

Very few studies have been conducted to date using standardised diagnostic tools for DSM IV Axis II disorders and also have been limited by lack of inclusion of control groups. The majority of studies examining personality in epilepsy use the Minnesota Multiphasic Personality Inventory (MMPI) which is a dimensional instrument rather than a diagnostic one. Those studies that have been conducted show an increased prevalence of between 4 and 38%. [80-83] Swinkles and colleagues showed more personality disorder traits than in the general population and hypothesised that this increase may reflect psychosocial consequences of living with epilepsy as a maladaptive reaction to chronic disorder or as a result of disrupted neuronal functioning. [80]

In addition to formal diagnoses of personality disorders, the concept of an 'epilepsy personality' has long been noted. Waxman and Geschwind described an interictal behaviour syndrome of deepened emotionality, circumstantiality, disrupted religious and sexual concerns, and hypergraphia.[84]

They note that these traits are not necessarily maladaptive, are not identified in all patients with epilepsy and can occur independent of epilepsy. Bear and Fedio designed an inventory to assess and identify these and other traits and suggest that they may result from a sensory-limbic hyper connection syndrome in which an epileptic focus leads to an enhanced association between affect and stimuli.[85]

In summary patients with epilepsy are at a higher risk of developing psychiatric disorders. However, information relating to clear risk factors is lacking, aetiological explanations are inconclusive and identification and management of psychiatric disorders is variable.

1.6 Treatment of epilepsy

1.6.1 Pharmacological treatment of epilepsy

For vast majority of patients, treatment of newly diagnosed epilepsy involves anti-epileptic drugs (AED) The initial choice of an AED for any individual patient with newly diagnosed or untreated epilepsy should include consideration of the strength of the efficacy and effectiveness evidence for each AED along with other variables such as the AED safety and tolerability profile, pharmacokinetic properties and formulations used. [86] A recent large multicentre trial (the SANAD trial) evaluating newer drugs in newly diagnosed epilepsy suggested that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in focal epilepsies.[87]

The 2012 NICE guidelines recommend that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom.

In the 2010 ILAE proposal document medically refractory epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination)[88]

1.6.2 Vagus Nerve Stimulation Treatment

In 1997 Vagus Nerve Stimulation (VNS) was approved in the USA for treatment of medically refractory seizures of partial onset and it has since been introduced worldwide. VNS involves the implantation of a programmable signal generator in the chest cavity from which stimulating electrodes carry electrical signals to the left vagus nerve. Components of the VNS are (a) a pulse generator; (b) a bipolar VNk lead; (c) a programming wand with accompanying software (d) a tunnelling tool; and (c) hand-held magnets. The hand held magnet briefly turns on the stimulation when held over the implanted device in the patient's chest. The exact mechanism of action is unclear but it has been shown to be well tolerated and safe in patients with partial onset epilepsy. Studies have attempted to clarify the circuitry in the brain which is activated during VNS but due to secondary effects which are difficult to monitor these studies are ambiguous. One study has suggested the locus coeruleus is important in the anticonvulsant effects of VNS possibly via the release of nor adrenaline.[89]

1.6.3 Surgical treatment

Approximately 50% of people with epilepsy will achieve good seizure control on one agent, 20-30% of non responders will achieve control with addition of a further agent but up to 30% will fail to respond to medication and in this subgroup surgery for treatment of refractory seizures should be considered. In patients with refractory epilepsy, advances in surgical procedures have offered considerable hope for improved outcomes giving seizure freedom in 50-70% of patients [90] with some variance in success rates according to epileptic focus and surgery program. Anterotemporal lobectomies are the most commonly performed procedure but in some centres amygdalohippocampectomy is performed as a first choice operation.[91]

1.7 Treatment of epilepsy and relationship to psychopathology

1.7.1 Surgery and psychopathology

As already discussed, patients with refractory epilepsy have a high prevalence of psychopathology and have an increased risk of pharmacoresistance. Psychiatric co morbidities have been associated with a worse surgical outcome after temporal lobectomy.[92] Early studies have linked surgery to serious psychiatric sequelae including increased rates of suicide, psychotic disorders, and depressive disorders.[66, 68] Later studies have shown conflicting results, i.e. an increase in rates of depressive and anxiety symptoms but no change in rates of suicide or psychosis.[93, 94]

In a systematic review, Macrodimitris and colleagues reported that most studies demonstrated either improvement in psychiatric outcome or no changes. [95] Only one study showed worsening in psychiatric symptoms post operatively with a higher anxiety in the context of ongoing seizures postoperatively. The main predictors of outcome were seizure freedom and presurgical psychiatric history. De novo psychiatric disorders occurred post operatively at rates of 1.1 to 18.1% with a predominance of milder psychiatric disorders. [95] Studies which show a decrease in the number of patients with postoperative psychopathology are complicated by the presumed rejection for surgery of patients with preoperative psychopathology.[96] As mentioned above some authors have noted a higher rate of de novo psychotic disorder in the post-operative population. However, lack of use of structured assessment and operational diagnostic criteria as well as the inclusion of immediately post-operative and possibly delirious patients complicates these findings. The methodology of this study was therefore specifically designed to address the shortcomings, i.e. prospective design, the use of gold standard diagnostic tools and adequate period of follow-up.

1.7.2 Surgical treatment and mood disorders

The most commonly reported psychiatric complications are mood changes and depression, generally occurring in the first 3 months post operatively which tend to be of brief duration. [97-99] In Devinsky's multi-centre trial which used the Beck Depression Inventory (BDI) assessment tool and Composite International Diagnostic Interview (although not performed by psychiatrists) it was found that the overall rate of depression decreased at 3 months after surgery and reduced further at 2 year follow up. [98]

The reported rate of de novo depression ranges from 5 -25%.[94, 98-100] The literature is unclear in distinguishing between depressive symptoms and depressive disorders. In one of the few prospective studies to use operational diagnostic criteria, Pintor and colleagues found decreases in depression (from 17.2% pre surgery to 4.3%) and anxiety disorders (from 21.5% to 14.2%) at 12 months post operatively.[101] In addition, patients with no pre surgical psychiatric condition had lower rates of post surgical psychiatric disorders than those with a psychiatric history and a de novo depressive disorder rate of 8%. However this study was limited by small numbers, limited follow-up time and quality of life indicators were not performed. Research to date on the rate of de novo depression cannot definitively clarify the rate of new onset depression post operatively for the reasons stated above- lack of prospective studies, lack of use of standardised diagnostic assessment and failure to distinguish between depressive symptoms and diagnosis of a depressive disorder. The methodology of this study was therefore specifically designed to address the shortcomings, i.e. prospective design, the use of gold standard diagnostic tools and adequate period of follow-up.

The likely predictors of postoperative depression are the existence of pre- operative depression and ongoing seizures also appears to be a risk factor.[89, 90] Laterality of resection as a risk factor remains unclear as does the age at time of surgery. The underlying mechanism for post operative depression also remains unclear although PET studies have found orbitofrontal hypometabolism in post operative depression [102].

It has been reported that depression can be improved by successful surgical treatment of epilepsy although continued psychotropics may be required to manage depression post operatively indicating that depression in epilepsy may be as a consequence of epileptic activity rather than a fixed structural defect.[97, 103] Other predictors such as age of epilepsy onset and gender appear to have a minimally predictive value in psychiatric outcomes postoperatively. Few studies have examined family history, social supports or life stress events as predictors of outcome.

1.7.3 Surgical treatment and psychosis

In the immediate post operative period symptoms such as agitation, somnolence, psychosis and dyphoria have been noted. However these are probably best considered as part of a delirium for which post-operative patients are significantly at risk due to a range of factors including use of steroids, barbiturates, anaesthetic agents and cerebral oedema.

Devinski at al demonstrated a 1.1% prevalence of de novo psychosis post operatively while Blumer et al found a higher rate of 14%.[97, 98] Broad ranges in findings could in part be explained by a lack of operational diagnostic criteria and a lack of standardised assessment tools.

It is unclear who is at risk of developing post operative psychosis. Factors such as abnormal personality traits preoperatively have been reported.[99] Unlike depression, there is no clear relationship between new psychotic symptoms postoperatively and seizure outcome.[99, 104]Laterality data examining psychosis is also conflicting with some studies reporting a higher rate of psychosis in those who undergo right sided temporal surgery [61, 104] but in other studies this has not been shown.[98, 99]

As in preoperative psychosis the aetiology of development of post operative de novo psychosis is unknown. It has been reported to occur more commonly with bilateral EEG abnormalities and structural abnormalities.[72] Axonal sprouting in projection sites around surgical area has been hypothesised as a factor. Following the surgery damaged axons may develop fine nerve processes however it is hypothesised that such aberrant re-innervation may result in development of de novo psychosis. Developmental lesions such as gangliomas and mesial temporal sclerosis may also be factors in de novo psychosis.[105] [69]. Despite the lack of clarity regarding risk factors and prevalence rates, identification of patients with psychosis both pre and post operatively is crucial in order to stabilise and improve adherence to post operative care.

1.7.4 Surgical treatment and personality disorders

Few studies have explored the influence of personality factors in surgical outcomes. The evidence that does exist suggests that patients with personality disorders are more likely to experience post operative psychiatric complications especially if they have ongoing seizures and right sided surgery.[99, 106]

1.7.5 Surgical treatment and quality of life outcomes

It is clear that health related quality of life (QOL) is impaired by seizures[107] and improves after surgery when seizures improve.[108] However most studies examine data with limited follow up periods and use retrospective assessments. To my knowledge, no study has been performed which has examined the relationship between QOL outcomes postoperative and psychiatric disorders.

1.8 Summary

While epilepsy surgery is associated with changes in mental state postoperatively, it remains unclear who is at risk for deterioration in mental health and conversely who is likely to benefit from surgical intervention. Quality of life outcome data related specifically to mental health is lacking as is the influence of personality factors in outcomes. Review of the literature has identified the primary hypothesis which requires examination –epilepsy surgery is detrimental to/impacts on mental health. In order to test this hypothesis a prospective cohort study of patients which examined a group of patients with pharmacologically resistant epilepsy before and after surgery was designed. In order to address the lack of standardised diagnostic tools in previous studies and to obtain a measure of severity of illness, this study used both the gold standard psychiatric diagnostic tool, the Structured Clinical Interview for DSM IV (SCID I) and uses the Hospital Anxiety and Depression Scale (HADS).

As already noted, the literature does not examine the question of the relationship of personality disorders to both surgical outcome and quality of life. This study tested the secondary hypothesis that personality factors influence both surgical outcome and quality of life measures. This study assessed patients for the presence of personality disorder using the SCID-II, a semi structured interview that can give dimensional scores of personality difficulties correlating to DSM-IV personality disorders.

Studies to date use seizure outcome as a proxy measure of overall quality of life outcome and no study was identified which examined the relationship between QOL outcomes postoperatively and psychiatric disorders. To test if mental health impacts more on quality of life than both seizure status and surgical outcome this study included a formal assessment of quality of life in epilepsy (QOLIE-89) and examined the association with psychiatric disorder, personality disorder and surgical outcome.

Chapter 2 Methodology

Overview.

In this chapter I will outline the methodology used in this thesis

2.1 Recruitment of the cohort sample:

The study was undertaken between July 2008 and July 2010, during which a total of 78 patients were admitted to the Epilepsy Monitoring Unit (EMU) for evaluation of suitability for surgery for medically refractory epilepsy. An additional 11 patients were recruited in 2011 as part of inter rater reliability evaluation. In total eighty nine potential participants were identified. Of these, seventy five participants agreed to participate in the study. During the time frame of the study, thirty one participants proceeded to surgery and were therefore evaluated postoperatively.

The author prepared the information leaflets, demographic and epilepsy information proforma, and consent forms which were distributed to study participants and these are included in Appendix 1.

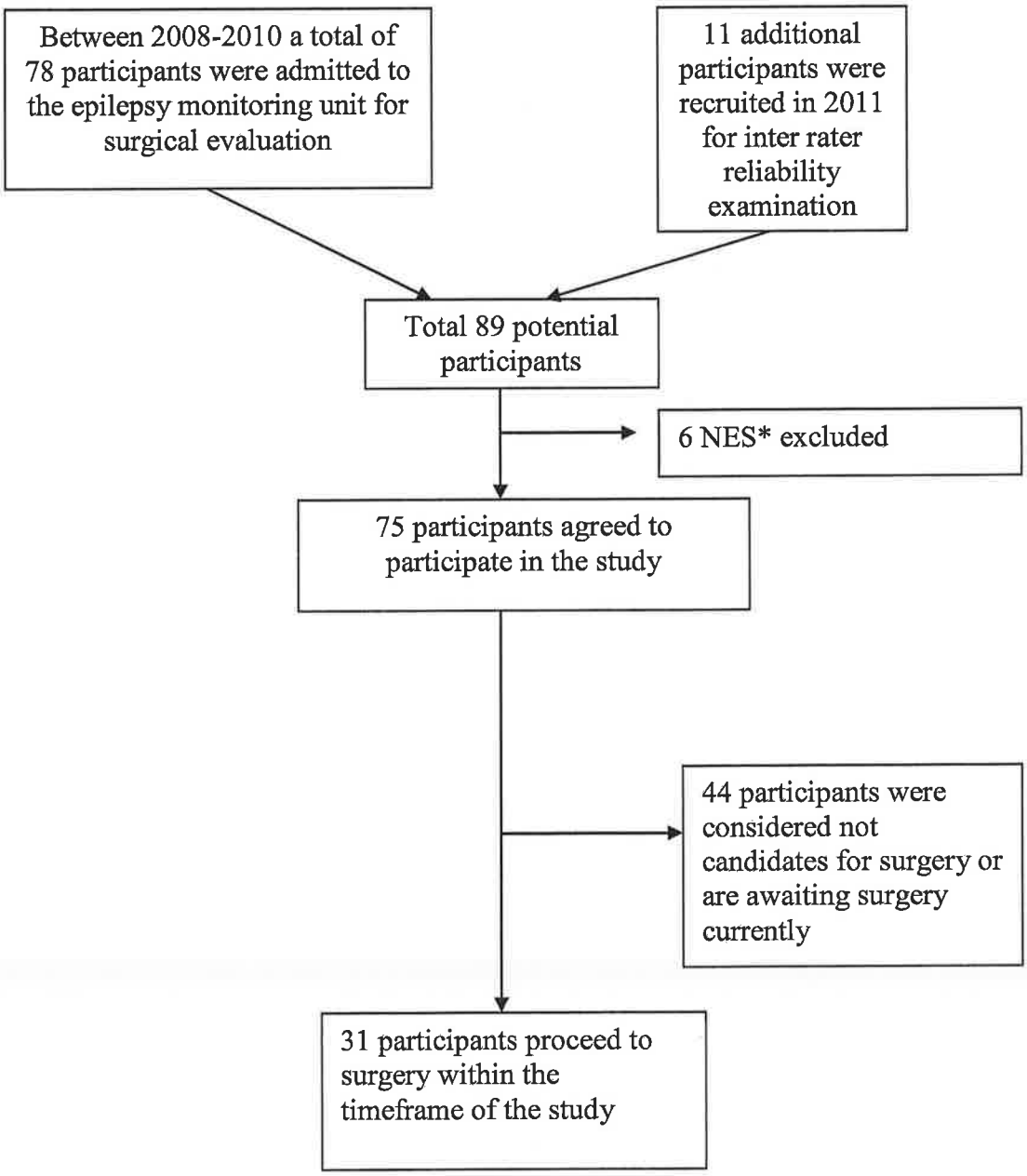

Figure 1 Flow Diagram: recruitment of participants. *NES - Non-epileptic seizure disorder

This research study was undertaken as part of a larger prospective study which aims to perform 1 and 2 year psychiatric assessment and follow up of medically refractory epilepsy patients who proceed to surgery.

Psychiatric evaluation is required as standard for preoperative assessment for all patients considered for epilepsy surgery in the National Neurosurgical Centre, Beaumont Hospital. Evaluation is performed on admission to the Epilepsy Monitoring Unit (EMU) or on attendance at the Neuropsychiatry outpatients department. Patients were admitted to the EMU department of Beaumont Hospital for seizure assessment through video EEG monitoring. Patients who presented psychiatric disorders at baseline assessment before surgery received pharmacological and/or psychological treatment according to the directions given by the responsible consultant psychiatrist.

2.2 Ethical approval

The study received ethical approval for all aspects of the study from Beaumont Hospital Research and Ethics Committee. Where significant psychiatric disorder was identified, patients were referred to the Department of Psychiatry for treatment. Patients were free to withdraw from the study whenever they desired without implications for their further treatment. (Letters of ethical approval, see Appendix 2)

2.3 Design

A prospective cohort study design was employed, allowing baseline pre-operative assessment of a cohort of medically refractory epilepsy patients and follow up postoperatively to determine impact of epilepsy surgery on psychiatric diagnosis and quality of life outcomes.

2.4 Participants

All patients admitted to the Epilepsy Monitoring Unit (EMU) or attending the Neuropsychiatric outpatients department (OPD) with medically refractory epilepsy and considered a candidate for epilepsy surgery and referred for psychiatric evaluation over a two year period were invited to participate in this study. All patients referred to EMU or OPD who are candidates for epilepsy surgery were identified as potential participants.

Approximately 90 patients are admitted to the EMU annually. A total of 75 patients with medically refractory epilepsy participated in the study. Assessments were performed by the author.

Thirty one patients proceeded to surgery within the timeframe of the study and were reassessed 3-6 months post operatively. Six patients were confirmed on assessment by video EEG to have non-epileptic seizure disorder and therefore did not proceed to surgery.

2.5. Demographics details of participants

Table 2.1 Demographic details of participants

	Pre-operative patients	Post-operative patients
Number of participants	75	31
Gender Male: female Percentage	28: 47 (36.8%:63.2%)	14:17 (45.2%:54.8%)
Mean Age	35 years	35 years

In the preoperative cohort, more females than males were assessed. This is most likely a reflection of the admission protocol to the 2 bedded epilepsy monitoring unit whereby males and females groups are admitted in block time periods. On examination of the data, gender did not have a significant impact on findings and data was normally distributed and therefore representative of the intractable epilepsy population generally.

2.6 Inclusion/Exclusion Criteria:

Inclusion criteria required participants to have a confirmed diagnosis of medically refractory epilepsy.

Exclusion criteria included patients below the age of 18 years and those unable to give informed consent.

2.7 Clinical evaluation of epilepsy

Epilepsy diagnoses were confirmed by EEG and neurological assessment. Seizures were classified using the revised International League against Epilepsy (ILAE) Commission on Classification and Terminology. This commission has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy. Generalized and focal are redefined for seizures as occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures is simplified. No natural classification for focal seizures exists; focal seizures should be described according to their manifestations (e.g., dys-cognitive, focal motor).[109]

2.8 Definition of medically refractory epilepsy

There are many varied definitions of medically refractory epilepsy. Many investigators define as seizures that are not controlled after an adequate trial with 2 first-line AEDs. Some advocate at least 3 regimens, including 1 trial of 2-drug therapy. If 3 trials of monotherapy with first-line drugs are not successful, the chance that the patient will respond to a fourth drug as monotherapy or polytherapy is only 5%. Determining intractability also requires an understanding of how the seizures affect the patients' quality of life (QOL) in terms of their psychological, interpersonal, and occupational functions; inability to drive may have a devastating effect of quality of life for someone reliant on car transport for occupation.

A consensus proposal by the Task Force of the International League Against Epilepsy (ILAE) Commission created an operational definition of medically refractory epilepsy. The ILAE defines medically refractory epilepsy as "a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."

Seizure freedom is defined as freedom from seizures for a minimum of 3 times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the preceding 12 months) or 12 months, whichever is longer.[88]

2.9 Other variables

Information on relevant variables was collected: age at epilepsy onset, history of febrile convulsions, birth or developmental abnormalities, family history of epilepsy, personal or family history of psychiatric disorders. Seizure frequency information was classified according to mean seizure frequency per month and presence of generalised tonic clonic seizures as indicators of severity of illness.

2.10 Post-Operative outcome assessment

Numerous classification systems as to surgical outcome are used by epilepsy centers. The Engel classification system, devised in 1987, is the most commonly used scale.[110] All seizure-outcome scales now in use contain subjective components, such as "worthwhile improvement" or "significant reduction." The Engel classification, for example, requires these subjective assessments to distinguish a class 3 outcome from a class 4 outcome, even though each center may have a different definition of worthwhile improvement.

The Engel classification system is as follows:

- Class 1 - Free of disabling seizures (completely seizure free; nondisabling, simple partial seizures only; some disabling seizures, but free of disabling seizures for at least 2 years; generalized convulsion with antiepileptic drug withdrawal only)
- Class II - Rare disabling seizures (initially free of disabling seizures, but rare seizures now; rare disabling seizures since surgery; more than rare disabling seizures, but rare seizures for at least 2 years; nocturnal seizures only)
- Class III - Worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 y)
- Class IV - No worthwhile improvement (significant seizure reduction; no appreciable change; seizures worse)

Class 1 includes patients with residual auras. Usually, auras do not bother the patient if they are infrequent. However, depending on the frequency and the nature of the auras (eg, intense fear), they can affect postoperative quality of life (QOL), even though they do not affect driving ability or independence

2.11 Evaluation of Quality of Life in Epilepsy

The Quality of Life in Epilepsy, 89-item (QOLIE 89) is health related quality of life self-report instrument that is specific for adults 17 years and older with epilepsy and covers 17 domains: (Seizure worry (5 items), Medication effects (3 items), Health discouragement(2 items), Work/driving/social function (11 items), Language (5 items), Attention/concentration (9 items), Memory (6 items), Overall quality of life (2 items), Emotional well-being (5 items), Role limitations: Emotional (5 items), Social isolation (2 items), Social support (1 item), Energy/fatigue (4 items), Health perceptions (6 items), Physical function (10 items), Role limitations: Physical (5 items) and Pain (2 items).

There are also 4 summary scales (Physical Health, Mental Health, Cognitive and Epilepsy-Targeted) and an Overall score. The time frame for some questions is the previous 4 week time period, unspecified for others.[111] (See Appendix 3)

Psychometric Properties: [111]

Scoring: 0 – 100 points with higher scores indicating a better quality of life.

Reliability: Internal consistency (Cronbach's α) was 0.97 for the overall score and 0 .78 - 0.92 for the subscales. Test-retest reliability was 0.88 for the overall score and 0.64 - 0.86 for the sub-scales. Thirteen of 17 subscales had test-retest reliability >0 .70.

Validity: Known-groups validity has been established for seizure frequency and severity, duration of post-ictal symptoms, AED toxicity, and employment. This correlates significantly with mood, neuroticism and objective measures of cognitive function

2.12 Structured Clinical Interview for DSM IV (SCID I)

All Psychiatric Diagnoses are categorized by the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition.[52] Better known as the DSM-IV, the manual is published by the American Psychiatric Association and covers all mental health disorders for both children and adults.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi-structured interview for making the major DSM-IV Axis I psychiatric diagnoses. The semi structured interview covers all major psychiatric diagnosis which meets diagnostic criteria as specified in the DSM-IV. Within each section the diagnosis is assessed for the presence of the symptom(s) currently or in the participants past.

Patients were assessed using the computerised Structured Clinical Interview of DSM IV I clinician administered version designed to be administered by a clinician or trained mental health professional.[112] This instrument was administered by the author.

The SCID I assessment is a well-established assessment tool with a reliability of between 0.6 and 0.93 for diagnoses of major depressive disorder and 0.64 and 0.95 for schizophrenia.[113] Reliability is enhanced by raters who are well trained and also by use in populations with a high base rate of disorders, as is the case in the epilepsy population. Superior validity of the SCID-I in comparison to standard clinical interviews has also been demonstrated. [114, 115] The administration time of the SCID-I is quite variable and can range from about 15 minutes on the short end (i.e., a subject with virtually no psychopathology or psychiatric history) up to several hours (i.e., a subject with extensive psychiatric comorbidity with a circumstantial style of speech). The administration time of the full SCID-I for a psychiatric patient likely averages around 90 minutes (whereas the administration time for a non-psychiatric patient is closer to one hour).

2.13 Structured Clinical Interview for DSM Personality Disorder (SCID II)

Diagnosis of personality disorder was assessed using the Computerised Structured Clinical Interview for DSM Personality Disorder (SCID II).[116] In addition to evaluating full criteria for personality disorder, the presence of personality disordered traits was also evaluated. Inter-rater reliability coefficients of this assessment tool range from 48 to 0.98 for categorical diagnosis (Cohen κ), and from 0.90 to 0.98 for dimensional judgements (Intra class correlation coefficient). Internal consistency coefficients were satisfactory (0.71-0.94). The results suggest that the SCID-II has adequate inter rater and internal consistency. [117] Skodol and colleagues[118] compared results of a personality assessment using the SCID-II with a longitudinal clinician observation diagnosis, and found that the diagnostic power of the SCID-II (ratio of true test results to total number of tests administered) to vary by diagnosis (from 0.45 for Narcissistic to 0.95 for Antisocial), with the diagnostic power being 0.85 or greater for five types of personality disorders. Several studies comparing the SCID-II to other measures of personality [119, 120] have shown rather poor agreement between the instruments; although no conclusion could be reached about which instrument was more valid.

2.14 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale has been found to be a reliable instrument for detecting states of depression and anxiety in the setting of an hospital medical outpatient clinic. (See Appendix 4) Unlike the SCID-I diagnostic tool, the anxiety and depressive subscales give valid measures of severity of disorders. The anxiety and depressive subscales are also valid measures of severity of the emotional disorder.[121] More than 200 published studies from most medical settings worldwide have reported experiences with the Hospital Anxiety and Depression Scale (HADS) which was specifically developed by Zigmond and Snaith for use with physically ill patients.[121] A review of validation data and clinical results undertaken by Hermann et al identified that in terms of reliability with few exceptions, the results show satisfactory or good item-total correlations within the two subscales.[122] Internal consistencies (Cronbach alphas) are also acceptable at 0.80 to 0.93 for the anxiety and 0.81 to 0.90 for the depression subscales . Retest reliability shows a high correlation, $r>0.80$, after up to 2 weeks.[122]

Validity:Factorial validity. Factor analysis of HADS resulted in nearly identical solutions with one depression and one anxiety factor. These factors remain stable across subgroups correlate highly with the corresponding subscales ($r>0.90$), and explain about 50% of variance.[122]

Discriminant and concurrent validity. There has been some discussion of whether the anxiety and depression subscales really measure different aspects of mood but subscale scores are clearly correlated in most patient groups. Nevertheless, there is sufficient evidence that both subscales differ in a clinically meaningful way. It has also been demonstrated that the HADS anxiety subscale shows significantly higher correlations with observer ratings and self-assessment questionnaires for anxiety (versus depression), while the depression subscale correlates better with external criteria for depression (versus anxiety). [122]

Sensitivity and specificity for identifying psychiatric "cases." One of the main purposes of the HADS is to identify psychological disturbances in medical patients. Like any other self-rating instrument it can indicate that a particular patient is probably a psychiatric "case" of anxiety or depression. It does, however, not allow one to make definite diagnoses and gives a dimensional rather than categorical representation of mood. There is no single, generally accepted cut-off score for the HADS. In their original study, Zigmond and Snaith [121] recommended two cut off scores for both subscales: 7/8 for possible and 10/11 for probable anxiety or depression (with possible ranges of 0-21 for each subscale).

2.15 Statistical Methodology

The data was analysed using the statistical package PASW, Statistics 18, Release Version 18.0.

2.15.1 Correlations

The principle aims of the study are as follows: To examine the prevalence and associations of psychiatric disorders in a cohort sample of patients with medically refractory epilepsy prior to undergoing surgical treatment, to examine the severity and associations of depressive and anxiety disorders in a cohort of patients with medically refractory epilepsy prior to surgical treatment, to evaluate quality of life in patients and examine associations with epilepsy variables and with psychiatric diagnosis variables. In line with these aims, the following *a priori* correlations were tested:

Medically refractory (term) cohort:

- Hospital Anxiety and Depression Scale (HADS) score and seizure frequency
- Quality of life in Epilepsy-89 (QOLIE-89) and seizure frequency
- Presence of psychiatric disorder and seizure frequency
- HADS and presence of psychiatric disorder
- HADS and QOLIE-89 scores
- QOLIE-89 score and presence of psychiatric disorder

Surgical cohort:

- Hospital Anxiety and Depression Scale (HADS) score and presence of psychiatric disorder
- HADS and Quality of Life in Epilepsy-89 (QOLIE-89) score
- QOLIE and presence of psychiatric disorder

In order to examine the impact of epilepsy surgery on psychiatric diagnosis, severity of psychiatric illness and on quality of life, I evaluated these post-operative correlations in relation to the success of surgery, as measured with Engel score, the Engel score was grouped into 3 or below, where benefit is displayed and 4 or above, no benefit seen. A variable was then calculated for change in QOLIE score and these two were correlated, controlling for the presence of a SCID dx.

2.15.2 T-test

The next aim of the study was to examine the impact of surgery in the medically refractory epilepsy cohort using a paired simple t-test, as the same people are tested twice and the test compares the means.

The t-test was used to test the following hypotheses:

- The prevalence of psychiatric diagnosis will be higher in the preoperative group compared with the post-operative group.
- The severity of depression and anxiety scores will be higher in the preoperative group compared with the post-operative group was
- The Quality of Life in Epilepsy 89 (QOLIE-89) scores will be higher in the post-operative group than preoperative group.
- The QOLIE-89 scores are associated with epilepsy severity and with presence and severity of psychiatric diagnosis.

2.15.3 ANOVA

In order to take into account various interactions, a repeated measures ANOVA because the same group was tested at two points in time, before and after was used.

As there was 2 with in subject variables, HAD score and QOLIE which changed over time, ENGEL outcome is the between subjects factor as this is the aspect of the group which was manipulated or changed. A significant result here means ENGEL outcome (or success in surgery) is shown to be having an effect or driving the changes seen in HAD and QOLIE so it can be stated that surgery is an effective intervention.

Chapter 3 Results

Overview

This chapter presents the results of the study, examining firstly the medically refractory epilepsy cohort, followed by the results pre and post operatively of the subgroup of participants who proceed to epilepsy surgery and finally examining the changes which occurred between the two groups. Demographic data, epilepsy data, psychiatric diagnosis and quality of life assessment results are presented for the entire cohort of 75 participants diagnosed with medically refractory epilepsy. This group are referred to throughout the chapter as the 'medically refractory epilepsy cohort' A subgroup of 31 participants from this medical refractory epilepsy cohort were assessed as suitable for surgical intervention and proceeded to surgery within the time frame of the study. The pre-operative and post-operative results of this cohort are presented separately, referred to as the 'surgical cohort'.

3.1 Medically refractory epilepsy cohort

3.1.1 Demographic data

Participants who were referred for surgical assessment to the epilepsy monitoring unit (EMU) and agreed to take part in the study were assessed and basic demographic information was collected.

All participants met the criteria for medically refractory epilepsy as defined by the International League Against Epilepsy criteria as "a failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom." [88]

Table 3. 2 shows the total cohort of seventy five participants (excluding those with non epileptic seizures), age at the time of assessment and gender. Demographics also include relationship status, employment, residential circumstance and level of education. Data was found to be normally distributed. The increased number of females in the cohort is a reflection of the admission policy to the 2 bedded epilepsy monitoring unit whereby males and females are admitted in gender blocks. The gender of participants was not found to be a statistically significant factor influencing results; also the gender difference of those who proceeded to surgery was not significant.

Table 3. 2 Demographic Data

Demographic data				
Participant	N= 75	Male =28 (36.8%)	Female = 47 (63.2%)	
Age	Mean Age 35yrs Range 18-62yrs			
Employment	Full Time 21 (27.6%)	Part Time 17 (22.4%)	Disability 20(26.3%)	Student 6 (7.9%) Other 11 (15.9%)
Relationship Status	Married 21(27.6%)	Single 53(71.1%)	Widowed 1(1.3%)	
Educational Level	Primary 13(17.3%)	Secondary 33(44%)	Tertiary 29(38.7%)	
Residence	Family 64(85.5%)	Alone 9(11.8%)	Other 1(1.3%)	Supported 1(1.3%)

3.1.2 Psychiatric history:

Thirty participants (40%) reported contact with psychiatric services or treatment of a psychiatric illness by their general practitioner prior to assessment while 45 (60%) had no such history. The psychiatric history was obtained by self report and by review of participant's medical chart. Table 3. 3 details the diagnosis reported by participants and/or noted in medical chart.

Table 3. 3 Psychiatric history

Psychiatric History	Number	Percentage
None	46	61.3%
Yes learning disability	2	2.6%
Yes psychotic disorder	5	6.6%
Yes depression/anxiety disorder	13	17.3%
Yes alcohol dependence syndrome	1	1.3%
Yes unclear diagnosis	8	10.7%
Total	75	100%

3.1.3 Family history of mental health problems

Forty six participants (61.3%) of the 75 participants had no family history of psychiatric disorder. Five (6.7%) had a family history of substance related disorders, 5 (6.7%) had a family history of schizophrenia or other psychotic disorders, 3 (4%) had a family history of mood disorder, 1 eating disorder family history and 9 (12%) were unsure of family history. Two participants (2.7%) had a family history of suicide. Of note this information was obtained by history from the participants and was not confirmed by medical records.

3.1.4 Family history of epilepsy

Forty seven participants (62.7%) had no family history of epilepsy, Nine (12%) had a first degree relative with epilepsy, six (8%) had a second degree relative affected, seven (9.3%) had a third degree relative with epilepsy and 2 (2.7%) had a relative with trauma related epilepsy. Four participants (5.3%) were unsure of their family history of epilepsy.

3.1.5 Birth complications, developmental delay or childhood illness

Fifty six (74.7%) had normal birth and no relevant childhood illness, 5 (6.6%) had a history of an abnormal birth (caesarean section, forceps etc.) and 7 (9.3%) had a history of developmental delay including 1 participant who was congenitally blind and 1 with a congenital hemi paresis. Five participants (6.6%) experienced a relevant childhood illness. Information was unknown in 2 (2.7%) participants.

Table 3.4 below also details additional relevant childhood illness. Twenty one (28%) of participants reported a history of febrile convulsions, 50 (66.7%) had no such history and 4 (5.3%) did not know if they had experienced febrile convulsions

Table 3.4 Birth or developmental abnormalities

Birth abnormalities/development delay/childhood illness	Frequency	Percent
apnoea episodes in infancy	1	1.3
blind congenital cataracts	1	1.3
breech delivery	1	1.3
caesarean-section birth	1	1.3
congenital right hemiparesis	1	1.3
developmental delay	5	6.7
difficult birth	1	1.3
encephalitis as a baby	1	1.3
fall age 10	1	1.3
forceps delivery	2	2.7
head injury age 7	1	1.3
Resection tumour in childhood	1	1.3
Nil	56	74.7
Unknown	2	2.7
Total	75	100.0

3.1.6 Epilepsy diagnosis according to site of origin

Epilepsy type was classified as either localization related epilepsy or generalized epilepsy. Localisation related epilepsy is also known as partial or focal epilepsy i.e. arising from a specific focus. Of the participants with localisation related epilepsies, sixty (78.89%) had a temporal lobe focus, nine (11%) had diagnosis of a frontal lobe focus, two (2.6%) had an occipital focus, one (1.3%) had a parietal focus and one(1.3%) patient had a co-morbid diagnosis of both Non- Epileptic Seizure Disorder (NES) and a temporal lobe focus.

Generalised epilepsies, in contrast, arise from many independent foci or from epileptic circuits involving the whole brain. Of the participants diagnosed with generalized epilepsy, one (1.3%) had Juvenile Myoclonic Epilepsy (JME), one (1.3%) had generalised idiopathic epilepsy (JIE) and one (1.3%) had generalized post traumatic epilepsy. The bar chart, Figure 3.1, shows epilepsy diagnosis according to site of origin.

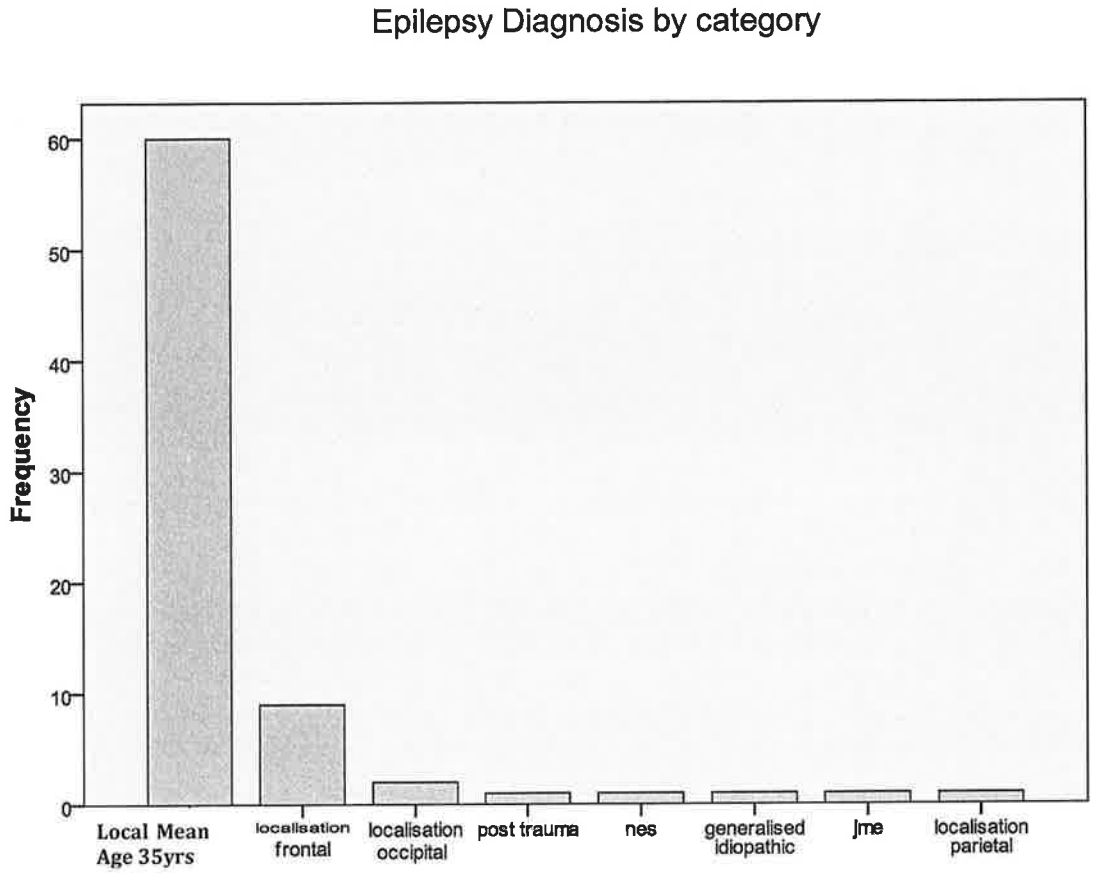

Figure 3.2 Epilepsy diagnosis categorised by site of origin. Non epileptic seizure (NES), Juvenile Myoclonic Epilepsy (JME)

3.1.7 Seizure Classification

Concepts and terminology for classifying seizures have, until recently, rested on ideas developed nearly a century ago. The Commission on Classification and Terminology of the ILAE have made specific recommendations to move this process along [109].

The recommendations include new terms and concepts for aetiology and seizure types as well as abandoning the 1989 classification structure and replacing it instead with a flexible multidimensional approach in which the most relevant features for a specific purpose can be emphasized. This is not a finished product and current published literature continues to use both the 1989 and 2010 classification systems. Due to these recent and as yet fully accepted changes epilepsy diagnosis in this study was classified using both systems. Table 3.5 shows seizure classification of the cohort according to 1989 guidelines while Table 3.6 characterises the group according to 2010 new classification system.

Table 3.5 Seizure classification according to 1989 International League Against Epilepsy Guidelines.

Seizure Type	Frequency	Percentage
Complex partial (cp) and 2 generalisation seizures	16	21.3
Simple partial (sp)	5	6.7
Sp and 2 generalisation seizures	1	1.3
Sp and cp seizures	10	13.3
Sp and cp and 2 generalisation	5	6.7
Cp and generalised tonic clonic (GTCS)	30	40.0
GTCS	3	4.0
Cp and aura	1	1.3
Unknown seizure type/missing information	4	5.3
Total	75	100.0

Table 3.6 Seizure classification according to International League Against Epilepsy 2010 guidelines.

Seizure Type	Frequency	Percentage
Generalised tonic clonic seizures	24	32%
Focal seizures w aura	1	1.3%
Focal w motor phenomena	18	24%
Focal w awareness altered	21	38%
Focal evolving to bilateral convulsive seizures	7	9.3%
Missing	4	5.3%
Total	75	100%

3.1.8 Seizure Frequency

Data on the number of seizures of any type per month also was gathered. The mean number of seizures per month was 20.87, standard deviation 33.31. This includes seizures of all types from simple partial to generalised tonic clonic seizures. Data was missing on 2 participants.

The frequency of seizure episodes per month was also subdivided as a measure of both the severity of epilepsy and presumed impact on the quality of life into groups: one or less seizures per month, between 2-4 seizures per month, between 5-15 seizures per month, between 5-30 seizures per month and greater than 30 seizures per month. Fifty two percent of participants had between 2 and 15 seizures per month. See Table 3.7

Table 3.7 Frequency of seizures grouped.

Frequency of seizures	Frequency	Percentage
1 or less per month	7	22.6%
2-4 per month	9	29%
5-15 per month	6	19.4%
16-30 per month	5	16.1%
30+ per month	4	12.9%
Total	31	100%

3.1.9 Handedness and hemisphere of seizure origin

Ten (13.3%) of participants were left handed, 65 (86.7%) were right handed. Thirty eight participants (50.7%) had seizures originating in the right hemisphere, 25 (33.3%) had left hemisphere origin while 9(12%) had bilateral points of origin. Hemisphere affected was unknown in 3 participants (4%).

3.1.10 Age of seizure onset

The mean age of seizure onset was 13.4 years of age (range 0-49 yrs, standard deviation 11.3yrs)

3.1.11 Psychiatric Diagnosis

Of the total cohort of seventy five participants, thirty seven (49.3%) participants had a Structured Clinical Interview for DSM IV(SCID I) diagnosis, thirty five (46.7%) had no diagnosis and data was missing in 3 participants.

Table 3.8 Psychiatric diagnosis of medically refractory epilepsy cohort

Psychiatric diagnosis	Frequency	Percentage
Yes	37	49.3%
No	35	46.7%
Missing	3	4%
Total	75	100%

Of these 16 (21.3%) had a diagnosis of a mood disorder: 9(12%) had major depressive disorder (MDD) in full remission, 1 (1.3%) had MDD on-going, 5 (6.7%) had depressive disorder not otherwise specified and 1 (1.3%) patient had depressive disorder due to a general medical condition. See Table 3.9 for details.

Table 3.9 Mood disorder in medical refractory epilepsy cohort. (NOS) Not otherwise specified, (GMC) general medical condition

Mood Disorder	Frequency	Percentage
No mood disorder	56	74.7
Major depressive disorder recurrent in remission	9	12.0
Major depressive disorder recurrent on going	1	1.3
Depressive disorder NOS	5	6.7
Mood disorder due to GMC	1	1.3
Missing data	3	4.0
Total	75	100.0

Eleven participants (14.5%) had a diagnosis of an anxiety disorder. Of these 1 (1.3%) had generalised anxiety disorder, 6 (8%) had panic disorder without agoraphobia, 1 (1.3%) had panic disorder with agoraphobia, 1(1.3%) had a specific phobia, 1 (1.3%) had social phobia and 1 (1.3%) had a diagnosis of post-traumatic stress disorder. Data was missing on 3 participants. Table 3.10 illustrates the details of anxiety disorder results.

Table 3.10 Anxiety disorder in medically refractory epilepsy cohort (PTSD) post-traumatic stress disorder

Anxiety disorder	Frequency	Percentage
No anxiety disorder	61	81.3
Generalised anxiety disorder	1	1.3
Panic disorder without agoraphobia	6	8.0
Agoraphobia without panic disorder	1	1.3
Specific phobia	1	1.3
Social phobia	1	1.3
PTSD	1	1.3
Total	72	96.0
Missing data	3	4.0
Total	75	100.0

Twenty three (30.6%) participants were diagnosed with a psychotic disorder according to DSM IV criteria. Data was missing on three participants. Of the participants diagnosed with a psychotic disorder, 2 (2.7%) were diagnosed with schizophrenia, 1 (1.3%) had a brief psychotic disorder, 7 (9.3%) had a psychotic disorder which could be directly attributed to a general medical condition i.e. epilepsy. The psychotic symptoms e.g hallucinations or delusions were directly temporally related to a seizure either as a delirium like state pre or post ictally or occurring as part of the seizure process itself. Thirteen participants (17.3%) had a psychotic disorder of longer duration which was related to seizures but which could not under the DSM classification system be attributed to a general medical condition (in this case epilepsy). These participants instead met the criteria of psychotic disorder not otherwise specified. This phenomenon has, under other classification systems, also been described as post or inter-ictal psychosis.

Table 3.11 Psychotic disorder in medically refractory epilepsy cohort (NOS) not otherwise specified, (GMC) general medical condition

Psychotic disorder	Frequency	Percentage
No psychotic disorder	49	65.3
Schizophrenia	2	2.7
Brief psychotic disorder	1	1.3
Psychotic disorder due to GMC with delusions	1	1.3
Psychotic disorder due to GMC with hallucination	6	8
Psychotic disorder NOS	13	17.3
Missing	3	4
Total	75	100

Four participants (5.3%) had a diagnosis of alcohol dependence or misuse disorder, 1 (1.3%) had an opiate dependence disorder.

Table 3.12 Substance or alcohol misuse in medically refractory epilepsy cohort

Substance or alcohol misuse	Frequency	Percentage
None	69	92
Alcohol dependence syndrome	4	5.3
Opiate dependence syndrome	1	1.3
Total	75	100

Forty nine participants completed the Structured Clinical Assessment of DSM IV criteria for personality disorder. Of these 2(2.7%) were diagnosed with avoidant personality disorder and 47(62.7%) had no personality disorder diagnosis.

Table 3.13 Personality disorder in medically refractory epilepsy cohort

Personality disorder	Frequency	Percentage
None	47	62.7
Avoidant personality	2	2.7
Missing	26	34.7
Total	75	100

3.1.12 Hospital Anxiety and depression Scale (HADS)

The mean Hospital Anxiety and Depression Scale (HADS) score for the cohort was 22.4 (std 16.4).

The mean anxiety subscale was 6.2. A score of 0-7 is normal, a score of 8 to 10 is suggestive of a disorder; score of greater the 11 indicates probable presence of a disorder.

The mean depression subscale score was 4.6.A score of 0-7 is normal, a score of 8 to 10 is suggestive of a disorder, score of greater the 11 indicates probable presence of a disorder.

3.1.13 Quality of Life in Epilepsy-89 (QOLIE-89)

Forty six participants of the 75 cohort completed the QOLIE- 89 questionnaire. The average overall total score was 46. This score is calculated using a weighted average of the multi-item scale score. Scores range from 0-100 where 100 indicate best possible quality of life.

3.1.14 Correlations in medically refractory epilepsy cohort

In order to test whether seizure frequency, as a presumptive measure of severity of illness, was related to QOLIE-89 or HADS score, the correlations between these factors were tested. I found no relationship in these scores with seizure frequency. This included no relationship between quality of life scores and seizure frequency.

However as would be expected HADS score, QOLIE and presence of a SCID diagnosis all correlated with each other. See Table 3.14 for details of results.

HADs and Presence of SCID I diagnosis, R =-0.332, p= 0.004

HAD and QOLIE, R = -0.626, p= 0.00 (This is the strongest correlation present)

QOLIE and Presence of SCID I diagnosis, R=0.449, p= 0.002

Table 3.14 Correlations between seizure frequency, SCID I diagnosis, Hospital Anxiety and Depression Scale (HADS) and Quality of Life in Epilepsy-89 (QOLIE-89) scores

		SCID I Diagnosis	Pre-op HADS Score	Seizure frequency grouped	Frequency of seizures pre-op	QOLIE total score pre-op
SCID I Diagnosis	Pearson	1	-.332**	-.023	-.096	.449**
	Sig. (2-		.004	.850	.428	.002
	N	72	72	70	70	46
Preoperative HADS Total score	Pearson	-.332**	1	.074	-.033	-.626**
	Sig. (2-	.004		.531	.784	.000
	N	72	75	73	73	46
Seizure frequency Grouped	Pearson	-.023	.074	1	.733**	-.012
	Sig. (2-	.850	.531		.000	.936
	N	70	73	73	73	45
Frequency of seizures pre-operatively	Pearson	-.096	-.033	.733**	1	.051
	Sig. (2-	.428	.784	.000		.739
	N	70	73	73	73	45
QOLIE total score pre-operatively	Pearson	.449**	-.626**	-.012	.051	1
	Sig. (2-	.002	.000	.936	.739	
	N	46	46	45	45	46

**. Correlation is significant at the 0.01 level (2-tailed).

3.2 Surgical Cohort

3.2.1 Demographic Data

Thirty one of the original cohort of participants with medically refractory epilepsy proceeded to surgery within the timeframe of the study. Forty four patients did not proceed to surgery within the time frame of study as the Beaumont Hospital Neurosurgical unit performs approximately 30 epilepsy surgeries per year. A small number of the cohort was deemed unsuitable for surgery by virtue of their lesion location or type or presence of multifocal epilepsy. The results of the assessments performed pre operatively and post operatively are presented in the following sections.

Table 3.15 shows the number of participants who underwent surgery, age at time of surgery and gender. Demographics also include relationship status, employment, residential status and level of education. Data was found to be normally distributed.

Table 3.15 Surgical group demographic data

Participants	**N= 31**	**Male =14**	**Female = 17**	
Percentage		**(45.2%)**	**(54.8%)**	
Age	Range		Mean	
	19-62		35 Years	
Employment	Full Time	Part Time	Disability	Student
	10 (32.3%)	9 (29%)	8 (25.8%)	1 (3.2%)
				Other
				3 (9.7%)
Relationship	Married	Single	Widowed	
Status	7 (22.6%)	23 (74.2%)	1 (3.2%)	
Educational	Primary	Secondary	Tertiary	
Level	2 (6.5%)	16 51.6%)	13 (41.9%)	
Residence	Family	Alone	Other	Supported
	27 (87.1%)	3 (9.7%)	1 (3.2%)	1 (3.2%)

3.2.2 Psychiatric family history

Eighteen participants (58.1%) reported no family history of psychiatric disorders. Three (9.7%) had a family history of substance abuse related disorders, 3 (9.7%) had a family history of schizophrenia or other psychotic disorder, 3 (9.7%) had a family history of mood

disorders, 1 (3.2%) reported suicide of a family member and family psychiatric history was unknown in 3 (9.7%) of participants. Of note this information was obtained by history from the participants and not confirmed by medical records.

3.2.3 Psychiatric history

Twenty four participants (77.5%) reported no previously contact with psychiatric services or treatment of a psychiatric illness by their general practitioner prior to assessment, 7 (24.4%) of participants reported a prior diagnosis of psychiatric illness. Of these, 1 participant had a reported history of psychosis, 1 had a history of a depressive episode, 1 had co-morbid depression and dysthymia, 1 had a history of overdose, and 2 reported a diagnosis of schizophrenia. The psychiatric history was obtained by self report and by review of participant's medical chart

3.2.4 Birth complications and developmental delay.

Twenty four participants (77.4%) had a normal birth and no history of illness in childhood or developmental delay, 1 (3.2%) had a history of developmental delay.

One (3.2%) reported apnoea episodes in infancy, 2 (6.4%) were delivered by forceps, 1(3.2%) was breech delivery, 1 (3.2%) reported a fall and head injury in childhood and 1 (3.2%) had resection of a cerebral tumour in childhood.

3.2.5 Febrile convulsions

Nine (29%) of surgical group had a history of febrile convulsion, 21 (67.7%) had no history. Data was unknown in one (3.2%) participant.

3.2.6 Handedness and hemisphere of seizure origin

Of the 31 surgical cohort, 4 (12.9%) were left handed and 27 (87.1%) were right handed. Fifteen (48.4%) had seizures originating in the right hemisphere, 14(45.2%) had a left sided seizure origin and 2 (6.5%) had bilaterally originating seizures.

3.2.7 Age at seizure onset

The mean age of seizure onset in the surgical cohort was 15 years of age, standard deviation 11.4.

3.2.8 Epilepsy diagnosis according to site of origin

Epilepsy type was classified as either localization related epilepsy or generalized epilepsy. Localisation related epilepsy is also known as partial or focal epilepsy i.e. arising from a specific focus. As would be expected in a cohort assessed as suitable for surgical intervention, the entire group had localisation related epilepsy. Of these 83.9% had temporal lobe localisation epilepsy, 12.9% had a frontal focus and 3.2% had an occipital focus.

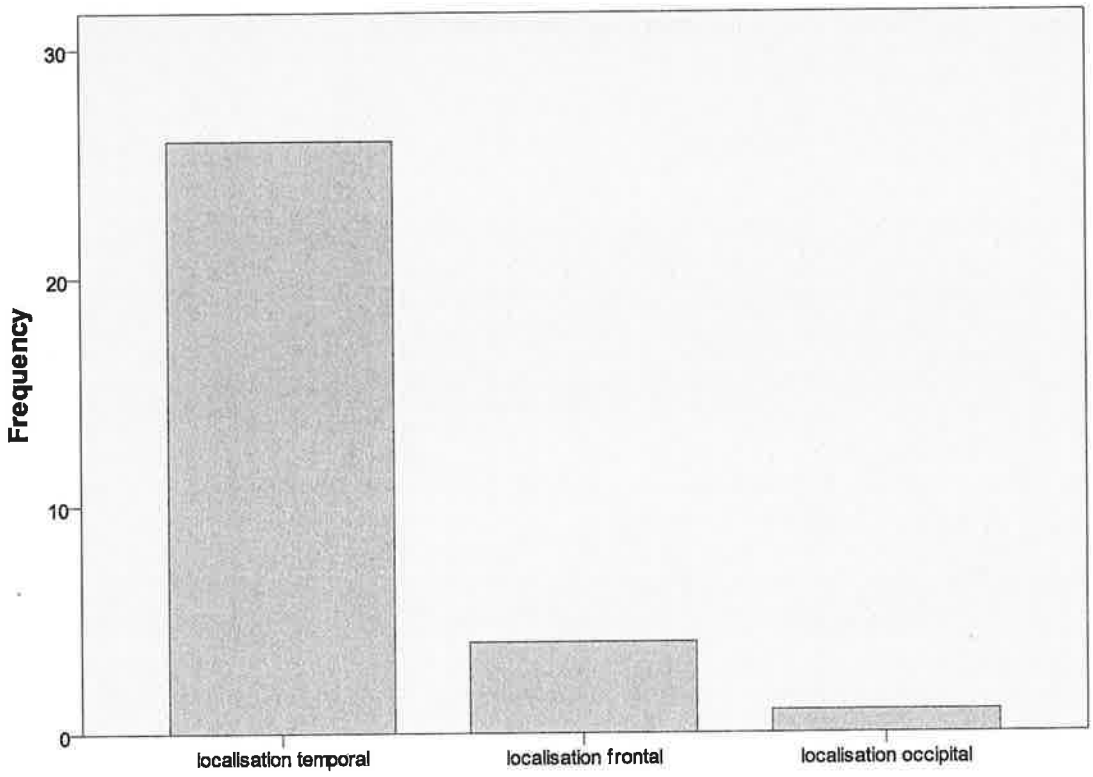

Figure 3.3 Surgical group: Frequency of epilepsy diagnosis by site of origin

3.2.9 Seizure classification

As previously discussed due to these recent and as yet fully accepted changes in seizure classification, epilepsy diagnosis in this study was classified using both the1989 and 2010 International League Against Epilepsy (ILAE) guidelines. Table 3.16 shows seizure classification of the cohort according to 1989 guidelines while Table 3.17 characterises the group according to 2010 new classification system. Both of these tables refer to seizures experienced preoperatively in this cohort who proceeded to surgery. Section 3.2.17 details the frequency and type of seizures experienced in this group following surgery, using the Engel classification of surgical outcome.

Table 3.16 Surgical cohort; seizure type according to International League Against Epilepsy 1989 classification. Table refers to the number of seizures experienced pre-operatively in the cohort who proceeded to surgery

ILAE 1989 classification seizure type	Frequency	Percentage
Complex partial (CP) and 2 generalisation	7	22.6
Simple partial (SP)	3	9.7
SP and 2 generalisation	1	3.2
SP and CP	5	16.1
SP and CP and 2 generalisation	1	3.2
CP and generalized tonic clonic (GTCS)	12	38.7
GTCS	1	3.2
Missing data	1	3.2
Total	31	100

Table 3.17 Surgical cohort: Seizure classification according to International League Against Epilepsy guidelines 2010. Table refers to the number of seizures experienced pre-operatively in the cohort who proceeded to surgery.

ILAE 2010 classification seizure type	Frequency	Percentage
Generalized tonic clonic seizures	8	25.8
Focal with aura	1	3.2
Focal with motor	3	9.7
Focal with awareness altered	6	19.4
Focal with awareness retained	2	6.5
Focal evolving to bilateral convulsive seizures	2	6.5
Missing data	9	29
Total	31	100

3.2.10 Seizure frequency

Data on the number of seizures of any type per month also was gathered. The mean number of seizures per month in the surgical group was measured preoperatively. The frequency of seizure episodes per month was also subdivided as a measure of both the severity of epilepsy and presumed impact on the quality of life into groups: one or less seizures per month, between 2-4 seizures per month, between 5-15 seizures per month, between 5-30 seizures per month and greater than 30 seizures per month.

Table 3.18 shows the number of seizures pre-operatively in the 31 patient cohort who proceeded to surgery according to this grouping. Table 3.19 shows the number of seizures post operatively in this 31 patient cohort.

Table 3.18 Surgery cohort: number of seizures experienced pre-operatively

Number of seizures per month	Frequency	Percentage
1 or less per month	7	22.6
2-4 per month		29
5-15 per month	6	19.4
16-30 per month	5	16.1
30+ per month	4	12.9
Total	31	100

Table 3.19 Surgery cohort: number of seizures experienced post-operatively

Number of seizures per month	Frequency	Percentage
1 per month or less	12	38.7
2-4 per month	19	61.3
Total	31	100

3.2.11 Psychiatric diagnosis

Table 3.20 Surgical cohort: psychiatric diagnosis. Data missing on 2 participants pre-operatively.

	Pre-operative assessment	Post-operative assessment
Participants	29	31
Psychiatric diagnosis	14 (48.3%)	12 (38.7%)
No psychiatric diagnosis	15 (51.7%)	19 (61.3%)

Preoperatively, 14 (48.3%) of participants were diagnosed with a psychiatric disorder, 15 (51.7%) had no psychiatric diagnosis.

Post operatively, 12 participants (38.7%) were diagnosed with a SCID I psychiatric disorder. Nineteen participants (61.3 %) did not meet criteria for a psychiatric disorder.

Preoperatively, 2 (6.9%) were diagnosed with a major depressive disorder in full remission, 2 (6.9%) had a depressive disorder not otherwise specified. Post operatively, 1 (3.2%) participant was diagnosed with a major depressive disorder ongoing and 1 participant met the criteria for depressive disorder not otherwise specified.

Preoperatively, 1 participant was diagnosed with schizophrenia, 2 (6.9%) met criteria for psychotic disorder due to a general medical condition (in this case epilepsy) while 6 (20.7%) had a psychotic disorder not otherwise specified.

In general this diagnosis was reached when participants experienced psychotic symptoms e.g. hallucinations around the time of seizures but either temporal relationship to seizures could not be definitively established or the duration of symptoms was not of sufficient length to make the diagnosis of psychotic disorder due to general medical condition. Post operatively 2 (6.5%) participants were diagnosed with schizophrenia, 1 had a psychotic disorder due to a general medical condition and 4 (12.9%) met the criteria for psychotic disorder not otherwise specified.

Preoperatively 2 participants (6.9%) had panic disorder without agoraphobia, 1(3.4%) had a specific phobia, 1 (3.4%) had post traumatic stress disorder. Post operatively 1 participant met the criteria for generalized anxiety disorder, 2 (6.5%) had panic disorder without agoraphobia , 1(3.2%) had agoraphobia without panic disorder , 1(3.2%) had a specific phobia and 1 (3.2%) had social phobia and 1 (3.2%) participant met the criteria for post traumatic stress disorder.

One participant met the criteria for alcohol dependence syndrome preoperatively but no longer met criteria post operatively.

No participants were diagnosed with a personality disorder preoperatively, however 2 (7.7%) of those who completed the Structured interview for DSM IV diagnosis of Personality Disorder met the criteria for Dependent Personality Disorder post operatively. Data was missing for 6 pre op participants and for post op participants.

Table 3.21 Surgical cohort: psychiatric diagnosis pre and post-operatively

	Pre-operative assessment N=29,		Post-operative assessment N=31		Significance
Psychiatric diagnosis	Yes	14 (48.3%)	12	(38.7%)	T= -2.2 P =0.03
	No	15 (51.7%)	19	(61.3%)	
Mood disorder	Yes	4 (13.8%)	2	(6.4%)	T=1.4 P=0.16
	No	25 (86.2%)	29	(93.5%)	
Psychotic disorder	Yes	9 (31%)	7	(22.6%)	T=1.7 P=0.83
	No	20 (69%)	24	(77.4%)	
Anxiety disorder	Yes	4 (13.7%)	7	(22.5%)	T=-0.6 P=0.6
	No	25 (86.2%)	24	(77.4%)	
Substance/alcohol misuse disorder	Yes	1 (3.5%)	0		T=1 P=0.33
	No	28 (96.5%)	31	(100%)	
Personality disorder	Yes	0	2	(7.7%)	T=2.8 P=0.007
	No	23 (100%)	24	(92.3%)	

3.2.12 Change in psychiatric diagnosis pre-operative to post-operative

As the sample cohort of participants was tested pre and post operatively, a paired t test was used to test for change in SCID I diagnosis between the 2 groups. T = -2.223 with significance level of 0.032, therefore a significant change has taken place, Table 3.22 for details.

Table 3.22 Paired T test change in SCID I diagnosis from pre to post-operative.

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 SCID I Dx pre-op -SCID I Dx post op	-.15	.43	.07	-.29	-.02	-2.22	39	.03

3.2.13 De Novo Psychiatric diagnosis post operatively

In order to clarify what changes had occurred, i.e. whether SCID diagnosis had resolved postoperatively or whether new de novo diagnosis had developed the cases were examined in more detail. Two patients (6.5%) developed de novo psychiatric disorders postoperatively, one generalised anxiety disorder and one developed a psychotic disorder not otherwise specified, (psychotic disorder NOS). Of the 13 patients who met the criteria for a SCID diagnosis preoperatively, 10 (32.3%) continued to meet the criteria for SCID diagnosis post operatively. Three patients (9.7%) no longer met the criteria for SCID diagnosis post operatively, i.e. the psychiatric disorder with which they were diagnosed pre operatively no longer was evident following surgery. Of these three patients, two were diagnosed preoperatively with psychotic disorder NOS and one was diagnosed with alcohol dependence.

3.2.14 Hospital Anxiety and Depression Scale (HADS)

Table 3.23 Surgical cohort: Hospital and Anxiety Scale pre and post-operative assessment. (SD) standard deviation

	Pre-operative	Post-operative	significance
HADS Overall Mean Score	22.3	7.7	T=4.94
(SD)	(16.3)	(6.9)	P<0.0001
HADS Anxiety Mean Score	5.6	5.2	
(SD)	(4.0)	(4.3)	
HADS Depression Mean Score	3.8	2.6	
(SD)	(3.2)	(3.0)	

Pre operatively the mean overall Hospital Anxiety and Depression Score (HADS) of the surgical cohort was 19.1(standard deviation 16.3). The mean anxiety score was 5.6(standard deviation 4.0). A score of 0-7 is normal, a score of 8 to 10 is suggestive of a disorder; score of greater the 11 indicates probable presence of a disorder. Preoperatively the mean depression score was 3.8(standard deviation 3.2). A score of 0-7 is normal, a score of 8 to 10 is suggestive of a disorder, score of greater the 11 indicates probable presence of a disorder.

Post operatively, the mean HADS total was 7.7 (standard deviation 6.9). The mean anxiety score was 5.2 (standard deviation 4.3). The mean depression score was 2.6, (standard deviation 3.0).

3.2.15 Quality of Life in Epilepsy (QOLIE) 89

Table 3.24 Surgical cohort QOLIE 89 score pre-operatively

Surgical cohort pre-operative QOLIE					
	N	Minimum	Maximum	Mean	Std. Deviation
QOLIE Total Score	22	46.5	96.6	69.3	13.7

Table 3.25 Surgical cohort QOLIE 89 score post operatively

Surgical cohort post-operative QOLIE					
	N	Minimum	Maximum	Mean	Std. Deviation
QOLIE Total Post Op	29	30.8	91.9	72.0	15.8

In this surgical cohort, the preoperative mean QOLIE score was 69 (standard deviation 13.7). Post operatively the mean QOLIE score was 72 (standard deviation 15.8).

This score is calculated using a weighted average of the multi-item scale score. Scores range from 0-100 where 100 indicate best possible quality of life.

3.2.16 Change in Hospital Anxiety and Depression Score

A paired t test was used to look at change between the groups of pre-operative and post-operative patients in the total HADS score.

The average Hospital Anxiety and Depression Scale (HADS) score of all 75 cohort pre operatively was 22.4 (std 16.4). Post operatively, the average HADS total was 8 Using a paired t test to examine change between these scores $t=4.936$, $p< 0.000$ therefore a significant change has occurred. Table 3.26 details these results.

3.2.17 Change in Quality of Life in Epilepsy 89 (QOLIE-89) score

A paired t test was used to examine change between the preoperative and postoperative group in Quality of Life in Epilepsy 89 Score (QOLIE-89). Pre operatively the average overall total score was 46. Post operatively the average QOLIE score was 72.
In QOLIE scores $t= -3.6$, $p= 0.002$, again a significant change has occurred. Table 3.26 3.25 details these results.

Table 3.26 Change in HADS score and QOLIE-89 score from pre to post operatively
Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 2	Pre-op HADS score overall - HADS score post op	12.68	14.98	2.57	7.45	17.90	4.94	33	P<0.00
Pair 3	QOLIE total score pre-op - QOLIE Total post Op	-7.28	9.27	2.02	-11.50	-3.06	-3.6	20	P=0.002

3.2.18 Surgical Outcome

Outcome of surgery was characterised according to the Engel Classification System as follows:

Class 1 - Free of disabling seizures (completely seizure free; non disabling, simple partial seizures only; some disabling seizures, but free of disabling seizures for at least 2 years; generalized convulsion with antiepileptic drug withdrawal only)

Class II - Rare disabling seizures (initially free of disabling seizures, but rare seizures now; rare disabling seizures since surgery; more than rare disabling seizures, but rare seizures for at least 2 years; nocturnal seizures only)

Class III - Worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 yrs)

Class IV - No worthwhile improvement (significant seizure reduction; no appreciable change; seizures worse)

Twenty seven participants (87%) scored between class 1 and class 3, which captures a range of outcomes from complete seizure freedom to a worthwhile improvement. Six participants (12.9%) met criteria for class four which described either no improvement or worsening of seizures.

3.2.19 Surgical Cohort Correlations

Examining the surgical group for the relationship between Structured Clinical Interview of DSM IV (SCID I) diagnosis, Hospital Anxiety and Depression Scales (HADS) score and Quality of Life in Epilepsy 89 (QOLIE-89) scale the following correlations were identified. The scores and diagnosis refer to assessments carried out on the surgical cohort post operatively.

HADS total score and presence of SCID I diagnosis, R= -0.44, p= 0.014, HADS total score and QOLIE, R= -0.827, p< 0.00 and QOLIE and presence of SCID I diagnosis, R= 0.569, p=0.001. See Table 3.27

Table 3.27 Surgical Cohort: correlations between Quality of life in Epilepsy-89 (QOLIE-89), Structured Clinical Interview for DSM IV (SCID I) diagnosis and Hospital Anxiety and Depression Scale (HADS) score Assessments performed following surgery.

Correlations		QOLIE Total post op	HADS score post op	SCID I DX post op
QOLIE Total post Op	Pearson Correlation	n/a	-0.827**	0.569**
	Sig. (2-tailed)	n/a	<0.001	0.001
	N	n/a	29	29
HADS score post op	Pearson Correlation	-0.827**	n/a	-0.438*
	Sig. (2-tailed)	<0.001	n/a	0.014
	N	29	n/a	31
SCID I DX post op	Pearson Correlation	0.569**	-0.438*	n/a
	Sig. (2-tailed)	0.001	0.014	n/a
	N	29	31	n/a

3.2.20 Relationship of surgery outcome to HADS, QOLIE-89 scores controlled for Psychiatric Diagnosis

In order to assess the relationship of surgical outcome to the above correlations, the surgical outcome as measured by ENGEL score was examined. ENGEL scores were grouped in to a score of 3 or below, where benefit is displayed and 4 or above where no surgical benefit was seen.

A variable was calculated for change in QOLIE score and these two were correlated, controlling for the presence of a SCID I diagnosis and a significant correlation was found, ENGEL outcome grouped and change in QOLIE, R= -0.483, significance level 0.036. See Table 3.28 for details. Therefore, as would be expected the surgical outcome influenced the improvement in quality of life scores.

Table 3.28 Relationship of surgery outcome to HADS, QOLIE-89 scores controlled for SCID I Diagnosis

Control Variables			Change in HADs	Change in QOLIE	Engel score Grouped	Engel score Outcome
SCID I diagnosis post-op	Change HADs	Correlation		-.375	.124	.215
		Significance (2-tailed)		.113	.612	.376
		df		17	17	17
	Change QOLIE	Correlation	-.375		-.483	-.450
		Significance (2-tailed)	.113		.036	.053
		df	17		17	17
	Engel grouped	Correlation	.124	-.483		.733
		Significance (2-tailed)	.612	.036		.000
		df	17	17		17
	Engel Outcome	Correlation	.215	-.450	.733	
		Significance (2-tailed)	.376	.053	.000	
		df	17	17	17	

3.2.21 ANOVA

In order to examine interactions further, repeated measures ANOVA was used as the same group was tested in two points of time. Two within subject variables changed over time: HADS score and QOLIE score, while the ENGEL classification of surgical outcome score is the 'between subjects' factor as this is the aspect of the group which was manipulated i.e. by surgical intervention. A significant result implies that success in surgery is shown to have been driving the changes in HADS score and QOLIE. However the results of analysis show the ANOVA giving a significant result for change but that the change is not relating to actual ENGEL outcome, therefore it cannot be stated that the surgical outcome was the factor driving the changes in test scores. It is worth noting that only 3 participants had an ENGEL score that was 4 or above and so 'not beneficial' , therefore the majority of participants had a successful reduction in ENGEL score with surgical intervention and it could be interpreted that statistically there were not enough people with an unsuccessful result for it to be used as a measure. Conversely the small number of unsuccessful surgical outcomes meant that the influence of the presence or absence of psychiatric disorder preoperatively could not be assessed in terms of its influence in affecting the outcome of surgery.

ANOVA of HADS and QOLIE scores with ENGEL outcome as the between subjects factor F= 761.736, significance 0.000, ENGEL outcome was not significant in result (F-1.237, sig 0.340)

ANOVA of SCID I Diagnosis and HADS score with ENGEL as the between subjects factor F= 293.610, sig 0.000, ENGEL outcome was not significant in result.

Chapter 4 Discussion

Overview

The principal aims of this thesis were to comprehensively assess and describe the psychiatric and psychosocial phenotype of a cohort of patients with epilepsy refractory to medical treatment by (1) examination of the prevalence and severity of psychiatric disorders and (2) assessment of quality of life and examination possible associations between psychiatric disorders, epilepsy variables, and quality of life. The secondary aim was to examine the impact of epilepsy surgery on psychiatric diagnosis, severity of psychiatric illness and on quality of life and examine possible associations between psychiatric diagnosis, quality of life and surgical outcome. The findings of the study are examined and considered in relation to the hypotheses formulated at the outset of the study.

In the thesis the following hypothesis were tested

1. In a sample of medically refractory epilepsy patients there will be a high rate of psychopathology, in particular mood, psychotic, anxiety and personality disorders.
2. In a sample of medically refractory epilepsy patients the prevalence of diagnosis will be higher in the preoperative group compared with the post operative group.
3. In a sample of medically refractory epilepsy patients the severity of psychiatric symptoms will be higher in the pre operative group compared with the post operative group.
4. Seizure frequency will be correlated with the presence and severity of psychiatric symptoms and with quality of life.

5. Surgical treatment of refractory epilepsy is associated with an improvement in quality of life.
6. Quality of life scores will be higher in the post-operative group than preoperative group.
7. Quality of life scores are associated with presence and severity of psychiatric diagnosis.

4.1 Summary of findings

This is the first Irish study to examine the relationship between psychopathology and medically refractory epilepsy which also prospectively assesses the impact of surgical intervention on psychiatric diagnosis and quality of life function. International studies to date have generally been limited by the failure to use standardised assessment tools for diagnosis.

The main findings of the examination of the medically refractory epilepsy cohort show that

1. Patients with medically refractory epilepsy have high rates of psychopathology (49%).
2. Seizure frequency is not correlated with the presence or severity of psychiatric symptoms Seizure frequency is not correlated with quality of life.
3. The presence of a psychiatric disorder and its severity is strongly correlated with quality of life.

The main findings of the assessment of the surgical cohort show that

1. There was a significant reduction in psychopathology following surgery.
2. There was a significant improvement in the severity of psychiatric symptoms experienced post-surgery.
3. There was a significant improvement in quality of life scores following surgery.
4. Surgery was associated with an improvement in quality of life and psychopathology but this improvement was not associated with the degree of success of the surgery.

4.2 Medically refractory epilepsy cohort

4.2.1 Medically refractory epilepsy cohort: psychiatric diagnosis

In this study 49% of participants with medically refractory epilepsy had a psychiatric diagnosis. Population based studies of epilepsy patients estimating rates of overall psychiatric co-morbidity are few, with studies estimating rates of between 11-35.5% [4, 5]. Smaller studies also consistently show higher rates of psychopathology in epilepsy although there is also consistent evidence indicating that psychiatric illness continues to remain under diagnosed or undertreated in patients with epilepsy.[7, 8] Studies examining the relationship between psychopathology and epilepsy to date have tended to be small, have used non representative sample and have failed to use standardised instruments.

The higher rate of psychiatric diagnosis found in this study therefore could be accounted for by the use of the standardised diagnostic instrument, therefore identifying more cases. A study which also used the Structured Clinical Interview for DSM IV (SCID 1) and examined a chronic epilepsy population found an identical rate of 49% of Axis 1 psychiatric disorder. [10] Also the population studied were those with severe medically refractory epilepsy therefore one can speculate that they more likely to have psychopathology than the general epilepsy population.

Forty per cent of the participants reported some contact with psychiatric services prior to the assessment for the purpose of this study. However only 28% of the cohort had been formally diagnosed with a psychiatric illness and only a small number were undergoing treatment for an identified psychiatric disorder. Therefore this study supports previous findings that not only are psychiatric illness underdiagnosed, disorders identified are also undertreated.

4.2.2 Medically refractory epilepsy cohort: mood disorders

Twenty one per cent of participants with medically refractory epilepsy were diagnosed with a mood disorder. This figure is similar to estimations of prevalence of mood disorder published to date. In a review, Herman and colleagues summarised the published prevalence rates of major depression in epilepsy and reported estimates ranging from 8-48% [9]

In one of the few multicentre studies which used operational diagnostic criteria, Jones and colleagues reported an identical figure of 21% for depressive disorder in patients with epilepsy [6]. The use of antidepressant therapy in epilepsy is well established and shown to be effective, with no impact on seizure threshold with the newer generation of antidepressant medications. It has also been demonstrated that treatment of depression can have a positive effect on the frequency of seizures. The need for comprehensive psychiatric evaluation and initiation of treatment of comorbid mood disorders in patients with epilepsy is therefore well established.

4.2.3 Medically refractory epilepsy cohort: anxiety disorders

Fifteen per cent of participants were diagnosed with an anxiety disorder; the majority of these were panic disorder without agoraphobia. This is consistent with previous published rates of anxiety disorders (21-32%) in this population[81, 101] The unpredictability and uncontrollability of seizures have been likened to the 'learned helplessness' model of Seligman thus predisposing potentially to the development of panic and/or depressive symptoms.

While many patients with epilepsy experience anxiety or panic type symptoms pre-ictally or as part of an aura, the use of the Structured Clinical Interview for DSM IV (SCID I) identifies those with true panic disorder i.e. panic symptoms occurring unexpectedly and not due to the direct physiological effect of a general medical condition. The use of the SCID I diagnostic interview therefore most likely accounts for this study identifying a percentage of participants with anxiety disorder at the lower range of the figures published.

4.2.4 Medically refractory cohort: psychotic disorder

Thirty per cent of participants were diagnosed with a psychotic disorder according to DSM IV criteria. This compares to population level studies which have shown the prevalence of psychosis in epilepsy in the range of 0.7-7%[4, 53, 54] These figures relate to the general epilepsy population rather than the medically refractory population evaluated in this study.

In studies which focused on temporal lobe or medically refractory populations the incidence of psychosis has been shown to be higher, ranging from 10-19%. [123] Of the participants in this study diagnosed with a psychotic disorder, 2.7% were diagnosed with schizophrenia, 1.3% had a brief psychotic disorder. Seventeen per cent had a psychotic disorder of longer duration which was related to seizures but which could not directly be attributed to a general medical condition (in this case epilepsy). These participants instead met the criteria of psychotic disorder not otherwise specified. Nine per cent had a psychotic disorder which could be directly attributed to a general medical condition i.e. epilepsy.

Confusion has developed as the application of DSM IV criteria can lead to a diagnosis of psychotic symptoms as 'psychosis secondary to a general medical condition' or 'primary psychotic disorder not otherwise specified' depending on a subjective judgement of epilepsy as a causative factor of psychotic symptoms.

The studies which showed lower rates of psychosis did not use the SCID I diagnostic interview which rigorously identifies all psychotic symptoms and codes according to DSM IV criteria. It is possible therefore that the studies which identified lower numbers of psychotic diagnoses disregarded psychotic symptoms directly related to seizures and focused instead on non-epilepsy related psychotic symptoms.

If this study excluded psychotic symptoms related to seizures or epilepsy (i.e. psychosis due to a general medical condition) then the rate of psychotic disorders was 21% which is similar to the rates published to date in similar populations.

4.2.5 Medically refractory cohort: Severity of mood and anxiety symptoms

It is generally accepted that a score of 8 or higher on both the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS) is indicative of probable 'caseness' i.e. the probable presence of an anxiety or depressive disorder.

In examination of the HADS anxiety subscales the mean score was 6.16. While the mean anxiety score of this population fell within the normal range, 11 of the 48 participants who completed this assessment met the criteria for suggestive of disorder or probable presence of a disorder i.e. 23% of participants had a score of 8 or higher on the anxiety subscale.

Similarly on the depression subscale the mean score was 4.63 but 23% of participants met the criteria for possible or probable presence of a depressive disorder. Research examining Hospital Anxiety and Depression Scale scores in the epilepsy population generally find 'caseness' numbers in the range of one third to half. [124]

It can be hypothesised that severity of epilepsy or seizure frequency may impact anxiety symptoms. However I found no significant correlation between HADS scores and seizure frequency suggesting that there is no direct relationship between the frequency of seizure episodes and the severity of anxiety or depressive symptoms.

Conversely, the presence of a psychiatric diagnosis, the HADS score and the QOLIE-89 scores all strongly correlated with each other. Therefore the findings of this study demonstrate that psychiatric symptoms and diagnosis impact significantly on quality for life in medically refractory epilepsy seizures but frequency of seizures does not. These findings, in addition to the published literature on the under diagnosis and treatment of psychiatric disorder further support the need for comprehensive psychiatric assessment and care for these patients with epilepsy, with important implications for potential improvements on quality of life.

4.2.6 Medically refractory cohort: Quality of life measures

The average total Quality of Life in Epilepsy-89 (QOLIE-89) score was 46. This figure is similar to those published to date in similar populations.[125] As indicated above, I found no relationship in Quality of Life score and seizure frequency although the presence of a psychiatric diagnosis and the severity of psychiatric symptoms was significantly correlated with Quality of Life scores. In recent years other studies have shown that the presence of a psychiatric comorbidity has a detrimental effect of quality of life but few have demonstrated that this is a more significant factor in determining quality of life than the severity of epilepsy symptoms.[126, 127]

4.3 Surgical cohort

4.3.1 Surgical cohort: Psychiatric diagnosis

There was a significant reduction in the rates of psychiatric diagnosis before and after surgery for epilepsy. Of the thirty one participants who proceeded to surgery within the timeframe of this study; preoperatively 48% were diagnosed with a psychiatric disorder while post operatively 38% were diagnosed with a disorder (p=0.032) . Therefore, the key hypothesis of this study, that the prevalence of psychiatric diagnosis will be higher in the preoperative group compared with the post operative group is proven.

This adds to the literature contradicting earlier studies which linked surgery to serious psychiatric sequelae including increased rates of suicide, psychotic disorders, and depressive disorders.[66, 68]Later studies have shown conflicting results, i.e. an increase in rates of depressive and anxiety symptoms but no change in rates of suicide or psychosis.[93, 94]

De novo psychiatric disorders have been reported as occurring post operatively at rates of 1.1 to 18.1% with a predominance of milder psychiatric disorders. [95] This study did identify de novo psychiatric disorder but, similarly, these tended to be of less severe type e.g. panic disorder, social phobia. These de novo diagnoses could be hypothesised to form part of an adjustment type spectrum following surgery and follow up study of the surgical cohort over a longer timeframe will establish if these diagnoses remain.

It has been hypothesised that studies which show a decrease in the number of patients with postoperative psychopathology are complicated by the presumed rejection for surgery of patients with preoperative psychopathology.[96] However no participants were rejected for surgery in this study based on presence of psychiatric pathology. This was the case despite the preoperative cohort demonstrating relatively high levels of psychopathology. This study therefore lends weight to the body of research establishing the potential benefit of surgery for patients with a comorbid psychiatric disorder.

The mechanism whereby psychiatric illness improved post operatively is not clearly understood. Removal of dysfunctional brain tissue may be a factor, reduced fear of seizures, the perception of an improved locus of control, and reduced antiepileptic drugs may all be factors.

4.3.2 Surgical cohort: Mood disorders

The most commonly reported psychiatric changes with surgery are mood changes and depression which have been reported to occur in the first 3-6 months following surgery. I examined the impact of epilepsy surgery of psychiatric diagnosis including depression on quality of life and examined possible associations between depression on quality of life and surgical outcome. Preoperatively 14% of participants were diagnosed with a depressive disorder. Although post operatively 6% met criteria for a depressive disorder, this did not reach statistical significance.

In one of the few other prospective studies to use operational diagnostic criteria, Pintor and colleagues[101] report similar findings with decreases in depression (from 17.2% pre surgery to 4.3%) at 12 month follow up. The numbers were sufficient in that study to establish that a significant change had taken place.

4.3.3 Surgical cohort: Anxiety disorders

Preoperatively 14% of participants were diagnosed with an anxiety disorder while postoperatively 19% were diagnosed with an anxiety disorder.

The increase in anxiety diagnoses post operatively were accounted for by 1 new diagnosis of agoraphobia, 1 of social phobia and 1 of generalised anxiety disorder. Previous studies have demonstrated a decrease in level of anxiety disorders[101] However the referenced study was carried out 12 months and longer following surgery. It could be hypothesised that the increase found in this study could be related to adjustment type symptoms following the potentially traumatic experience of undergoing surgery. Follow up and reassessment of the participants at longer time intervals may impact on the numbers meeting criteria for an anxiety disorder. Interesting while the majority of studies demonstrated a decrease in anxiety, a review by Macrodimitris et al identified three studies which noted similar findings of worsening anxiety symptoms post operatively and one study which reported a significant relationship between anxiety in the case of on-going seizures. [95, 98, 103, 128]

4.3.4 Surgical cohort: Psychotic disorder

This study found that 31% of the surgical cohort had a psychotic disorder preoperatively while 23% had a diagnosis at post-operative evaluation. Therefore an improvement in presence of psychotic disorders was found but the change did not achieve significant level, probably reflective of the small numbers studied. (t= 1.7, p= 0.83)

Some authors have noted a higher rate of de novo psychotic disorder in the post-operative population. However, lack of use of structured assessment and operational diagnostic criteria as well as the inclusion of immediately post-operative and possibly delirious patients complicates these findings.

The findings of this study support the position that epilepsy surgery does not increase the risk of developing a de novo psychotic illness.

4.3.5 Surgical cohort: Severity of anxiety and depression symptoms

Pre operatively the mean Hospital Anxiety and Depression Scale (HADS) score was 19.13, with a mean anxiety sub score of 5.59 and a mean depression score of 3.77.

Post operatively this study showed a reduction post to a mean score of 7.7, an anxiety subscale score of 5.19 and mean depression score of 2.58. This change was demonstrated to be statistically significant. The HADS tool is a well-established instrument for identifying the presence of and also assessing severity of anxiety and depression

symptoms in a medically unwell population. The second hypothesis, that the severity of anxiety and depression symptoms will be higher in the pre operative group compared with the post operative group is therefore proven.

The results therefore further support that surgical intervention for medically refractory epilepsy is shown to have a beneficially effect on the presence of and the severity of mood and anxiety symptoms.

As with the medically refractory epilepsy cohort, the HADS score correlated significantly with Quality of Life in Epilepsy 89 (QOLIE-89) scores and with the presence of a psychiatric diagnosis, in line with the hypothesis that quality of life is associated with both the presence and severity of psychiatric diagnosis.

4.3.6 Surgical cohort: Quality of life

The Quality of life in Epilepsy 89 (QOLIE-89) assessment pre and post operatively was shown to demonstrate significantly improvement (p=0.002). The hypothesis that surgical treatment of refractory epilepsy is associated with an improvement in quality of life is demonstrated. As with the entire cohort of medically refractory epilepsy participants, there was a significant negative correlation between the presence of a psychiatric disorder and the quality of life score.

4.3.7 Surgical cohort: Surgical outcome

A secondary aim of this thesis was that surgical outcome was a significant factor impacting on psychiatric diagnosis, severity of psychiatric symptoms (as assessed by the HADS) and on quality of life outcomes. Controlled for psychiatric diagnosis, surgical outcome was correlated to quality of life outcomes. As would be expected, the better the surgical outcome, the better the quality of life score.

In more detailed examination of the findings however, it could not be shown that surgical outcome was the factor driving the change in QOLIE and HADS score. In other words having surgery, irrespective of outcome was shown to improve scores, but whether surgery was successful or not did not impact on QOLIE and HADS scores. It must be noted that the vast majority of participants had a successful surgical outcome with Engel scores of less than 4, so therefore there were too few unsuccessful outcomes for it to be used as a measure. These findings are in keeping with the literature where there is a lack of clarity in relation to the link between success of surgery and psychopathology.[94, 98, 101] Undergoing surgery may also have a placebo impact, improving the self-report of psychiatric symptoms and also resulting in higher quality of life scores.

4.4 Critique of study design methods, sample and limitations

4.4.1 Was sample representative?

The Epilepsy Monitoring Unit (EMU) in Beaumont Hospital from which the study participants were recruited accepts referrals nationally of all patients deemed to be medically refractory and potentially candidates for surgery. As a result it can be assumed to be representative of the medically refractory epilepsy population in Ireland.
The increased number of females in the cohort is a reflection of the admission policy to the 2 bedded epilepsy monitoring unit whereby males and females are admitted in gender blocks. The gender of participants was not found to be a statistically significant factor influencing results; also the gender difference of those who proceeded to surgery was not significant.

Previous similar studies have considered that a selection bias may arise as patients with severe psychiatric co morbidities may not be considered surgical candidates and therefore not referred for surgical evaluation. However, in addition to primary role of surgical evaluation, the EMU in Beaumont Hospital also considers patients with medically refractory epilepsy for evaluation of seizures, Vagus Nerve Stimulator workup, and clarification of diagnosis if they are deemed not suitable for surgical intervention. These are all situations where the presence of a psychiatric disorder does not exclude referral for consideration for epilepsy surgery. It is therefore unlikely that the recruitment sample was a biased one in favour of those with less psychiatric comorbidities.

The findings of the study are limited by the relatively small sample that proceeded to surgery within the timeframe of the study. However of a potential 89 participants who were admitted to the EMU during the study timeframe, 75 agreed to participate. The high proportion of potential candidates who agreed to participate further reduces potential selection bias.

The absence of a control group is another potential limitation of the study. However the surgical group were comprehensively assessed at two points in time, pre and post operatively, effectively functioning as their own control group.

The self-report questionnaires, the Hospital Anxiety and Depression Scale (HADS) and the Quality of Life in Epilepsy 89 (QOLIE-89) Questionnaire together required approximately forty minutes to complete. As the participants were given the assessments to complete while admitted to the epilepsy monitoring unit, the response rate for these questionnaires was relatively high- approximately 61% for the QOLIE 89 and 64% for the HADS reducing the risk of a sampling bias.

4.4.2 Critique of evaluation and measures implemented in study

The Structured Clinical Interview for DSM IV (SCID I) was used to assess for psychiatric illness in this study. This is a well validated standardised diagnostic interview. As noted previously this diagnostic interview does not specifically consider the occurrence of psychotic phenomena in the context of seizures. As a result some diagnostic lack of clarity arose- depending on duration and temporal relationship to seizures; some of these psychotic symptoms were designated as psychosis not otherwise specified or psychosis due to a general medical condition.

A previous version of the SCID I diagnostic interview was designed for use in the epilepsy population i.e. the SCID-E. This may have resulted in an improved clarity in the diagnosis of psychotic disorders but this version is no longer available.

As noted in Chapter 1, a variety of disorders have been identified as specific to epilepsy such as interictal dysphoric disorder. Such disorders are not identified by the SCID I assessment diagnostic interview.

The Hospital Anxiety and Depression Scale (HADS) is well validated and has been extensively used in patients with epilepsy. Unlike other mood or anxiety self-assessment scales it focuses on the cognitive rather than the physical features of psychiatric symptoms and therefore is reliable in patients with comorbid physical illness.

Classification of epilepsy and seizure type was complicated by a number of factors. Firstly the international standard for diagnosis is unclear, with confusion between the previous International League Against Epilepsy Guidelines and the more recently published revised version in 2010.

In addition, while the assessor had access to the medical notes and therefore could classify as per the treating neurologists classification and self report, at times the notes were unclear as to exact diagnosis according to ILAE standards and required the assessor to make a judgement as to epilepsy or seizure type classification.

Although the Quality of Life in Epilepsy 89 tool is an internationally accepted one, it requires approximately thirty minutes for completion. Shorter versions of this assessment tool e.g. the QOLIE 31 have been shown to be valid, with equitable sensitivity and specificity therefore may be an option for use in follow-up studies.

4.2.3 Other limitations of the study

The study participants were selected due to their medically refractory epilepsy diagnosis. However while the majority had temporal lobe epilepsy there was a large degree of heterogeneity in organic diagnosis within this group, making it difficult to extrapolate the findings to any specific epilepsy diagnosis.

While the participants were assessed at two time periods thus functioning as their own control group, controlling for confounders such as family history of psychiatric illness, drug or alcohol use, it may have been useful to reassess those who did not proceed to surgery at the same time points in order to assess the course of psychiatric illness in those who do not have surgery. The relatively short period of between 6 months to a year follow up of the study is another potential limitation which may bias the prevalence rates of psychopathology in patients who underwent surgery in view of the relatively low prevalence and long latency period of some psychiatric disorders.

I was not blinded to the psychiatric diagnoses of those who underwent surgery. This may have led to interviewer bias at the follow up assessment with an attempt to detect changes coinciding with expectations. This bias may led to a decrease in the identification of psychiatric symptoms post operatively. However the use of a structured assessment tool in addition to self-administered questionnaires reduced this potential interviewer bias. IN addition, the numbers of subjects interviewed and the time period between assessments further reduced this potential interview bias. The fact that improvements post operatively were demonstrated by both the SCID I structured interview and also by the self-reported questionnaires supports this point.

Participants may also overestimate the occurrence of symptoms preoperatively and underestimate post operatively due to an inherent expectation of positive impact of surgery leading a recall bias. Again the use of a structured interview reduces this risk. Also the HADS and QOLIE 89 self-report specifically refer to symptoms experienced in the last 2 weeks or month respectively, again reducing the risk of recall bias.

Another potential bias of the prospective cohort design is loss to follow-up. However all participants who proceed to surgery within the time frame were followed up therefore eliminating loss to follow up bias. It could also be argued that as only 31 of the original 75 cohort proceeded to surgery within the timeframe of the study, the additional 44 participants should be reassessed at the same time points as the surgical cohort in order to control fully for bias and other potential confounders. As most of these participants do not continue to attend the epilepsy program it would have been logistically difficult to include these participants as a control group.

4.5 Implications for clinical practice

Patients with epilepsy have significantly higher prevalence rates of psychiatric disorder than the general population.

All patients with medically refractory epilepsy should be assessed for psychiatric comorbidity. The presence of psychiatric comorbidities has been shown to have a more significant impact on quality of life than seizure frequency. Therefore identification and treatment of these co morbidities is vital to improve quality of life.

This study demonstrated a positive effect of surgery for medically refractory epilepsy on mental health. Therefore the presence of a psychiatric disorder should not be considered a contraindication for surgical treatment when medically indicated.

4.6 Implications for future clinical research

This study demonstrated that surgical intervention for refractory epilepsy is associated with an overall improvement the presence of psychiatric diagnosis as well as a reduction in the severity of psychiatric symptoms experienced and an improved quality of life. Future study over a longer time frame would establish the natural course of these improvements.

Future studies with larger cohorts may clarify the relationship between the above outcomes and the success of surgery, if such a relationship exists. The current study findings were limited for the very few participants who had a negative surgical outcome.

The current study did not assess the impact of treatment of the identified psychiatric disorders and the potential impact on seizures.

The present study found that quality of life was influenced more by psychiatric comorbidity than by seizure frequency. Future study would establish the impact of treating these psychiatric comorbidities.

4.5 Conclusions

In this study, I have shown the high prevalence of psychiatric comorbidity (49%) in patients with medically refractory epilepsy.

In addition, I have demonstrated that the presence of a psychiatric disorder and the severity of the symptoms of psychiatric illness are correlated strongly with quality of life.

Overall, this study has demonstrated that undergoing surgery for medically refractory epilepsy has an overall positive impact on mental health with a significant reduction in the severity and prevalence of psychiatric symptoms and an improved quality of life.

List of Tables

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Appendices

1. Patient Information Leaflets
2. Consent Form
3. Hospital Anxiety and Depression Scale
4. Quality of Life in Epilepsy-89

Appendix 1

Patient Information Leaflet

Protocol Title:

Treating refractory epilepsy: Psychiatric and psychosocial morbidity before and after surgical treatment.

You are being invited to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

WHY IS THIS STUDY BEING DONE?

Epilepsy is associated with an increased risk of mental health problems (such as low mood), in addition to psychological and social problems related to the condition (e.g. employment and driving restrictions). People with epilepsy that is poorly controlled by medication have an increased risk of these problems. Unfortunately doctors have little knowledge of the extent of these problems and the characteristics of those at increased risk. Many patients with epilepsy that responds poorly to medication are referred for surgery- to either remove any lesions causing the seizures or insert a device called a vagal nerve stimulator. These treatments can help to reduce the number and severity of seizures and need for medication. In addition they can also

improve psychological and social functioning. Unfortunately some patients can experience problems after treatment related to mental health and social functioning

. This study aims to find out the frequency and severity of any difficulties before and after surgery.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is being organised by the Department of Psychiatry in Beaumont Hospital. The study is not being funded by a pharmaceutical company.

HOW WILL IT BE CARRIED OUT?

This study is due to commence in August. Approximately one hundred patients will be involved in the study. All patients who have been admitted to the epilepsy monitoring unit or Beaumont Hospital for surgery will be asked to participate in the study.
This is a follow up study, which means that patients who agree to participate will be reviewed by a neuropsychiatrist after surgery when they attend the clinic for follow-up. The rates of mental health and social problems will be compared to results before treatment.

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

This study will involve two assessments, one before and one after surgery. You may withdraw from this study at any time including prior to the second assessment should you wish. A neuro-psychiatrist (Dr Helen Barry) assesses all patients admitted to the Epilepsy Monitoring Unit during their stay. If you are willing to participate in this study you will also meet with Dr Barry when you attend outpatients 6 months after surgery or insertion of vagal nerve stimulator. In outpatients you will be interviewed for approximately sixty minutes and be given some questionnaires to complete.

WHAT ALTERNATIVE TREATMENTS ARE AVAILABLE TO ME?

It is up to you whether to take part or not. Even if you do decide to take part you are free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive.

BENEFITS:

The aim of this study is to gather more information on mental health of people with epilepsy, which may be of benefit in future treatment/assessment of patients. You will receive a comprehensive psychiatric assessment prior to surgery whether you participate in the study or not.

CONFIDENTIALITY ISSUES:

As part of the study the investigators will review your medical notes. Your general practitioner will be informed that you are participating in the study although the contents of assessments will be confidential. Further information may be elicited from a family member by interview but only with your permission. All information that is collected about you during the study will be kept strictly confidential and restricted to the researchers. This information may be used in future studies subject to ethics committee approval. Statistical results of the study may be presented in medical journal but no identifiable information about you will be given to any outside party.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study, or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be effected.

For additional information now or any future time please contact:

Dr Helen Barry, Neuropsychiatry Fellow, Beaumont Hospital

Phone No. 018093740

Appendix 2

CONSENT FORM FOR STUDY

Treating refractory epilepsy: Psychiatric and psychosocial morbidity before and after surgical treatment.

Participant Name _____

Name of Doctor and Telephone Number: Dr Helen Barry (Co-Investigator);8093740

Please tick the appropriate answer.

I confirm that I have read and understood the Information Leaflet dated _____ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered. ☐**Yes** ☐**No**

I understand that my participation in this study is entirely **voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care. ☐**Yes** ☐**No**

I understand that records may be viewed by members of the research team for this study only ☐**Yes** ☐**No**

I understand that my spouse/family members' identity will remain confidential at all times. ☐**Yes** ☐**No**

I have been given a copy of the Information Leaflet and this Consent form for my records. ☐**Yes** ☐**No**

FUTURE USE OF ANONYMOUS DATA:
I agree that I will not restrict the use to which the results of this study may be put. I give my approval that coded data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.) ☐**Yes** ☐**No**

Patient _____ _____
Signature and dated Name in block capitals

To be completed by the Principal Investigator or his nominee.

I the undersigned, have taken the time to fully explained to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, the experimental nature of the treatment, as well as the possible benefits and have invited him/here to ask questions on any aspect of the study that concerned them.

Signature:	**Name in Block Capitals:**	**Qualification:**	**Date:**

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.

Appendix 3

Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

A I feel tense or wound up':

Most of the time 3

A lot of the time 2

From time to time occasionally 1

Not at all 0

D I still enjoy the things I used to enjoy:

Definitely as much 0

Not quite so much 1

Only a little 2

Hardly at all 3

A I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly 3

Yes, but not too badly 2

A little, but it doesn't worry me 1

Not at all 0

D I can laugh and see the funny side of things: As much as I always could 0

Not quite so much now 1

Definitely not so much now 2

Not at all 3

A Worrying thoughts go through my mind a great deal of the time 3

A lot of the time 2

From time to time, but not too often 1

Only occasionally 0

D I feel cheerful:

Not at all 3

Not often 2

Sometimes 1

Most of the time 0

A I can sit at ease and feel relaxed:

Definitely 0

Usually 1

Not Often 2

Not at all 3

D I feel as if I am slowed down:

Nearly all the time 3

Very often 2

Sometimes 1

Not at all 0

A I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all 0

Occasionally 1

Quite Often 2

Very Often 3

D I have lost interest in my appearance:

Definitely 3

I don't take as much care as I should 2

I may not take quite as much care 1

I take just as much care as ever 0

A I feel restless as I have to be on the move:

Very much indeed 3

Quite a lot 2

Not very much 1

Not at all 0

D I look forward with enjoyment to things:

As much as I ever did 0

Rather less than I used to 1

Definitely less than I used to 2

Hardly at all 3

A I get sudden feelings of panic:

Very often indeed 3

Quite often 2

Not very often 1

Not at all 0

D I can enjoy a good book or radio or TV program:

Often 0

Sometimes 1

Not often 2

Very seldom 3

Scoring (add the As = Anxiety. Add the Ds = Depression). Zigmond and Snaith (1983)

Appendix 4

QUALITY OF LIFE IN EPILEPSY
QOLIE-89 *(Version 1.0)*

Patient Inventory

Do Not Write in This Space

Today's Date____/____/____

Patient's Name_____

Patient's ID#_____

Gender: ☐ **Male** ☐ **Female** **Birthdate**____/____/____

INSTRUCTIONS

This survey asks about your health and daily activities. **Answer every question** by circling the appropriate number (1, 2, 3. . .).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

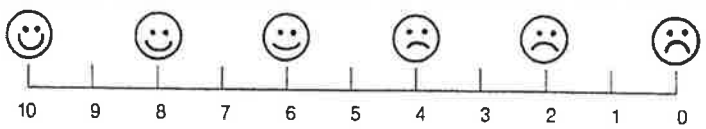
Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is: (Circle one number)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Overall, how would you rate your quality of life?

(Circle one number on the scale below)



Best Possible Quality of Life

Worst Possible Quality of Life (as bad as or worse than being dead)

3. **Compared to 1 year ago**, how would you rate your health in general **now**?

Do Not Write in This Space

	(Circle one number)
Much better now than 1 year ago	1
Somewhat better now than 1 year ago	2
About the same as 1 year ago	3
Somewhat worse now than 1 year ago	4
Much worse now than 1 year ago	5

4–13: The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, **how much?**

		(Circle 1, 2, or 3 on each line)		
		Yes, limited a lot	Yes, limited a little	No, not limited at all
4.	*Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
5.	*Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
6.	Lifting or carrying groceries	1	2	3
7.	Climbing *several* flights of stairs	1	2	3
8.	Climbing *one* flight of stairs	1	2	3
9.	Bending, kneeling, or stooping	1	2	3
10.	Walking *more than one mile*	1	2	3
11.	Walking *several blocks*	1	2	3
12.	Walking *one block*	1	2	3
13.	Bathing or dressing yourself	1	2	3

The following questions are about your regular daily activities, such as working at a job, keeping house, taking care of children, attending school, volunteer work, or taking part in community services.

Do Not Write in This Space

14–18: During the **past 4 weeks**, have you had any of the following difficulties with your regular daily activities or work **as a result of any physical problems**? (Please answer **YES or NO** for each question by circling 1 or 2 on each line)

		YES	NO
14.	Cut down on the *amount of time* you spent on work or other activities	1	2
15.	*Accomplished less* than you would like	1	2
16.	Were limited in the *kind* of work or other activities you do	1	2
17.	Had *difficulty* performing the work or other activities you do (for example, it took extra effort)	1	2
18.	Did your work or other activities *less carefully* than usual	1	2

19–23: During the **past 4 weeks**, have you had any of the following difficulties with your regular daily activities or work **as a result of any emotional problems** (such as feeling depressed or anxious)? (Please answer **YES or NO** for each question by circling 1 or 2 on each line)

		YES	NO
19.	Cut down on the *amount of time* you spent on work or other activities	1	2
20.	*Accomplished less* than you would like	1	2
21.	Were limited in the *kind* of work or other activities you do	1	2
22.	Had *difficulty* performing the work or other activities you do (for example, it took extra effort)	1	2
23.	Did work or other activities *less carefully* than usual	1	2

24. How much **bodily pain** have you had during the **past 4 weeks**?

	(Circle one number)
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

25. During the **past 4 weeks**, how much did **bodily pain** interfere with your normal work (including both work outside the home and housework)?

	(Circle one number)
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

26. During the **past 4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

	(Circle one number)
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

Do Not Write in This Space

27–35: These questions are about how you **FEEL** and how things have been for you during the **past 4 weeks**. For each question, please indicate the one answer that comes closest to the way you have been feeling.

Do Not Write in This Space

How much of the time during the **past 4 weeks**. . .

(Circle one number on each line)

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
27.	Did you feel full of pep?	1	2	3	4	5	6
28.	Have you been a very nervous person?	1	2	3	4	5	6
29.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
30.	Have you felt calm and peaceful?	1	2	3	4	5	6
31.	Did you have a lot of energy?	1	2	3	4	5	6
32.	Have you felt downhearted and blue?	1	2	3	4	5	6
33.	Did you feel worn out?	1	2	3	4	5	6
34.	Have you been a happy person?	1	2	3	4	5	6
35.	Did you feel tired?	1	2	3	4	5	6

36–43: How much of the time during the **past 4 weeks**. . .

(Circle one number on each line)

Do Not Write in This Space

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
36.	Has your epilepsy limited your social activities (such as visiting with friends or close relatives)?	1	2	3	4	5	6
37.	Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
38.	Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
39.	Were you discouraged by problems related to your health?	1	2	3	4	5	6
40.	Have you worried about having another seizure?	1	2	3	4	5	6
41.	Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6
42.	Were you discouraged by your epilepsy-related problems?	1	2	3	4	5	6
43.	Have your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?	1	2	3	4	5	6

44–48. Please choose the answer that best describes how **TRUE or FALSE** each of the following statements is for you. (Circle one number on each line)

Do Not Write in This Space

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
44.	I seem to get sick (any kind of sickness) a little easier than other people	1	2	3	4	5
45.	I am as healthy as anybody I know	1	2	3	4	5
46.	I expect my health to get worse	1	2	3	4	5
47.	My health is excellent	1	2	3	4	5
48.	When there is an illness going around, I usually catch it	1	2	3	4	5

49. How has the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?

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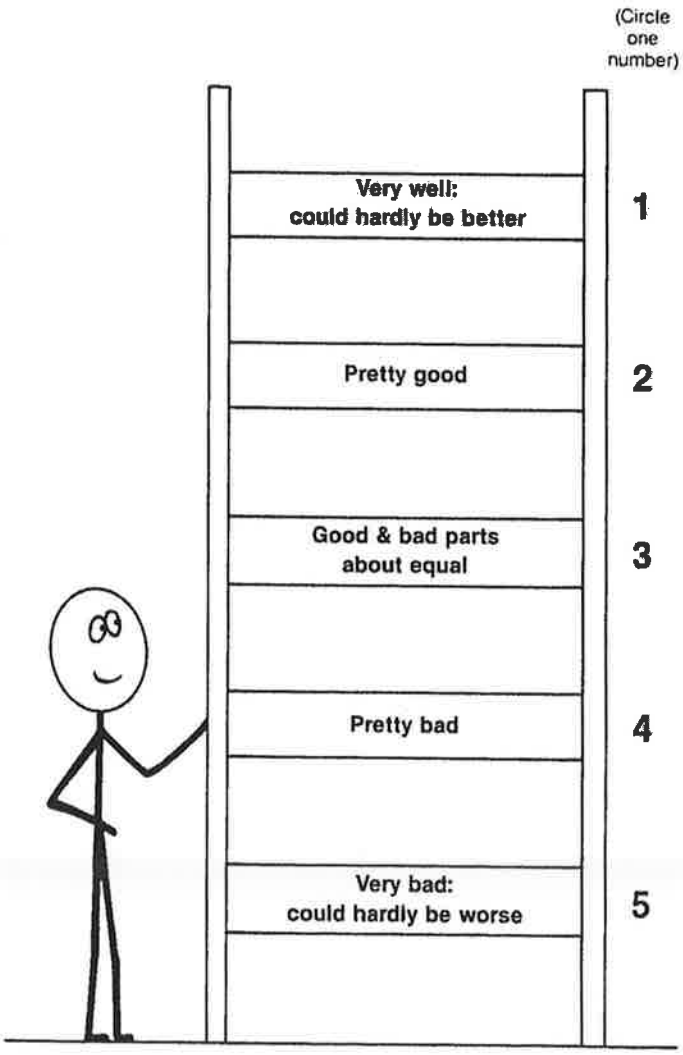

The following question is about **MEMORY.** (Circle one number)

Do Not Write in This Space

		Yes, a great deal	Yes, somewhat	Only a little	No, not at all
50.	In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

51–54: Circle one number for **how often** in the **past 4 weeks** you have had trouble *remembering* or **how often** these memory problems have interfered with your normal work or living.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
51.	Names of people	1	2	3	4	5	6
52.	Where you put things	1	2	3	4	5	6
53.	Things people tell you	1	2	3	4	5	6
54.	Things you read hours or days before	1	2	3	4	5	6

55–59: The following questions are about **LANGUAGE** problems you may have. Circle one number for **how often** you have trouble speaking or **how often** these problems have interfered with your normal work or living.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
55.	Finding the correct word	1	2	3	4	5	6
56.	Understanding what others are saying in conversation	1	2	3	4	5	6
57.	Understanding directions	1	2	3	4	5	6
58.	Understanding what you read	1	2	3	4	5	6
59.	Writing	1	2	3	4	5	6

60–64: The following questions are about **CONCENTRATION** problems you may have. Circle one number for **how often** in the **past 4 weeks** you had trouble concentrating or **how often** these problems interfered with your normal work or living.

Do Not Write in This Space

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
60.	Concentrating on conversations	1	2	3	4	5	6
61.	Concentrating on a task or job	1	2	3	4	5	6
62.	Concentrating on reading	1	2	3	4	5	6
63.	Concentrating on doing one thing at a time	1	2	3	4	5	6
64.	How often do you feel you react slowly to things that are said or done?	1	2	3	4	5	6

65–68: The following questions are about problems you may have with certain **ACTIVITIES**. Circle one number for **how much** during the **past 4 weeks** your epilepsy or antiepileptic medication has caused trouble with. . .

		A great deal	A lot	Somewhat	Only a little	Not at all
65.	Working	1	2	3	4	5
66.	Friendships and relationships (romantic)	1	2	3	4	5
67.	Leisure time (such as hobbies, going out)	1	2	3	4	5
68.	Driving	1	2	3	4	5

69–73: The following questions relate to the way you **FEEL** about your **seizures**.
(Circle one number on each line)

Do Not Write in This Space

		Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
69.	How fearful are you of having a seizure during the next month?	1	2	3	4

		Worry a lot	Occasionally worry	Don't worry at all
70.	Do you worry about hurting yourself during a seizure?	1	2	3

		Very worried	Somewhat worried	Not very worried	Not worried at all
71.	How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	1	2	3	4
72.	How worried are you that medications you are taking will be bad for you if taken for a long time?	1	2	3	4

		Very poorly	Not well	Fair	Well	Very well
73.	How well do you do with complicated projects that require organization or planning?	1	2	3	4	5

74–80: For each of these **PROBLEMS**, circle one number for **how much they bother you** on a scale of 1 to 5, where 1 = Not at all bothersome, and 5 = Extremely bothersome.

Do Not Write in This Space

		Not at all bothersome				Extremely bothersome
74.	Seizures	1	2	3	4	5
75.	Memory difficulties	1	2	3	4	5
76.	Driving limitations	1	2	3	4	5
77.	Work limitations	1	2	3	4	5
78.	Social limitations	1	2	3	4	5
79.	Physical effects of antiepileptic medication	1	2	3	4	5
80.	Mental effects of antiepileptic medication	1	2	3	4	5

81–83: In terms of **your satisfaction with your family and social life**, circle one number to indicate the following:

		Poor	Fair	Good	Very good	Excellent
81.	The amount of togetherness you have with your family and/or friends	1	2	3	4	5
82.	The support and understanding your family and/or friends give each other	1	2	3	4	5
83.	The amount you talk things over with your family and/or friends	1	2	3	4	5

84–88: In terms of **your satisfaction with your family and social life**, circle one number to indicate the following:

Do Not Write in This Space

		Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
84.	Overall, how satisfied were you with your sexual relations during the **past 4 weeks**?	1	2	3	4	5

		Much more limited	Somewhat more limited	About the same	Somewhat less limited	Much less limited
85.	How limited are your social activities compared with others your age because of your epilepsy or epilepsy-related problems?	1	2	3	4	5

		Yes, as much as I wanted	Yes, quite a bit	Yes, some	Yes, a little	No, not at all
86.	During the **past 4 weeks**, was someone available to help you if you needed and wanted help?	1	2	3	4	5

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
87.	How much of the time during the **past 4 weeks** did you feel left out?	1	2	3	4	5	6

		Always	Very often	Fairly often	Some-times	Almost never	Never
88.	During the **past 4 weeks**, how often did you feel isolated from others?	1	2	3	4	5	6

89. How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 100 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**

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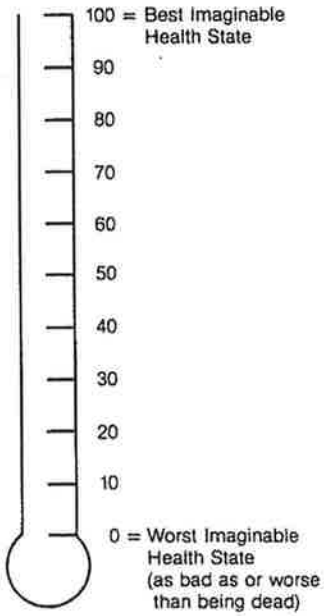

Comments (if any)