The impact of epilepsy on the quality of life of patients with benign meningioma

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Abstract

Meningiomas account for 20% of all brain tumours. They are usually benign and around 35% will develop epilepsy. Despite surgery or anti-epileptic drug (AED) use, intermittent seizures can remain. This may be significant as AED use and continued seizures can lead to reduced quality of life.

The aim of this study was to evaluate the impact of epilepsy on the quality of life of patients with benign WHO grade 1 meningiomas. Quality of life questionnaires were posted to meningioma patients with and without epilepsy, and the scores were compared between the two groups. An epilepsy control group (without meningioma) was also included so that the role of meningioma could be evaluated. This is the first study to directly compare quality of life between meningioma patients and meningioma patients with epilepsy.

The study hypothesis is that the QoL of meningioma patients with epilepsy will be more impaired than the scores of meningioma patients without epilepsy. It is additionally hypothesised that meningioma patients with epilepsy will have QoL scores that are more impaired than the scores of epilepsy patients without meningioma. In total 229 patients participated in this study: 109 had a meningioma, 56 had meningioma and epilepsy, and 64 had epilepsy without a meningioma. Each group was sent three questionnaires: the Short Form 36 (SF-36), the Functional Assessment of Cancer Therapy with brain subscales (FACT-BR) and the Liverpool Adverse Events Profile (AEP). The demographics and comorbidities of all patients were reviewed, as were the tumour and epilepsy characteristics.

Quality of life scores were impaired in the meningioma with epilepsy group but only the FACT-BR detected a significant difference. Quality of life was more impaired in the epilepsy without meningioma group when compared to the meningioma with epilepsy group, but this difference was not significant in any of the questionnaires. In a multiple regression analysis of the meningioma and meningioma with epilepsy groups, unemployment, depression, the number of meningioma symptoms, and the use of AEDs were repeatedly shown to predict impaired quality of life scores. In a regression model containing epilepsy patients and meningioma patients with epilepsy, meningioma symptoms did not significantly predict impaired quality of life.

It was concluded that epilepsy does have a negative impact on the quality of life of meningioma patients. However, as epilepsy severity in meningioma patients is mild, so is the impact on quality of life. The effect of the meningioma in epilepsy patients was not as strong as the effect of epilepsy in meningioma patients.

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Knowledge is in the end based on acknowledgement.

Ludwig Wittgenstein

Authors Declaration

This thesis is entirely my own work and the information contained herein has not been presented for any other degree or qualification.

The study was carried out at the Department of Neurological Sciences, University of Liverpool, UK and The Walton Centre NHS Foundation Trust, Liverpool, UK.

My contribution was in obtaining ethical approval, the identification and recruitment of patients, data collection and analysis and the presentation of this thesis.

Contents

Abbreviations

Acetylcholine	ACH
Anti-epileptic Drug	AED
Liverpool Adverse Events Profile	AEP
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	AMPA
Bodily Pain	BP
Brain Cancer Subscale	BRCS
Central Brain Tumour Registry of the United States	CBTRUS
Creatinine kinase	CK
Central Nervous System	CNS
Cerebrospinal Fluid	CSF
X-ray Computed Tomography	CT
Deep Brain Stimulation	DBS
Electrocardiogram	ECG
Electroencephalogram	EEG
Emotional Wellbeing	EWB
Functional Assessment of Cancer Therapy-Brain questionnaire	FACT-BR
Functional Assessment of Cancer Therapy	FACT-G
Fluid-attenuated Inversion Recovery Imaging	FLAIR
Functional Wellbeing	FWB
gamma-Aminobutyric acid	GABA
General Health	GH
International Classification of Diseases	ICD
International League Against Epilepsy	ILAE
Intensity-modulated Radiation Therapy	IMRT
Joint Epilepsy Council	JEC
Karnofsky Performance Score	KPS
Mental Health Summary	MCS
Multicentre study of early Epilepsy and Single Seizures	MESS
Mental Health	MH
Magnetic Resonance Imaging	MRI
Magnetic resonance spectroscopy	MRS
Subsample Size	n

Abbreviations Cont.

Neurofibromatosis Type 2 ..... NF2

National Institute of Clinical Excellence ..... NICE

N-Methyl-D-aspartic acid ..... NMDA

NHS National Research Ethics Service ..... NRES

Number ..... #

P Value ..... p

Physical Health Summary ..... PCS

Photon Emission Tomography ..... PET

Physical Functioning ..... PF

Physical Wellbeing ..... PWB

Quality of Life ..... QoL

Randomised Controlled Trial ..... RCT

Role Emotional ..... RE

Role Physical ..... RP

Standard Deviation s or ..... SD

Standard and New Antiepileptic Drugs ..... SANAD

Surveillance Epidemiology and End Results Program ..... SEER

Short Form 36 ..... SF-36

Social Functioning ..... SF

Stereotactic Radiosurgery ..... SRS

Sudden Unexpected Death in Epilepsy ..... SUDEP

Social/Family Wellbeing ..... SWB

T-score ..... t

The Health Improvement Network ..... THIN

Vagal nerve stimulation ..... VNS

Vitality ..... VT

World Health Organisation ..... WHO

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Chapter 1: Meningioma

1.1. Introduction

Meningiomas are a group of tumours that arise from the fibrous arachnoid meninges of the brain and spinal cord[1,2]. Due to their proximity to sensitive and crucial structures, it is fortunate that meningiomas are rare and in the great majority of cases benign[2,3].

Over the centuries meningiomas have attracted the attention of anatomists, pathologists and surgeons because of the varied symptoms and great mass they can present with[4]. The earliest known meningioma description is thought to be written by Felix Plater in 1536[4]. His patient presented with a 3 year history of gradual mental and physical decline after sustaining a head injury[4].

Since this early description our understanding of meningioma has gradually evolved. This is especially evident within histopathology where advances have influenced numerous nomenclature and systems of classification. It was in 1922 that the term meningioma was coined by Harvey Cushing replacing previous and frequently changing names, such as Epithelial Cancer (1858) and Sarkome Der Dura Mater (1863)[4,5]. He decided that basing the tumours name on tissue, as opposed to histology or location, would be most appropriate and this idea has persisted since[4].

1.2. Histopathology and Pathology

Debate regarding the exact cellular origins of meningioma exists but it is widely accepted that meningiomas emerge from the cap cells of the arachnoidal granulations and villi due to histological and ultrastructural similarities*[6,7,8]. These cells have a heterogeneous ontogenesis, display mesenchymal and epithelial functions, and are morphologically diverse which is in keeping with the complexity and heterogeneity of meningioma histopathology[7,9,10]. There is no recent interest in ascertaining the true cellular origin of meningiomas.

There are many histological subtypes of meningioma and some tumours contain many subtypes of cell[6,11]. There are fifteen subtypes in total and they are summarised in the World Health Organisation (WHO) grading system below (Table 2)[6]. The precise distinction between these subtypes serves little clinical importance as all but six types, which correlate to higher grades, display similar clinical behaviours and are less likely to display aggressive characteristics or recur[6,11,12].

Meningiomas are closely related to the inner dural layer and their blood supply is usually incorporated from the dura[11,13]. If the dura is penetrated a characteristic reactive hyperostosis may be found in the adjacent inner table[6,11]. When the outer table is involved a palpable lump can be felt[11].

Some meningiomas grow en-plaque across the dural surface instead of spherically[11]. Tumour texture varies from firm and fibrous, to soft and gritty[5]. Calcified deposits called psammoma bodies can often be found in the tumours[6,11,14].

Oedema can develop in the surrounding brain, the mechanism of which is unclear but venous obstruction, pial–meningeal anastomoses, capillary permeability and tumour secretion have been implicated[11]. The arachnoid mater appends to cerebral arteries and meningiomas in such locations can attach to or encase these vessels[6,15].

*Similarities between meningiomas and cap cells include: formation of whorls by cells, complex intertwining cell processes, intracellular junctions and intracellular intermediate filaments which stain positive for vimentin[5].

1.3. Location

The anatomical location of meningiomas has great bearing on symptoms and extent of resection[16,17]. It is useful to describe meningiomas in terms of location instead of precise histology[18]. Growth can occur anywhere arachnoidal cells are located which is usually the venous sinuses, possibly due to the concentration of cap cell clusters[7,10]. The usual sites for meningioma are listed in Table 1[16,19].

Table 1: Distribution of Intracranial Meningiomas[19]

Location	Proportion (%)
Parasagittal and falx	25
Convexity	19
Sphenoidal wing	17
Suprasellar	9
Olfactory groove	8
Posterior fossa	8
Ventricle	1-2
Optic sheath	1-2
Foramen magnum	1-2

Meningiomas of the spine account for 10% of tumours and very rarely meningiomas are found outside the craniospinal axis[6,10,12]. The latter occurs when arachnoid tissue is trapped in ectopic locations during development, and these sites include: the frontal and occipital areas in the scalp, the ear and temporal bone, the sinuses, the mandible, the mediastinum, the lungs, the muscles, and the feet[11,18].

1.4. Grading

A universal system to grade meningiomas was developed by the WHO in 2000[14]. This superseded the 1993 criteria, which was heavily criticised for being vague and subjective[14]. It was the incorporation of histopathological findings from two Mayo Clinic studies that resulted in the creation of an accurate and reproducible meningioma grading framework[14,17,20]. Despite being retrospective, these studies are powerful on account of their large sample size, reasonable follow up period and most importantly, their transparent and objectified criteria for histological analysis. The 2000 criteria remained unchanged until 2007 where some minor additions were made for the consideration of brain invasion (Table 2)[21].

Table 2: World Health Organisation (WHO) Meningioma Grading System 2007

WHO grade	Frequency	Pathological features	Histologies	Recurrence Rate
Grade I	80%–90%	Pleomorphic; occasional mitotic figures; lacks criteria of anaplastic or atypical meningiomas.	Meningothelial, psammomatous, secretory, fibroblastic, angiomatous, lymphoplasmacyte rich, transitional, microcystic, metaplastic	7%–20%
Grade II (Atypical)	5%–15%	4 mitotic figures per 10 high-power fields and three of the following: (a) increased cellularity, (b) small cells with high N:C ratio, (c) prominent nucleoli, (d) sheet-like growth, (e) necrosis or brain invasion	Clear cell, chordoid, atypical.	30%–40%
Grade III (Anaplastic)	1%–3%	20 mitotic figures per 10 high-power fields or frank anaplastic features.	Papillary, rhabdoid, anaplastic .	50%–80%

A strong, blinded and dual observer Scottish re-grading study retrospectively analysed 201 meningioma resections from before 2001 according to the 2000 criteria, finding a 39% increase in the proportion of atypical tumours[22]. A more recent retrospective Norwegian re-grading study found a similar 30% increase in the proportion of atypical tumours as a result of the 2000 criteria[10].

Additionally, one study has found a 13% increase when taking the 2007 criteria into account[10]. This study of 196 samples re-graded on account of the 2000 and 2007 criteria but lacked blinding and dual observer analysis. The latter point is important as despite its improvements, the 2007 WHO criteria still suffers from a degree of subjectivity and inter-observer bias[10,14,22].

1.5. Epidemiology

Meningiomas account for at least 20% of all intracranial tumours and are the most common benign brain tumour[10,23]. After puberty, they are twice as common in females, and for both genders the incidence increases with age[19,23,25]. The incidence of meningioma has been quoted at 6 per 100,000 persons per year[12]. This does not take into account incidental meningiomas, which are a common autopsy finding and could be found in 2.3% of the population[24].

In their most recent statistical report of over 300,000 patients, the Central Brain Tumor Registry of the United States organisation (CBTRUS) concluded that meningiomas are the most frequently reported central nervous system (CNS) tumour with an annual incidence rate of 7.22 per 100,000 persons in the population[25]. CBTRUS obtains pathology, histology and demographic data from two national tumour registries: the Centers for Disease Control and Prevention National Program of Cancer Registries, and the National Cancer Institute Surveillance Epidemiology and End Results program (SEER)[25]. The results from CBTRUS are not entirely representative of intracranial meningiomas. Firstly there is no distinction between meningiomas of the spine and the cranium and secondly, 49% of the meningiomas accounted for in the analysis were included on the basis of radiological confirmation.

In the United Kingdom (UK), a study utilising the health improvement network (THIN) database found the incidence rate of meningioma to be 5.3 per 100,000 persons per year[26]. The THIN database prospectively collects electronic medical records from over 450 general practice surgeries across the UK[27]. One study has validated THIN for epidemiological research by finding comparable data on four common diseases in the validated General Practice Research Database[27]. The THIN meningioma study made no distinction between cerebral and spinal meningiomas.

The differences in incidence between CBTRUS and the THIN study could be explained by the methodical differences in sampling, but geographical and genetic differences could also be implicated, as suggested by the increased incidence of meningioma in black and Hispanic populations and the relatively large incidence rate of 13 per 100,000 persons per year in Italian populations[6,25].

Overall the results from CBTRUS are more accurate on account of the large population covered and the use of dedicated registries for brain cancer. Both studies were weakened in not distinguishing between spinal and cranial meningioma. In either case, meningiomas

would be considered rare by the European Commission for Public Health rare disease incidence threshold of 1 per 2000 individuals per year[28].

1.6. Aetiology and Risk Factors

1.6.1. Genetics

The most common genetic abnormalities found in meningioma are monosomy deletions of chromosome 22 which is thought to occur in 50-80% of sporadic tumours[16,29]. This mutation can produce most histological types of meningioma, with 70-80% of transitional, fibroblastic, atypical and anaplastic meningiomas carrying this mutation[30]. In meningothelial meningiomas this mutation is only responsible for 25% of cases[30]. Neurofibromatosis type 2 (NF2), which can lead to multiple en-plaque meningiomas is associated with a deletion on chromosome 22 (q12.2)[12,29]. This gene codes for the merlin and schwannomin proteins[12,29]. There is a gene on chromosome 18 (p11.3) that codes for proteins homologous with merlin, the deletion of which has been implicated in familial meningiomas and meningioma progression[12]. Many other chromosomal alterations are implicated albeit to a lesser extent and these involve chromosomes 1, 6, 9, 10, 11, 13, 14, 18 and 19[16].

The importance of genetic susceptibility in patients with a meningioma is demonstrated by a large Swedish study, which observed a standardized incidence rate of 3 per 100,000 persons per year if a parent had meningioma and a rate of 4 per 100,000 persons per year if a sibling was affected[31]. A similar Israeli study suggests that inherited susceptibilities to ionizing radiation increases meningioma risk[32].

1.6.2. Radiation

Ionizing radiation exposure is the strongest modifiable risk factor described for meningioma[19]. The link has been reported for many years and suggestive case reports have been published as early as 1969[33]. This link is reinforced by the increased incidence of meningioma in the survivors of the Hiroshima and Nagasaki atomic bomb blasts, the incidence of which increases as the distance to the epicentre decreases[19,34]. Other examples of radiation exposure leading to meningioma include radiation therapy for intracranial tumours and paediatric leukemia[12,35,36].

Larger studies have associated radiation therapy for tinea capitis of the scalp and dental radiographs with meningioma (both result in an approximated exposure of 1-2 Grays (Gy) to

the head)[37,38]. These interventions however, have not been in mainstream use since the 1960s and the impact of new radiation sources, such as X-ray computed tomography (CT) scanners remains to be examined[35,39]. There is a paucity of recent large scale studies of radiation and its influence on meningioma[35,39] but one study, the largest of its kind, has linked meningioma with leukaemia and thyroid cancer[40].

Radiation associated meningiomas can be multiple, have a long latency period of 17-36 years, are associated with a higher grade and have a high recurrence [19,41]. There is a dose response relationship with higher doses resulting in worse outcomes[37].

1.6.3. Hormones

The increased incidence of meningioma in females (particularly before menopause), the presence of sex hormone receptors in some tumours, the change in size of meningioma during the luteal phase and pregnancy, the association with exogenous sex hormones and the in-vitro proliferation of meningioma cells after oestrogen exposure are collectively indicative of a significant hormonal influence in meningioma risk[35,37,40].

The majority of meningiomas have a type ii oestrogen receptor subtype, which has a relatively low affinity and specificity to oestrogen[16,42]. Oestrogen will bind to less than 30% of meningiomas[16,43]. Conversely, progesterone receptors are found in 50-100% of meningiomas[16,43]. Receptor status however does not seem to be influenced by gender[43].

The significance of receptor expression is not yet fully appreciated due to a variation of results from limited in-vitro studies, but due to its inverse correlation to mitotic index and grade, it is thought that progesterone plays a more essential role in the formation of benign meningiomas[19,45]. Absence of progesterone receptors is correlated to higher grades of meningioma, but poor specificity means that other histological parameters must be relied upon[6].

The clinical importance of reproductive hormones is harder to define. While case control studies show little evidence of increased risk due to hormonal replacement therapy, cohort studies find significant associations[44,45]. A recent case control study and review of the literature by Claus et al found that meningioma risk was associated with current exogenous hormone use, a finding that is supported by other concordant results in the literature[45]. With regards to endogenous hormone production, a significant association with meningioma risk has generally not been found[40]. It is interesting that current as opposed to

previous sex-hormone use is related to meningioma risk, implicating a promoting and not an initiating influence on meningiomas[40]. The study by Claus et al was powerful on account of its large sample size, transparent report and comprehensive literature search, but the case control study itself was limited by a higher socio-economic status in controls and the small number of patients who reported current contraceptive use.

1.6.4. Natural History

Advances in imaging technology have resulted in the increased identification of people with asymptomatic meningioma[46,47]. The majority of these tumours are slow growing and surgical intervention in this cohort is not necessary unless specifically warranted for a reason other than presence of tumour[46,47]. In the majority of cases, the growth rate of asymptomatic meningiomas is less than 1cm per year[47]. Tumour doubling time is another measure of growth and the average tumour doubling time is calculated to be 21.6 years[47]. Younger patients have shorter doubling times and higher growth rates[47].

1.6.5. Presentation

Symptomatic meningiomas are usually brought to the attention of patients in the form of headaches and seizures[6], but presentation will usually occur in three ways:

1. Focal neurological signs: these depend on the meningioma location and occur due to local brain or cranial nerve compression[12,16]. Meningiomas can also mimic transient neurological deficits, such as TIA[48].
2. Epilepsy is a presenting feature in 27-67% of cases of which secondary generalised seizures are the most prevalent[12].
3. Raised intracranial pressure; which can manifest with: headache, nausea, vomiting, papilloedema and reduced conscious level[12].

1.7. Investigations

When meningioma is suspected, radiological investigations are instrumental in establishing diagnosis and tumour location. Intracranial radiology for meningioma has been utilised for over 100 years but since then, imaging techniques have become increasingly sophisticated[4].

1.7.1. CT

Plain CT scans will detect and display meningiomas as a slightly hyperdense (or less commonly isodense) mass relative to surrounding brain tissue[12,13,16,49]. Following the administration of intravenous iodinated contrast, meningiomas are homogenously enhancing and easily identifiable[16,49]. CT is also useful for identifying hyperostosis and tumour calcification, the latter of which is visible in 50% of tumours[16,49].

1.7.2. MRI

Magnetic resonance imaging (MRI) is the gold standard neuroimaging method for meningioma and is usually performed as the initial scan[18]. It is a versatile technique that has reduced in price, increased in availability and can clearly show features specific to meningiomas[12,18]. It should be noted that the characteristics of the scan can vary due to haemorrhage, cysts and calcification, but not by histology[49].

1.7.2.1. T1

On T1 weighted images, meningiomas are usually isointense or slightly hypointense[11,49]. Following gadolinium contrast meningiomas will enhance intensely and homogenously and this technique is particularly useful for delineating en-plaque lesions and vital neurovascular structures, especially in skull base meningiomas[11,12,18,41]. T1 weighted images can identify dural thickening due to the meningioma, known as the dural tail. The criteria adopted for identifying a true tail are as follows[18,49]:

1. The tail should be seen in 2 consecutive 5-mm sections or 3 consecutive sections on thinner slices.
2. There should be smooth tapering of the tail away from the tumour.
3. Enhancement of the tail should be more than that of the tumour itself.

1.7.2.2. T2

In T2 weighted images, 50% of meningiomas are hyperintense and the other half are isointense relative to grey matter[18,49]. Such images are useful for identifying blood vessels and peritumoral oedema, the latter of which is more often associated with atypical and anaplastic meningiomas as opposed to typical lesions[18,49]. MRI venography and angiography are helpful in identifying encasement and patency of dural sinuses and major arteries[12,18].

1.7.3. Future of imaging

MRI lacks specificity for meningioma and the following conditions can mimic its appearance: sarcoidosis, lymphoma, plasmocytoma, bony metastases and particularly, dural based metastases[5,12,49]. There is scope for the use of advanced imaging techniques, such as diffusion weighted MRI, magnetic resonance spectroscopy (MRS), photon emission tomography (PET) and PET CT[5,41]. Of particular interest is the use of MRS which can detect levels of alanine, choline, phosphate and N-acetyl compounds and PET which measures levels of radio-labelled glucose metabolism[5,13,41]. The significance of an alanine peak (1.5mm) on MRS is unclear due to varied results in the literature. This variation may be due to insufficient MRI field strength, voxel size or tumour size[50].

1.7.4. Angiography

Catheter angiography was the investigation of choice before CT and MRI[12]. It could distinguish between vertebral or carotid supply and meningiomas would appear as a characteristic blush[12,16]. Now it is indicated to clarify diagnosis in the presence of ambiguous CT/MRI findings, to determine blood supply and to prepare for pre-operative embolisation[12].

1.7.5. Confirmation of Diagnosis

Histopathology diagnosis of meningioma is necessary to confirm meningioma type and most importantly grade. Current imaging techniques cannot reliably differentiate between tumour grades[5].

1.8. Treatment

Meningioma management is tailored to the individual patient and this is due to their heterogeneity[12,19]. The decision to proceed with observation, surgery or radiotherapy is influenced by retrospective data as currently there are no randomized controlled trials comparing such options[51].

For all patients, a course of steroids or anti-epileptic medications may be warranted in the presence of oedema and seizures respectively[12]. Steroids are useful pre and post-operatively to aid surgery and promote recovery[5,16]. The role of anti-epileptic drugs is less clear and this will be explained thoroughly in the next chapter.

1.8.1. Observation

For asymptomatic and benign meningiomas the management focus is directed at monitoring for symptom and or disease progression[19]. In certain cases, particularly those with minimal symptoms, the threshold for performing surgery is less obvious and decisions are made on balance of risk[5]. Important factors include:

- Advanced patient age; meningiomas are slow growing and surgery might not be necessary in older patients[18]. The healthy aging population makes this harder to ascertain[52].
- Tumour location; skull base tumours are rarely completely resected and are associated with significant risk of neurovascular damage and mortality[53].
- Future tumour growth; small parasagittal tumours are easier to resect prior to sagittal sinus invasion[5].
- Patient choice; some patients decide against surgery[5].
- Imaging features; calcified lesions on CT and hypointense lesions on MRI are more likely to remain asymptomatic[12].
- Tumour size and patient health status are also taken into account[19].

Interestingly a recent analysis from the SEER database in the USA stated that survival is significantly improved for patients who undergo surgical resection of their meningioma[54]. Unfortunately the reasons for rejecting surgery were not available. This is significant as patients may have limited access to healthcare as a result of low socioeconomic status, or may have tumours with difficult surgical access, both of which could feasibly influence outcomes.

1.8.2. Surgery

In the majority of symptomatic cases, surgical removal is warranted[12]. Surgical aims are largely dependent on tumour position, but five basic principles for all locations apply[5,52]:

1. Optimal patient positioning, incision and exposure.
2. Early tumour devascularisation.
3. Internal decompression and extracapsular dissection.
4. Early localization and preservation of adherent or adjacent neurovasculature.
5. Removal of involved dura and bone.

There is a catalogue of surgical techniques standardised for each tumour location and it is outside of the scope of this thesis to delve into each. The general aim of surgery is to remove the entire tumour[12,52]. The Simpson's grade, published in 1957, provided an objective scale to the completeness of tumour removal in order to predict risk of tumour recurrence[55]. The significance of exctricating the dural attachment and bony infiltration, and the correlation of Simpson's grade to prognosis, was highlighted in Simpson's and subsequent studies[5].

1.8.3. Pre-operative Embolisation

Meningiomas are vascular lesions which when resected can lead to significant and sometimes catastrophic intra-operative haemorrhage[52]. In some patients this can be prevented by delivering adhesives such as polyvinyl alcohol (PVA) and n-butyl cyanoacrylate (NBCA) to tumour feeding vessels via femorally inserted microcatheters[52].

The efficacy of pre-operative embolisation is debatable and many studies are limited by small sample size, lack of a comparison group, retrospective analysis and selection bias[56,57,58,59]. The strongest study on this topic prospectively compared the short term outcomes of a centre performing pre-operative embolisation to a centre which did not[60]. The authors concluded that completely de-vascularised tumours had a significant effect on operative blood loss[60]. Embolisation made no difference to transfusion requirements, duration of surgery, Simpson's Grade and length of hospitalisation[60].

Embolisation is indicated in the minority of cases; usually when the tumour is large, hypervascular, basal, or supplied by vessels with difficult surgical access[52]. There is scope for a large prospective RCT (randomised controlled trial) to test these indications as to date

none currently exists and the decision to embolise must be balanced against costs and potential complications.

Effective embolisation permanently obstructs vascular supply. This is also the mechanism for their complications, which can occur when normal structures share vascular supply with the tumour or when embosilate reflux occurs[52]. While these risks are reduced in procedures involving denominations of the external carotid artery (ECA), damage may occur in the presence of extracranial-intracranial anastomoses or patent foramen ovale[52]. Careful pre-intervention planning is crucial to identify and manage these risks[52].

There is concern that embolization may influence tumour grading[12]. Perry et al assessed the grading and clinicopatholigical features of 64 embolised meningiomas concluding that morphological changes were rarely sufficient to result in over-grading[61]. Importantly, it was concluded that the meningiomas graded as atypical in Perry's study behaved more aggressively, a factor ignored in the more recent studies of Matsuda et al[62] and Jiménez-Heffernan JA et al[63].

Embolisation has been attempted as the primary treatment for meningiomas unsuitable for surgery. The largest series is of 7 patients by Bendszus et al[64] which resulted in 6 patients demonstrating tumour shrinkage and symptomatic relief.

1.8.4. Post-Operative Management

This involves the routine care of patients following a craniotomy, with particular attention to minimising cerebral oedema[16]. Steroid therapy is continued initially and gradually tapered. Care is taken to avoid excessive hydration and the patient is nursed with the head elevated to promote venous return[16]. Neurological deterioration may indicate post-operative haemorrhage or cerebral oedema warranting a CT scan[16].

1.8.5. Radiotherapy

Radiotherapy is a diverse and evolving field which utilises sophisticated equipment and techniques to deliver ionizing radiation. Radiation damages cells through direct cytotoxic injury, DNA damage and vascular or stromal obliteration[65]. Radiotherapy plays an important part in the management of meningiomas.

1.8.5.1. Conventional Radiation Therapy

Conventional radiation is efficacious in treating meningioma, particularly after subtotal resection or tumour recurrence[51]. Several studies agree that 10-20 years of tumour control is achieved in 70-80% of patients[51]. These studies are small and retrospective, but collectively they cover many variables, such as meningioma grade, location and timing of radiotherapy[51]. Since conventional radiation therapy targets the tumour and a margin of normal parenchyma, there is concern that damage to healthy tissue and radiation induced tumours may occur[5]. In practice the rates of these and other complications are low which could be due to insufficient follow up, or the minimisation of parenchymal damage through the use of computerised planning systems and fractionation[51,66]. Computerised planning systems use imaging data from CT or MRI scans to contour radiation to the outline of the tumour improving progression free survival[67].

Fractionation is reliant upon the α/β ratio of target tissues[68]. In this context, α and β are parameters that quantify the susceptibility of tissues to radiation damage whereby a high α/β ratio indicates greater sensitivity to lower but fractionated doses of radiation[69,70]. Tissues that exhibit high α/β ratios of around 10Gy include the skin, intestinal epithelium and malignant tumours[70]. Tumour sensitivity to fractionation as a concept is not fully understood, but several theories exist[68]:

1. Hypoxic cells are resistant to radiation related killing and tumours contain hypoxic cells. A single fraction of high dose radiation will fail to kill all cells, but multiple fractions will allow for re-oxygenation and further cell destruction during subsequent fractions.
2. Cells are more resistant to radiation at certain points of the cell cycle and fractionation will allow for cells to pass into vulnerable stages in-between doses.
3. Cycling cells, such as tumour cells, are more susceptible to radiation than non-cycling cells, such as normal cells, thus increasing the safety of fractionation.

The α/β ratio for meningiomas is approximately 3.76Gy, only slightly greater than the surrounding neuroparenchyma which has a ratio of 2.5Gy[68]. For meningiomas

hypofractionated regimes are theoretically recommended as fractionation has no benefit when α/β ratios are equivalent, but in practice fully fractionated regimes are adopted[68].

1.8.5.2. IMRT

Intensity-modulated radiation therapy (IMRT) boosts the efficacy of conventional radiotherapy and planning techniques through the use of multileaf collimators, which actively manipulate the radiation field[5]. In doing this radiation exposure is optimised to tumour and minimised to neuroparenchyma, which is particularly useful when radiosensitive neural structures are in close proximity[71]. In one 40 patient strong study of skull base meningioma, IMRT resulted in a 5 year progression free survival for 88% of participants[71]. IMRT was the sole treatment in 27% of recruits[71]. The results of two large RCT's are anticipated[71].

1.8.5.3. Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) utilises stereotactic imaging, sophisticated dose planning and radiation sources to deliver mutli-source radiation towards a common focus point with sub-millimetre precision[5,72]. As a result, higher doses can be specifically delivered to target tissues reducing the need for fractionation[5].

Despite contradicting fractionation radiobiology, single shots of radiation delivered through this method can produce excellent results. One retrospective study compared SRS with surgical resection for small to medium sized benign meningiomas and observed progression free survival rates of 95% at seven years; which was comparable to their patients who had Simpson's grade 1 surgical resection[73]. This study was weakened by selection bias and a relatively short observation period. After larger long term observation and RCT evidence is available, it is likely that SRS will be recommended as primary treatment for certain meningiomas.

It is important to note that SRS is only appropriate for targets less than 3.5cm in diameter with a sharply defined border and regular shape that is not enveloping eloquent structures[74]. This is due to dose spill into surrounding areas which can lead to post radiation reactions such as oedema and radiation necrosis[74]. This could be prevented with fractionation[72]. Fractionated stereotactic radiotherapy looks promising with minimal complications and local control rates of 90-100%[74].

1.8.5.4. Indications

Currently, definitive radiotherapy is indicated for inoperable meningiomas and adjuvant radiotherapy is indicated for incompletely resected meningiomas or meningiomas of high grade[16]. The number of indications will increase with the production of long term follow up data and RCT evidence.

1.9. Prognosis

1.9.1. Survival

Compared to other intracranial tumours, patients with a meningioma fare well in terms of survival, but this is not the case when comparing patients with the general population[19]. Several large[†] observational studies calculated the survival rate of patients at 10 years post diagnosis to fall to 80% of that observed in the general population[75,76,77,78,79]. They were completed before the creation of the WHO grading criteria in 1993 and so may include tumours which would now be regarded as atypical or malignant. Some studies did not attempt to differentiate between grades in their analyses.

One recently published study by Alkemade et al retrospectively observed the post-surgical outcomes of 233 benign meningiomas for a maximum of 23 years[80]. While the authors have stated that only WHO grade 1 tumours were analysed, patients were included from 1985-2003 and there is no mention of revisiting slides or re-grading cases to account for up to date guidelines. Despite this, the survival rates of this study are higher than stated previously at 91% of the general population[80].

Several studies agree that age, tumour grade and surgical resection are strong predictors of survival[19]. There are varied results on the age ranges that predict survival. Some studies suggest that short term and long term survival is significantly reduced with progressively increasing age[75,79]. Alkemade et al found that survival in patients under 45 and over 65 is as predicted but significantly worse in the 45-65 year group[80]. This was thought to be a result of recurrent tumour and stroke in the 45-65 group, and sampling bias in the over 65s, as only those who were fit underwent aggressive resection[80].

The varied results between these studies could be a product of the differences in study and comparison group population, or differences in the methods used to predict survival.

[†] Sample sizes ranged from 225 to 1986 patients in the large meningioma survival studies.

It is unsurprising that histological grade is inversely proportional to survival, with one study quoting 5 year survival rates of 70% and 55% for benign and malignant meningiomas respectively[79]. It is interesting that the atypical meningiomas in this study had a 75% survival and while the authors make no comment on this, it appears that this result could be due to the relative younger age of the atypical cohort. Furthermore, it is unclear on which criteria these tumours were graded and future studies using the current 2007 criteria are warranted.

A link between extent of resection and survival has been postulated since 1959, when Donald Simpson published a paper on the recurrence of meningiomas after surgical treatment[55]. His criteria of surgical resection is presented below[55]:

- "Grade I.-This is a macroscopically complete removal of the tumour, with excision of its dural attachment and of any abnormal bone. Where the tumour arises from the wall of a dural venous sinus, such an operation necessarily entails resection of the sinus.
- Grade II.-This denotes a macroscopically complete removal of the tumour and of its visible extensions, with endothermy coagulation (usually to the point of charring) of its dural attachment.
- Grade III.-This denotes a macroscopically complete removal of the intradural tumour, without resection or coagulation of its dural attachment, or alternatively, of its extradural extensions, e.g., an invaded sinus or hyperostotic bone.
- Grade IV.-This denotes a partial removal, leaving intradural tumour in situ.
- Grade V.-This is a simple decompression, with or without biopsy (pages 24 and 25)".

Simpson's study illustrated that the completeness of surgical excision is a key factor influencing survival. Despite his series being retrospective; and before the use of CT, MRI or microsurgery; subsequent modern studies have mostly agreed with these results[12]. Kalio et al analysed the outcomes of 935 postsurgical meningiomas and found that after 15 years the relative survival ratio (RSR) was 78% of what was observed in a non-meningioma group[81]. It was concluded that survival was largely dependent on the extent of resection with an RSR of 84% following complete resection (Simpson grades 1 and 2) and 50% following incomplete resection (Simpson grades 3-5)[81].

1.9.2. Recurrence

Tumour recurrence is a significant endpoint in its own right, but its influence on survival has not been focused upon in the literature. In isolation is a comment by Alkemede et al, who found an association between poor survival and tumour recurrence[80]. This notion remains unexplored.

Simpson's grade of resection is strongly associated with tumour recurrence. Table 3 summarises the findings of three studies that demonstrate this.

Table 3: Summary of Three Studies examining Simpson's Grade of Resection and Meningioma Recurrence Rate

	Simpson[55]	Melamed[82]	Chan[83]
Simpson's Grade	**Recurrence %**	**Recurrence %**	**Recurrence %**
1	9	8	11
2	19	15	22
3	29	29	-
4	44	33	33
5	-	-	100
Follow Up Period	Up to 28 Years	7-17 Years	Average 9 Years

Seemingly in opposition is a retrospective study by Oya et al, which finds a significant difference in recurrence free survival (RFS) between Simpson grades 1-3 and 4, but not between grades 1, 2, or 3[84]. The reduced distinction between grades 1-3 could be a result of shorter follow up or lead time bias due to advances in scanning equipment and follow up regimes.

Tumour location influences outcomes indirectly as meningiomas with difficult access are more likely to be incompletely resected[5]. This is represented in a post-surgical outcomes study by Mirimanoff et al[76]. It was found that convexity tumours were completely excised in 96% of cases leading to a 5 year progression free survival rate of 97%. In comparison, parasellar meningiomas were completely excised in 57% leading to a progression free survival rate of only 81%. This study included spinal meningiomas which have the best recurrence free survival rates.

1.9.3. Neurological Outcome

Symptomatic relief or progression is an important outcome for patients. In addition to observing survival and recurrence, Alkemade et al monitored patients for symptom outcomes in the short and long term[80]. After a year of follow up, 61%, 13% and 22% of patients experienced some resolution, no change, or worsening of symptoms respectively. Long term symptomatic observation was obtained for a minimum of 5 years; of the responders, 33% experienced no symptoms, 67% of patients experienced at least one symptom and 27% of patients experienced severe symptoms that interfered with quality of life[80]. Cerebellar symptoms were most likely resolved after 5 years, while cognitive and motor symptoms were most likely to persist in mild and severe forms respectively in the same time frame[80].

1.9.4. Quality of Life

The literature on Quality of Life (QoL) and meningioma has covered many topics, namely:

- QoL after surgery, radiotherapy or surgery and radiotherapy[83,85,86,87,88,89,90,91,92 and 93].
- Analysis of the factors affecting QoL and their predictive power (not including seizure frequency) by Miao[94].
- Patient satisfaction after surgery by Akagami[95].
- The development of internet-based, self-reporting outcome instruments by Zlotnik[96].

Findings from these studies are not entirely consistent due to variations in sample population and questionnaire used. The most commonly used QoL measure was the Karnofsky Performance Score (KPS), a questionnaire that rates the ability of a person to undertake daily activities on a scale of 0 – 100. This questionnaire is particularly effective at identifying problems with physical function.

Studies using the KPS have found that the presence of symptoms due to the meningioma, such as cranial nerve dysfunction and hemiparesis score significantly[85]. Other influencing factors include tumour size, extent of resection and tumour grade[94].

Chapter 2: Epilepsy

2.1. Introduction

Epilepsy is a disorder of the cerebral cortex where a tendency to "an excessive and disorderly discharge of cerebral neurones‡ (page 3109)"[97] can manifest as recurrent seizures of numerous form that are stereotyped to the individual[7,98]. It can exist as a primary disorder of the CNS or secondary to other pathological processes[11]. Like meningioma, epilepsy is a heterogenous condition which produces some difficulty in definition and classification.

2.2. Definition

The word Epilepsy is derived from the Greek epilambánein which means to seize upon. Rather confusingly, epilepsy can be incorrectly used as a colloquial term for fit, seizure or convulsion by a lay member of the public[99].

Modern definitions agree that a patient is said to have epilepsy when two or more unprovoked seizures occur[7,11]. This clinical definition targets those that are likely to have further seizures and thus may benefit from counsel and anti-epileptic drug (AED) prophylaxis as proven by observation studies[7].

2.3. Classification

Patients are currently classified on the basis of two schemata: seizure type and epilepsy syndrome. In 1982 The International League Against Epilepsy (ILAE) released the International Classification of epileptic seizures; a refined product of Gastaut's 1970 classification system[7,11]. It identifies seizures by their clinical form and electroencephalographic (EEG) features, which separates seizures into two main categories of partial and generalised attacks depending on whether seizure activity originated in one hemisphere or both hemispheres simultaneously; this separation is useful for prognosis to a certain extent[100]. In 1989 the ILAE introduced the classification of the epilepsies, which consists of three groups[100]:

- Idiopathic
- Symptomatic
- Cryptogenic

‡This quote originates from the writings of Hughlings Jackson (1870).

The understanding in 1989 was that idiopathic, symptomatic and cryptogenic epilepsies usually correlated with primarly generalised epilepsies with a genetic basis, partial epilepsies due to a structural lesion and partial seizures with no apparent cause respectively[11]. Advances in genetic understanding, neuroimaging and neurophysiological techniques have led to the realisation that epilepsy is more complex than originally presumed and certain cases do not fit neatly into these groups[100].

The ILAE have thus recently updated both classification systems to simplify classification and allow for future alterations[100]. This classification of seizures differs from the 1981 classification in concept and content in the following ways[101]:

1. The omission of the concept that focal and generalised seizures represent a dichotomous pair (although this is still implicit).
2. The inclusion of neonatal seizures.
3. Absence seizures have been categorised in a simpler manner and myoclonic absence seizures and eyelid myoclonia have been included.
4. The inclusion of spasms. There was some debate as to whether these represented focal or generalised seizures, but ultimately they were categorised separately.
5. Myoclonic atonic seizures are included.

One major change is omission of distinction between simple and complex partial seizures. This distinction is poorly understood and the seizures inconsistently categorised[101]. Description of seizures based on their ictal phenomenology is still recommended but in the following form and under certain circumstances[101]:

- Simple partial seizures: Without impairment of consciousness or awareness with observable motor or autonomic components.
- Complex partial seizures: With impairment of consciousness or awareness

The classification of epilepsies has been simplified to pragmatically represent aetiologies as follows[101]:

- Genetic
- Structural
- Unknown Cause

They replace the terms idiopathic, symptomatic and cryptogenic which had a significant degree of overlap[100]. Additional concepts of epilepsy were also offered; to rename the concept of idiopathic epilepsy to self-limiting or pharmacoresponsive epilepsy and to add the concept of epileptic encephalopathy to describe the observation of epilepsy specific cognitive impairment[101].

The previous ILAE classification systems have been highly influential on a global scale. The WHO, in constructing the current International Classification of Diseases manual (ICD-10), based their epilepsy section on the previous ILAE systems[102]. The ICD-10 is utilised by a range of disciplines worldwide and so changing the epilepsy classification schema is significant. The WHO are drafting the ICD-11 head of its release in 2015, the epilepsy section of which is based on the current ILAE classification systems[102].

2.4. Epidemiology

Epilepsy is a relatively common neurological condition that is thought to affect at least 50 million people worldwide[103]. There is difficulty in obtaining accurate figures for the incidence and prevalence of epilepsy and this is a product of difficulty in case definition across studies, clinical misdiagnosis and failure to seek medical attention due to fear of stigmatisation or ignorance of symptoms[104].

The prevalence of epilepsy in the UK is uncertain. The National Institute of Clinical Excellence (NICE), which uses prospectively collected primary care Quality and Outcomes Framework data, estimated the prevalence of epilepsy to be between 362,000 and 415,000[105]. The Joint Epilepsy Council (JEC) used prospectively collected primary care data (read and Pegasus coding systems), estimating the prevalence of epilepsy to be 600,000 in the UK (0.97% of population)[106]. The data from both organisations is limited due to reliance on GP coding systems and lack of validation, which will include many patients who are misdiagnosed. Compounding this issue is the belief that 25% of epilepsy diagnoses are incorrect in the UK[107]. Furthermore, the JEC estimates are based on patients with a diagnosis of epilepsy and a prescription for AED, which is not representative of all persons with epilepsy.

Both NICE and the JEC are in agreement that the incidence of epilepsy is likely to amount to 50 cases per 100,000 of the population per year[118,119]. A systematic review and meta-analysis of 167 studies before 1999 quoted a similar incidence rate at 50.7 per 100 000 for

males and 46.2 per 100 000 for females[108]. It is generally shown (not always significantly) that epilepsy is more common in males due to a higher incidence of cerebral injury leading to symptomatic/structural epilepsy[104].

The Rochester Minnesota study examined the prevalence of epilepsy between 1940 and 1980; epilepsy was classified as idiopathic or cryptogenic in 75% of cases and symptomatic in the rest[109]. No distinction was made between idiopathic or cryptogenic epilepsy, but it was stated that with thorough investigation the majority of cases would be cryptogenic[109]. In an almost identical population to the above, 65% of incident cases were classified as idiopathic or cryptogenic[110]. The relatively increased proportion of symptomatic patients in the incidence study is explained by the high mortality associated with these epilepsies and thus reduced prevalence.

Overall, focal seizures are more incident than generalised seizures with one large UK study finding 59% of seizures to be focal[111]. In developed countries, there is a 59% majority in the prevalence of focal seizures and the opposite is observed in developing countries[104]. The proportions of seizure types seen also varies by age. Absences and myoclonic seizures are highly incident in children, while complex partial seizures are the most incident type of seizure in adults: at least 40% of adult seizures are complex partial. Age is significantly associated with incidence rates: bimodal peaks are frequently demonstrated in studies[104]. This is a product of the various aetiologies for epilepsy and the ages at which they are likely to present. In the very young, recurrent seizures are likely to be secondary to congenital structural or metabolic conditions[7]. Up to early adulthood, the proportion of seizures due to acquired disorders or recognised genetic generalised epilepsy increases[7,112]. After adolescence the role of acquired disease becomes more influential, with infections, tumours and cerebrovascular disease being found responsible for the majority of epilepsy[7]. Symptomatic seizures in late adulthood lead to an overall increase in the incidence of epilepsy[7].

2.5. Pathophysiology

A precise pathological understanding of seizure generation is currently non-existent, but in broad terms, a seizure is said to occur when electrical discharges of high voltage and paroxysmal high frequency, or synchronous low frequency, propagate to surrounding neurones and structures[7]. The concept of excessive discharges leading to seizures was famously theorised by Hughlings Jackson in the 19th century and reinforced with the advent of the EEG in the 20th centrury[11].

Numerous observations on a smaller scale are continuously increasing our understanding of epilepsy. Studies focussing on hereditary epilepsies have revealed a polygenic mode of inheritance and unsurprisingly numerous genes involved with neuronal discharge are implicated[113]. Abnormalities pertaining to code and epigenetic modulation have been found for sodium and potassium channels, receptors for acetylcholine (ACH) and gamma-Aminobutyric acid (GABA)[7,11]. Such mutations are implicated in the primary generalised epilepsies: they have a strong familial inheritance and genetic mutations that influence neuronal excitation are increasingly being found[7]. Spontaneous bilateral spike or polyspike and slow wave discharges can be seen on the EEG, the frequency of which varies by seizure type and phase[7]. It is clear that subcortical structures play a significant role in producing generalised seizures, but whether this is in producing or modulating seizure activity is not known[7].

Studies on seizure foci have revealed biochemical abnormalities such as increased levels of extracellular potassium around glial scars and increased sensitivity of foci to ACH[7,114]. Levels of GABA, taurine, glycine and glutamic acid are altered in excised seizure foci[7]. Furthermore, there is growing evidence that abnormal glial cells can manipulate seizure activity through the modulation of ions, neurotransmitters and inflammation[115]: seizure threshold is reduced in Knock out mouse models of glial neurotransmitter transporters[116].

Animal models with penicillin induced lesions have shown that epileptogenic foci spontaneously depolarise and are suppressed by surrounding hyperpolarised inhibitory GABA neurones[117]. How much of this applies to humans is unclear, but when electrical activity manages to spread beyond the focus, that is when a seizure is believed to occur[7].

For this to happen, the following is thought to be required[7]:

1. Population of pathologically excitable neurons
2. Increased excitatory glutaminergic activity
3. Decreased inhibitory gabanergic activity

It is not understood how focal lesions can lead to the spontaneous and synchronous discharge of neurons, but one theory is that the offending neurones have been de-afferented[7]. This is known to occur after CNS injury and has been implicated in epilepsy, complex regional pain syndrome and spasticity[118]. De-afferented neurones remain in a state of partial depolarisation, which makes them hyper-excitable[7]. The mechanism underpinning this is not fully understood, but potential factors could include alterations of neuronal networks due to the malfunction of inhibitory afferent neurones or the sprouting of new excitatory collaterals[119]. Additionally, or alternatively, intrinsic hyper-excitability may be a factor, a manifestation of physiological GABA receptor up-regulation or alterations in the function of ion channels[118].

Modern EEG techniques have led researchers to discover that trace abnormalities may be found several minutes and even days before the onset of a seizure, suggesting that the influence of subcortical rhythms or a cascade of electrical events may be influential in initiation or modulation[7,120].

Precisely how isolated areas of cortical activity lead to seizures is not understood[7].

2.6. Investigations

In most cases, the diagnosis of epilepsy can be made on clinical grounds and investigations are important for supporting the diagnosis, seeking an underlying cause and classifying the epilepsy.

2.6.1. EEG

When there is clinical suspicion of epilepsy after a seizure, most patients will receive an EEG. During the basic 30 minute trace of an awake patient with epilepsy, abnormalities can be found in 50% of recordings[121]. This was first observed in a study of 308 persons with epilepsy, in whom 55.5% demonstrated an identifiable paroxysmal discharge on their first EEG[122]. These were definite cases of epilepsy which perhaps is not representative of the clinically indiscernible cases a clinician sees. Other studies have found abnormalities in 30-50% of inter-ictal traces and this variation could be explained by variances in age, seizure proximity, seizure frequency and epilepsy syndrome[7,122].

When an EEG is recorded in close proximity to a seizure or if seizure frequency is high this will increase the chance of recording an abnormality[122]. An increased yield is also found in younger patients: patients over 60 have a decreased yield with abnormalities found in 35% of patients with previous epilepsy and 26% of patients with seizure onset after 60 years[123]. As is expected, the majority of these patients had focal epilepsy. The reduced yield in these patients seems to be a result of age and epilepsy syndrome; non idiopathic epilepsy had a reduced yield[123]. Sample size was small in this regard and comment on this was not entertained.

In idiopathic epilepsy, characteristic inter-ictal epileptiform discharges can be found in 50% of grand mal seizures and 30% of absence seizures[7]. Of the focal epilepsies, temporal lobe epilepsy will produce characteristic abnormality in 70-90% of cases[124]. In extra-temporal focal epilepsies, aberrations of normal EEG patterns are sought, the sensitivity of which varies by the localisation of the epilepsy:

- In frontal lobe epilepsies, 40% of cases will demonstrate abnormal inter-ictal patterns[125].
- Parietal lobe epilepsy will infrequently demonstrate EEG abnormalities and when they do they are poorly localised[125].
- Epilepsies of the occipital lobe frequently produce localised abnormalities[125].

In most epilepsy patients, the yield of abnormalities can be increased with activation procedures (hyperventilation and photic stimulation), multiple recordings, sleep deprivation and sleep EEG[121,124]. When a combination of repeated awake and sleep EEG recordings is used, the yield can be as high as 92%[121].

The EEG is more specific than it is sensitive. In the general population, only 1% of people will demonstrate activity[121,126]. When focusing on populations of patients with cerebral injury and yet no seizures, abnormalities can be found in 17% of patients with congenital or perinatal brain injuries: 11% of patients after cranial surgery and 8% of patients with brain tumours[127]. In psychiatric patients, one study of 3000 psychiatric inpatients suggests that abnormalities can be seen in 2.6%: a consequence of medications and probable metabolic disturbance, drug abuse or cerebral injury[128]. Furthermore, there are normal sharp wave phenomena that look similar to epileptiform activity, but they occur in healthy people and sleep or drowsiness may precipitate them[126].

In the fortunate circumstance that a seizure is captured by EEG, the sensitivity and specificity of this is far superior to inter-ictal EEG[129]. This is the basis of video EEG which monitors patient movement, EEG activity and electrocardiogram (ECG) activity and proves a useful tool for establishing a seizure diagnosis, seizure frequency and localization of foci for clinical or surgical management[129]. During prolonged recordings, a seizure can be captured in around 50-70% of cases and in 20% of cases previously unrecognized seizures may be identified[129,130]. It should be noted that absence of abnormal activity during ictal EEG can occur in simple partial seizures and auras and rarely occur in the context of complex partial seizures[130]. Contrary to this, almost all types of generalized seizure will produce ictal EEG abnormalities[7].

Scalp electrodes can be relatively poor at identifying seizure activity. Synchronous epileptiform activity over a $6cm^2$ area of cortex is required for scalp electrode recognition, which can be the case in simple partial seizures[124]. Furthermore, the signal travelling to scalp electrodes is altered by parenchyma, meninges, skull and scalp; electrical activity arising in deeper structures may not be identified[124]. These issues can be resolved with the use of surface or depth electrodes which can identify electrical activity with millimeter precision; albeit at a risk of infection, haemorrhage and cortical damage[131]. Such measures are usually reserved in cases of refractory epilepsy, where surgery may be indicated and great precision in localising foci is required[131].

2.6.2. Neuroimaging

Structural imaging techniques are required to rule out a structural cause for epilepsy[11]. NICE recommend that neuroimaging be used in all patients[105]. X-ray computed tomography (CT) scans are relatively insensitive and can miss lesions such as small tumours, cortical dysplasia or hippocampal sclerosis[11]. MRI is the preferred investigation, it is recommended by NICE and the ILAE[105,132]. In patients with a first seizure or newly diagnosed epilepsy, 13-14% of patients will have an identifiable lesion on magnetic resonance imaging (MRI)[133]. Of note is the study by Griffith et al who found abnormalities in 26% of patients with epilepsy if 3-Tesla scanners are used and localisation related epilepsy is suspected[134]. These results are particularly applicable to a UK population, as NICE guidelines were followed in the study design and method. The images of 120 patients were analysed by two reporters with 100% agreement and the most common abnormality was mesial temporal lobe sclerosis, which was found in 8% of all scans[134]. Other abnormalities included[134]:

- 4 brain tumours: 2 glioma, 1 dysembryoplastic neuroepithelial tumour and 1 epidermoid tumour
- Brain malformations
- Vascular malformations
- Encephalomalacia due to infarction

Lesions of the temporal lobe predominated this series: they were found in 69% of patients[134]. In some series, sensitivity of MRI can be 50%, so a standard protocol of T2 weighted, 3-5mm sliced scans are recommended for screening[132]. Griffiths et al utilised fluid-attenuated inversion recovery imaging (FLAIR) which allows for detection of more subtle grey matter changes[132,134]. Abnormalities can be found in up tp 83% of patients[134]. In a pre-surgical series of 385 patients with epilepsy, this high yield was obtained by using a combination of 3D T1, T2, FLAIR and contrast techniques[135].

In the immediate period after a seizure, MRI with FLAIR or contrast techniques focal can identify cortical swelling and other signal changes[7]. They are thought to be associated more with focal seizures and increased seizure severity; these changes be seen for around two days[7].

2.6.3. Other Investigations

In addition to imaging changes after a seizure, biochemical abnormalities associated with a seizure may include[7,136]:

- Cerebrospinal fluid (CSF) pleocytosis
- Lactic acidosis
- Raised Creatinine Kinase (CK)
- Raised prolactin (after generalised or complex partial seizures, but not absence or myoclonic)

These abnormalities are not specific to seizures; syncopal episodes can lead to raised CK and raised prolactin[7].The following investigations are usually performed to identify the cause of the seizure, rule out alternative diagnoses, and screen for any potential contra-indications for commencing AED therapy[7,105,136]:

- Complete blood count
- Blood biochemistry
- Liver Function test
- Thyroid Function test

There are numerous conditions which need to be ruled out when investigating patients with possible epilepsy. If cardiovascular events, such as vasovagal syncope and cardiac arrhythmias, are not ruled out by the history, EEG, prolonged ECG, tilt table testing, holter monitors, cardiac stress tests and CK levels may help[7,11]. Hypoglycaemia can be excluded through the use of blood sugar estimation when patients are symptomatic[11]. Transient ischaemic attacks could be indicated by the presence of abnormalities from carotid doppler, echocardiograms and biochemistry studies[137]. Serum CK levels are usually normal after attacks due to non-epileptic attack disorder[7].

2.7. Management

Epilepsy has a significant impact and this is especially evident when observing epilepsy in under-developed countries[138]. One study from Cameroon with matched controls found that persons with epilepsy had a 6-fold increase in mortality[139]. The most common causes of death in the epilepsy group were seizure related; i.e: status epilepticus, sudden unexpected death in epilepsy (SUDEP) and drowning[139]. As will be highlighted later, the mortality associated with epilepsy in developed countries is lower[138]. This disparity can be partly explained by a lack of treatment with anti-epileptic medication, which is a testament to their effectiveness[140].

2.7.1. Anti-epileptic drugs

Approximately 65% of newly diagnosed patients will eventually experience a degree of seizure freedom after commencement on an AED[141]. This is shown in SANAD (Standard and New Antiepileptic Drugs), the largest RCT performed in epilepsy, where in focal epilepsy AED treatment led to a remission of at least 24 months in 64% of cases after 6 years across all treatment groups[142]. For generalised epilepsy, AED treatment led to a 24 month remission after 6 years in 82% of cases[143].There are currently 23 AEDs available for use in the United kingdom (UK) and for the most part they are each unique in their use and mechanism of action[144,145].

2.7.1.1. Mechanisms of action

AEDs prevent seizures and no conclusive evidence exists to suggest that they exhibit anti-epileptogenic properties in humans[146,147]. Hopeful areas of anti-epileptogenesis research involve immunosuppressant's, anti-inflammatory drugs, plasticity modulatory drugs and proconvulssants[147].

The anti-seizure properties of most AED were discovered after the screening of drugs in animal models and it is only after this that their mechanism of action has been elucidated[145]. The anti-seizure properties of phenobarbital, the first known AED, was being tested for hypnotic efficacy at the time of discovery[146].

Current AEDs utilise numerous modes of action, but each AED can be broadly assigned to a category of anti-seizure action[146]:

1. Modulation of voltage dependent sodium, calcium or potassium channels.
2. Modulation of neurotransmitter release via presynaptic mechanisms, with an action on glutamate release being most relevant.
3. Alterations in GABAergic inhibition via actions on GABAA receptors or on GABA synthesis, reuptake, or degradation.
4. Decreased synaptic excitation via actions on ionotropic glutamate receptors.

Voltage gated sodium channels are responsible for sodium flux and thus neuronal depolarisation during the action potential[145]. They can rapidly cycle through active and inactive states which is important in normal neuronal function and also epileptic activity[145]. High frequency repetitive firing is thought to be essential in spreading partial and generalised seizure activity and AEDs dampen this by targeting sodium channels in the inactivated (depolarised) state[145]. This means that AED preferentially target neurones that are over-active, sparing their action on neurones displaying normal physiological activity[145]. Drugs that predominantly target sodium channels include phenytoin, lamotrigine, carbamazepine, oxcarbazepine and zonisamide[145]. While these drugs do not directly alter synaptic activity, their effect on presynaptic action potentials can inhibit synaptic output, and this is especially true for glutamate[145].

High voltage activated calcium ion channels are a key component of presynaptic neurotransmitter release[145]. Specific calcium channels are thought to be targeted by gabapentin, but exactly how this leads to reduced seizure activity has not been proven[145,146]. Other proposed secondary mechanisms for gabapentin include the synthesis of GABA transporters and the induction of increased sensitivity to GABA on receptors[148]. Other AEDs are found to mediate high voltage activated calcium channels, but it is not felt that this is their main mode of action. They include: phenobarbital, lamotrigine and leviteracetam[145].

Low voltage calcium channels regulate neuronal firing and are strongly associated with oscillatory thalamic activity during generalised absences[145]. Ethosuximide has a low affinity for these channels, but is very effective in reducing generalised absences[145]. This drug does not act on sodium channels or high voltage calcium channels and this in part explains its

ineffectiveness for partial and generalised seizures[145]. Interestingly, lamotrigine is also effective against generalised absences, but does not share this mechanism of action[145].

GABA mediated neurones are sparse in areas associated with epilepsy, for example the neocortex, hippocampus and the amygdala, which contain a higher number of excitatory synapses[145]. Despite this, they are crucial in dampening epileptic activity by preventing synchronisation and are a mode of action for some AED[145]. Phenobarbital was the first recognised anti-epileptic substance and it works by increasing receptor sensitivity to GABA and potentiating resultant signal propagation[145]. There are other drugs in which the main anti-epileptic mechanism is GABA modulation and they include the benzodiazepines, vigabatrin and tiagabine. Furthermore, drugs such as valproate, utilise GABA mechanisms secondarily[145]. These drugs work by targeting receptors, enzymes or transporters and are effective against most seizure types, with the exception of absences[145].

Glutamate is an important excitatory neurotransmitter that influences stimulation at the majority of CNS synapses[149]. There numerous glutamate receptor ion channels of which there are four families: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), kainate, NMDA (N-Methyl-D-aspartic acid) and delta receptors[149]. While no AED is solely associated with glutamate receptors, several mediate their effects at least in part through this method[145]. Felbamate exhibits action on GABA and NMDA glutaminergic synapses and is the only drug that is proven to clinically ameliorate seizures through NMDA[146]. Topiramate is effective against partial and generalised seizures and its mechanism is thought to include AMPA/kainate receptors: in addition to voltage-gated sodium channels, high-voltage activated calcium channels, GABAA receptors and carbonic anhydrase isoenzymes[146]. AMPA receptors are key mediators of seizure spread[145].

2.7.1.2. Non Seizure Effects

The CNS and AEDs are both complex and it is unsurprising that some AEDs do not solely prevent seizures. They can be used to treat migraine and neuropathic pain, probably as a result of overlapping pathophysiological mechanisms[150]. Furthermore, they have benefit for psychiatric disorders such as bipolar disorder, depression and schizophrenia, perhaps through influences on neuronal structural integrity and synaptic plasticity[151]. These are but a few of their non-epilepsy indications. Unfortunately, this varied benefit also relates to a risk of widespread adverse events.

2.7.1.3. Adverse Events

Choice of AED and dose is a compromise between seizure reduction and tolerability of side effects[141]. Data from SANAD highlights the importance of this; 50% of patients with focal epilepsy (arm A) reported adverse events at least once during the 6 year period of study[142]. This was the sole reason for treatment failure in 34% of patients, which was 17% of all patients[142]. It was the superior tolerability and side effect profile of lamotrigine over carbamazepine that made it the best drug of the trial, despite similar seizure preventing efficacy[142]. This finding has subsequently influenced clinical guidance, with lamotrigine and carbamazepine being considered first line treatment in focal epilepsy[95]. While SANAD reported that most clinicians would have prescribed modified release versions of carbamazepine, which has an improved side effect profile, critics argue that such preparations may not have been used and thus, carbamazepine was disadvantaged[142,152]. While this is unlikely to have altered the results in SANAD, special mention of carbamazepine and the use of modified release preparations has been included in the most recent NICE guidance[105].

Dose dependent adverse events include sedation, drowsiness, incoordination, nausea and fatigue[153]. They can be prevented with dose titration[153]. Other common side effects include headache, slurred speech and cognitive effects (including sedation)[153]. Organ systems other than the CNS are also adversely affected by AED. Such adverse events include liver failure, hypersensitivity reactions and aplastic anaemia to name a few[141].

It is important to note that different AEDs have different side effect profiles and that some side effects occur at different times after commencement of therapy (Table 4)[154]. Some of the newer anti-epileptic drugs do not induce hypersensitivity reactions, weight problems and do not require routine laboratory monitoring; unlike carbamazepine and valproate, where white cell counts and liver function tests respectively are routinely performed[147].

The most common idiosyncratic reactions are skin eruptions[7]. They vary in severity from a maculopaular rash to toxic epidermal necrolysis[7]. Such reactions are more strongly associated with the aromatic compounds in phenytoin, carbamazepine, phenobarbital and lamotrigine[7]. The milder rashes usually develop within the first month of treatment and will resolve in a matter of days after AED discontinuation[7].

Table 4: Early Onset and Late Onset Adverse Events after Commencing AEDs[154]

Early-onset adverse events	Late-onset adverse events
Somnolence	Sedation
Dizziness	Encephalopathy
Seizure aggravation	Depression
Gastrointestinal	Behavioral problems
Liver failure	Psychotic episodes
Hypersensitivity Rash	Leukopenia
	Aplastic anemia
	Thrombopenia
	Megaloblastic anemia
	Pancreatitis
	Nephrolithiasis
	Osteoporosis
	Hyponatremia
	Weight gain
	Weight loss
	Impaired Cognition

Other issues to consider are interactions with medications, worsening of seizures and teratogenic effects[141]. Carbamazepine, phenobarbital and phenytoin alter the hepatic cytochrome p450 system and valproate inhibits glucuronidation[154]. Newer drugs have little or no metabolism by the cytochrome p450 system and these drugs include oxcarbazepine, gabapentin, levetiracetam, lacosamide, lamotrigine, pregabalin, topiramate and zonisamide[154]. Older AEDs are also more likely to reduce therapeutic levels of drug when used in combination, e.g. carbamazepine reducing the plasma concentration of valproate[141].

Seizure worsening after AED is a particular risk for patients with idiopathic generalised epilepsy[154]. Typical absences are aggravated by carbamazepine, vigabatrin, tiagabine and gabapentin, and confusingly, idiopathic generalised epilepsies may respond therapeutically to these drugs[154].

AED drug monotherapy during pregnancy increases the risk of major congenital malformations in the foetus two to threefold when compared to the general population[155]. One Manchester based study took 277 women with epilepsy and compared their pregnancy outcomes to controls from the general population[155]. Of the epilepsy group, 67% of mothers took at least one AED and major congenital malformations were found in 6.6%, three times that of the control group[155]. Valproate was found to be significantly associated with abnormalities found in 16.7% of babies exposed with valproate polytherapy and 11.3% of those with valproate monotherapy[155]. Data on the teratogenic effects of AED has grown

due to registries in Europe and in the UK[156]. Topiramate increases the incidence of cleft palate by eleven times[156]. Phenobarbital, carbamazepine and lamotrigine are more loosely associated with teratogenic effects[156]. While monotherapy is preferred, polytherapy with carbamazepine or lamotrigine and any drug other than valproate does not seem to increase the risk of malformations[156].

2.7.1.4. Indications

It has already been mentioned that AED are matched to patients on the basis of their efficacy in treating different seizure types and while clinician and patient preference also influence AED choice it is important that prescribing practice in the UK follows NICE guidance[105,157]. Current NICE guidance for prescribing AEDs is included in appendix I.

2.7.2. Lifestyle Management

2.7.2.1. Sleep

It is clear that sleep deprivation increases the incidence of interictal spike wave discharges on the EEG and that sleep deprivation aggravates seizures in patients with generalised epilepsy[7]. For focal seizures, such a relationship is less clear. One survey study found that sleep deprivation alone did not account for seizures, but sleep deprivation, stress and fatigue in combination did[158]. Another study observing patients with and without sleep deprivation on video telemetry found that seizures were not increased by alternate days of sleep deprivation over a period of 6 days[159]. Possible reasons for these contrasting results include: patient difficulty in distinguishing between fatigue, stress and lack of sleep; and an observation period that was too short in the EEG study, or insufficient sleep deprivation. Either way, it is clear that it is harder to associate sleep deprivation with increased seizures in focal than primary generalised epilepsy.

Other than sleep deprivation, patients should also be aware that the following can trigger seizures: emotional stress, infections, fever, the menstrual cycle and more importantly: alcohol use, caffeine use, fasting, flashing lights and heat or humidity[158,159]. After sleep deprivation, fatigue andfever or illness are most likely to be reported by patients to aggravate seizures[158].

2.7.2.2. Accidents

In a telephone and interview based cohort study of 1000 epilepsy patients across Europe, it was found that epilepsy patients were over two times more likely to have an accident

leading to injury or financial loss while at home, at work and in the street[160]. When discounting seizure related injuries, epilepsy patients were still experiencing more accidents at a slightly increased rate when compared to controls[160]. Interestingly, there was no increased risk during sporting activities[160]. The authors believed that epilepsy patients undertook less sporting activities than controls, explaining this finding[160].

Moderate amounts of supervised exercise is permissible and with proper supervision swimming and boating can be safe, but patients with incompletely controlled seizures should avoid unguarded machinery, ladders, baths alone and driving for risk of harm to self and others[7].

2.7.2.3. Driving

Most countries ban patients from driving after a seizure, but the duration of the ban and deciding who is fit to drive is still debated[161]. In the UK, any form of seizure will lead to a driving ban by law. Patients that do not drive heavy good vehicles are able to re-apply for a licence after one year of seizure freedom.

New guidance states patients with an isolated seizure (defined as seizures occurring within a 24 hour time period only with no prior seizure history) can re-apply for their licence in 6 months, provided that there are no further seizures and there are no features in the case suggestive of an increased risk of further seizures, such as a cerebral lesion or abnormalities on an EEG[162].

Previously, patients with seizures isolated to sleep had to wait 3 years to reapply for their licence, but this has now reduced to one year. Patients that have focal seizures and are able to fully control a car during a seizure are able to re-apply for a licence after a one year period if this established pattern of seizures is maintained. These and patients with isolated sleep seizures can drive and continue to have seizures so long as the nature of these seizures do not change[162].

If a patient experiences a breakthrough seizure due to a change in medication, they are now allowed to re-apply for a licence after a seizure free period of 6 months with their previous medication[162].

These recent changes in driving legislation reflect an improvement in our understanding of seizure recurrence, which is a result of data from large studies, like the Multicentre study of

early Epilepsy and Single Seizures (MESS)[163]. This RCT randomised 637 patients who had a single unprovoked seizure to groups of immediate and delayed treatment. In patients like these, the decision to commence pharmacological management is difficult and MESS only recruited patients where the clinician was unsure whether to start treatment or not[163]. There were some concerns surrounding the external validity of the study as a result of this, but nonetheless, this study has influenced guidance.

The main findings of MESS can be summarised as follows[163]:

- "Six months after an index seizure the overall risk of recurrence in the following 12 months was significantly below 20% for people who started anti-epileptic drug treatment (page 7)."
- "Seizure while asleep and abnormal electroencephalogram results significantly increase the risk of a seizure recurrence in the next 12 months according to a multivariable analysis (page 7)."

For the first time, individualised risk is being calculated to inform decisions surrounding driving and this poses interesting questions about the availability of service provisions to match our knowledge.

2.7.3. Surgery

In 20-40% of patients, AED treatment is ineffective at controlling seizures[164]. It is estimated that surgery should be considered in 25% of all patients and that half of these would benefit from surgery[7,164]. However, delays in the identification of suitable patients, and hesitancy in referral, mean that surgery is underutilised[165]. Some authors argue that surgery should be considered earlier in the course of disease, as this may improve seizure freedom and quality of life[7,164]. Whilst this concept may seem implied, there is no supporting evidence from observational or RCT studies[166].

Before surgery can occur, a thorough pre-surgical workup including MRI, EEG, video telemetry, neuropsychological assessment and the Wada test may be performed to identify and confirm the site of the epileptogenic lesion and the areas of the cortex that are essential for function[167].In cases where the lesion is difficult to identify, for example mesial temporal lobe epilepsy with bilateral interictal spikes or extra-temporal epilepsy with non-correlating MRI and EEG findings, invasive EEG monitoring may be indicated[168]. An arrangement of subdural strips, subdural grids or intracerebral electrodes is tailored to each

patient's presumed epileptogenic zone[168]. Subdural strips and grids or strips and intracerebral electrodes are often used in combination[168]. Complications are infrequent, as infection and haematoma occur in 2.5% and 3% respectively with subdural electrodes and 1.8% and 0.8% respectively with intracerebral electrodes[168].

Refractory patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis are particularly favourable for surgery[164]. In these patients, class I RCT evidence suggests that temporal resection will lead to seizure freedom in around 60% after one year[169]. Numerous RCTs have been performed, all quoting significant seizure improvement in 60-80% of patients[164]. Unfortunately only half of these patients will remain seizure free after 10 years, even with commencement of AED treatment[7].

Excision of extra-temporal foci is not as commonly performed and results generally are not as good as temporal cases[170]. One observational study by Kral et al found that 72% of 39 patients with refractory extra-temporal epilepsy experienced a significant seizure improvement, were patients had at worst only 2 seizures per year, after a 50 month average follow up period[171]. In the same study, 79% of temporal cases had a significant improvement of their seizures[171].

2.7.3.1. Neurostimulation

When drugs and surgery are not successful, or when respective surgery is not indicated, neurostimulation may be attempted as an alternative[172]. Neurostimulation for epilepsy is delivered in the following forms: vagal nerve stimulation (VNS), trigeminal nerve stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation (DBS) and cortical stimulation[172]. The evidence level of these methods varies from RCT to experimental pilot studies[172]. Strong RCT evidence exists for VNS, DBS of the anterior thalamus and closed loop stimulation[173]. In the UK, VNS is recommended by NICE guidance for use in adults and children with refractory epilepsy[105]. NICE suggest that when DBS is used, further actions such as informing clinical governance and auditing outcomes be performed due to the relative limitations in DBS understanding[174].

Vagus nerve stimulation has proven efficacy and safety[172]. Seizure improvement, in terms of seizure frequency, duration and intensity, seems to start 6-8 weeks after initiation of treatment and the effect of seizures will continue to improve after a plateau is reached, where in 44% of patients experience a reduction in seizure frequency after 2 years[172]. A long term study from Sweden found that after 5 years, 44% of patients experienced seizure

reduction[175]. A recent series of 90 patients found seizure improvement after 5 years in up to 64% of patients[176]. Seizure reduction was complete or over 90% improved in 21% of cases and complications were present in 13%[176]. In vagal nerve stimulation, complications include[172]:

- Tingling of the throat and hoarseness of the voice
- Vocal cord paresis
- Left anterior neck muscle movement
- Hiccup
- Cough
- Shortness of breath of exertion
- Bradycardia
- Ventricular asystole

Despite these potential complications, VNS is well tolerated and stimulation is discontinued most often as a result of lack of seizure reduction[172].

2.7.4. Ketogenic Diet

The ketogenic diet can be used in all refractory epilepsy patients to reduce seizures[177]. The effectiveness of the diet varies in different patient populations[177]. The diet is usually prescribed to children[177]. In one series of 150 children with frequent generalised seizures despite polytherapy on AEDs, 7% were seizure free, 20% had a greater than 90% reduction in seizure frequency and 23% had a 50-90% seizure reduction[178]. Follow up studies demonstrate that the effectiveness in reducing seizures is maintained 3-6 years after initiation of treatment and that seizure freedom can occur in patients with only a partial response to the diet initially[177]. Most studies are aimed at generalised epilepsies in children, but one study comparing the efficacy of the ketogenic in focal and generalised epilepsy demonstrated that the seizure reduction between the two groups was not significant[179]. NICE guidelines recommend that the ketogenic be considered in children and young adults with epilepsy that have not responded to AED[105].

2.8. Prognosis

2.8.1. Quality of Life

Epilepsy is a lifelong condition that can impact on most domains of a person's life; the right to drive and the risk of accident has already been mentioned[161]. QoL is representative of overall life satisfaction and both are influenced by all life domains[180]. It is not surprising therefore that patients with epilepsy have a reduced QoL[138].

It is widely quoted that the quality of life of children with epilepsy is poorer than that of children in the healthy population, but this statement may not be generalizable to all children with epilepsy[181,182]. Studies that have shown significant differences in QoL between patients and controls recruited patients that either had refractory epilepsy or a significant proportion of severe neurological comorbidities[183,184]. One study compared the quality of life of 31 children with well controlled epilepsy and healthy controls[185]. Apart from 6, all of the epilepsy children were seizure free and off medication[185]. There was no significant difference found in the quality of life of either groups and this could be due to the genuine wellness of the epilepsy cohort, or due to reduced sensitivity to poor quality of life because of low sample size or the use of an inappropriate tool; the QoL questionnaire used was designed for children with short stature[172]. Predictors of poor QoL in children include[181]:

- Older age
- Lower socioeconomic status
- Increased seizure severity
- Multiple AED use
- AED neurotoxicity and
- Co-morbid neurological impairment

While still complex, the quality of life of adults is far easier to establish and there is a large amount of research on the topic. Data from two large population based studies in the USA and Canada demonstrate that the quality of life of people with seizures or epilepsy is significantly poorer than healthy people and people with other chronic diseases in the general population[186,187]. There was a high proportion of comorbid conditions in the USA epilepsy population when compared to the general population and these were: stroke, cancer, arthritis, lower neck pain, lower back pain and asthma[186]. Comorbid medical and psychiatric conditions combined can explain 14% of the variance in QoL scores in Epilepsy[188].

Both studies demonstrated that people with seizures or epilepsy were more likely to report lower levels of education, unemployment and physical activity, and increased levels of psychological distress and recurrent pain[186,187]. A study looking at predictive factors for poor quality of life in outpatient attendees with epilepsy identified the following as negatively predictive[189]:

- Increased seizure frequency
- Lack of Seizure freedom
- Depressive state
- Short duration of epilepsy in older persons
- Temporal lobe epilepsy (through mood and cognition)
- Young females due to AED adverse effect concerns

Extending on the point of epilepsy duration, Jacoby and Baker performed a thorough literature search to estimate quality of life trajectories for patients with epilepsy at different stages of management[188]. They found that patients with isolated or very few seizures had an initial dip in QoL around the time of the event which eventually normalised to that of the general population[188]. Active epilepsy, defined by varying degrees of seizure frequency ranging from 1 in 2 years to 1 in 3 months, significantly depresses QoL and the resultant trajectory varies by the clinical trajectory that follows[188]. For example, patients with intractable epilepsy were suggested to have peaks and troughs in QoL depending on seizure frequency and patients that eventually are seizure free will gradually improve in QoL until normalisation[188]. After epilepsy surgery, QoL will improve towards normal, unless clinical outcome is poor[188]. Another finding from this review was that the time taken for QoL to improve seemed to be 1-2 years for patients with single seizures and 2 years for patients with remission after epilepsy treated medically or with surgery[188].

2.8.2. Epilepsy outcomes

2.8.2.1. Seizure Reduction

One of the primary aims in epilepsy management is to reduce the number of seizures a patient has. As patients with epilepsy are usually commenced on an AED, the long term likelihood of the condition entering remission without intervention is not certain[138]. It is unethical to withhold medication during prospective studies and retrospective studies are hampered by inaccurate data[138]. One prospective study in Kenya recruited 249 patients with epilepsy; for inclusion they needed to have at least 2 witnessed generalised tonic clonic seizures and to be started on either carbamazepine or phenobarbitone[190]. After 6 months, a quarter of patients had a significant (50%) reduction of seizures and after a year, 50% of patients were seizure free[190].

The minority of patients will develop epilepsy after one seizure, but after a second seizure, the risk of further seizures is 75%[138]. Studies that monitor the effects of delayed treatment, like the aforementioned MESS study, help to ascertain the risk of seizures after an AED is started[163]. There is a 20% chance of seizure in the 12 months following commencement of AED treatment[163]. Studies with a longer follow up or observation period demonstrate that approximately 65% of patients will eventually enter remission[138]. After remission, approximately 24% of patients in remission will relapse[138]. The following are found to be negative predictors of long term seizure prognosis[138]:

- Symptomatic epilepsy
- Epilepsy associated with Cerebral Palsy and Learning Difficulties
- Partial Seizures, particularly complex partial
- Status Epilepticus in childhood
- Focal slowing of the EEG in childhood

According to the ILAE, patients with refractory epilepsy should be defined as “failure of adequate trials of two tolerated and appropriately chosen and used AEDs to achieve sustained seizure freedom for a sufficiently long period of time (page 1076)”[191]. In this definition, a sufficiently long period of time is either three times the longest seizure-free period, or one year, whichever is longer[191].

2.8.2.2. Adverse Effects of AEDs

Approximately 50% of patients will report adverse effects when started on an AED[142]. Overall adverse effects are unpredictable, but certain drugs have different side effect profiles, increased doses are more likely to lead to side effects and pharmacogenetics can predict who is at risk; for example, Stevens-Johnson syndrome in an Asian patients with HLAB* HLA allele[141].

2.8.2.3. Drug resistance

Long term observational studies show that 7% of newly diagnosed patients will prove to be extensively drug resistant, never achieving one year remission[192]. A further 15-20% will relapse and remit[194]. It has been observed that a high frequency of seizures before the onset of therapy suggests an increased risk of having refractory epilepsy[141].

2.8.2.4. Tolerance

AED can lose their anti-seizure properties after long periods of administration due to pharmacodynamic tolerance[193]. It is difficult to identify the effect of tolerance on efficacy of medication, but studies looking at outcome shifts from responder to non-responder may be suggestive[193]. In Loscher et al.'s review of the literature on tolerance, it was stated that for older generation drugs, the transition from responder to non-responder occurs in 7-58%[193]. It is lower for drugs that act predominantly on sodium channels[193]. For second and third generation drugs this same effect occurs in around 25%[193]. These figures vary by drug[193].

2.8.2.5. Mortality

When compared to the general population, the standardised mortality ratio (SMR) for epilepsy has ranged between 1.6 and 4.1 in hospital and community based studies[125]. The SMR is high in symptomatic epilepsy, ranging between 2-6; and for patients with neurodevelopmental problems, it ranges from 11-25[138]. Predictors of higher SMR include[138]:

- Male gender
- Age: childhood or the elderly
- Duration of epilepsy (being within few years of diagnosis)
- Generalised tonic clonic seizures
- Myoclonic seizures

The increased mortality in epilepsy can be accounted by the co-morbid condition leading to epilepsy, for example stroke, neoplasia and pneumonia, but also by epilepsy related causes,

such as SUDEP. According to a 40 year follow up population based study, the overall risk of SUDEP was 7% for patients not in 5 year remission and 12% for those who were unmedicated[194].

Chapter 3: Quality of Life

3.1. Introduction

It is not difficult to understand the concept of quality of life (QoL). Most people will know what QoL represents and can predict the factors that are relevant in its overall assessment. Defining QoL and measuring it however, is difficult due to variable opinions on definition, the significance of many factors on quality of life and the variability of QoL between subjects and indeed within subjects.

3.1.1. What is Quality of life?

The constituents required for a good life have been debated and there is a range of overlapping models to help describe this concept[195,196]. Frequently proposed themes include, happiness, a sense of purpose, wisdom, creativity, a philosophy of life, achievement and the experience of love[195]. Aristotle argued that all of these components ultimately lead to happiness[195]. Large cross cultural surveys on the perceived importance of life goals conclude that happiness is considered to be most important goal, more important than good health, a high income, high intelligence, being attractive, experiencing love and finding meaning and purpose in life[197].

According to Daniel Haybron, a modern professor in philosophy, there are three parts to happiness[197]:

- Psychological Happiness; a state of mind involving feelings of joy, serenity and affection as a result of hedonic experiences (sensory thrill).
- Prudential Happiness; a state of mental and physical wellbeing. Life satisfaction (a cognitive assessment of happiness or wellbeing) is important in this regard.
- Perfectionist Happiness; a moral life that is good in all aspects. This is similar to the association of virtue as described by the Greek philosophers, Plato, Socrates and Aristotle.

Despite the existence of such theories and concepts, a pragmatic and broad approach is adopted in QoL research on account of a lack of clarity, overlap and inconsistency in theories[196]. Reinforcing this point is a systematic review by Bakas et al, which found that out of 1,552 articles reviewed on the topic of QoL research in healthcare, only 100 articles

mentioned a QoL model[180]. Furthermore, there was little consensus between studies for the model used when one was mentioned[180].

QoL can be defined as "An essentially subjective judgment of the way people perceive themselves as contented and happy or otherwise and able to function physically, emotionally and socially (page 1)"[198]. It is important to note that there is no consensus on the definition of QoL, which differs especially by field of study[199]. Most would agree that QoL "is a multidimensional construct, encompassing aspects of psychological, social and physical well-being (page 24)"[199].

3.1.2. Utilisation of Quality of Life

The concept of Quality of Life was first mentioned in 1953 by the economist Samuel to describe concerns surrounding unlimited economical growth and its negative ecological effect[200]. In the subsequent decades, understanding of QoL grew and its application utilised in medicine for identifying patient needs and as an outcome measure for treatment[199].

3.1.3. Health Related Quality of Life

Within the field of medicine, interest in QoL increased in the early 1970's: possibly as a result of the improvement in medical technology; and the need to evaluate quality of life when quantity of life increases[201]. Health related quality of life can be defined as:

"a concept encompassing a broad range of physical and psychological characteristics and limitations, which describe an individual's ability to function and to derive satisfaction from doing so (page 24)"[199].

In 1980, the World Health Organisation released an International Classification of Functioning, Disability and Health (WHO ICF)[180]. It has evolved since to the current 2007 version and lists factors that are important in evaluating wellbeing, health and disability on a physical, mental, social and environmental level[202]. The ICF has since been used for policy development, economic assessment and in research[203].

QoL research interest has increased particularly since 1974 as shown in Figure 1 when "quality of life" was inserted into pubmed[204].

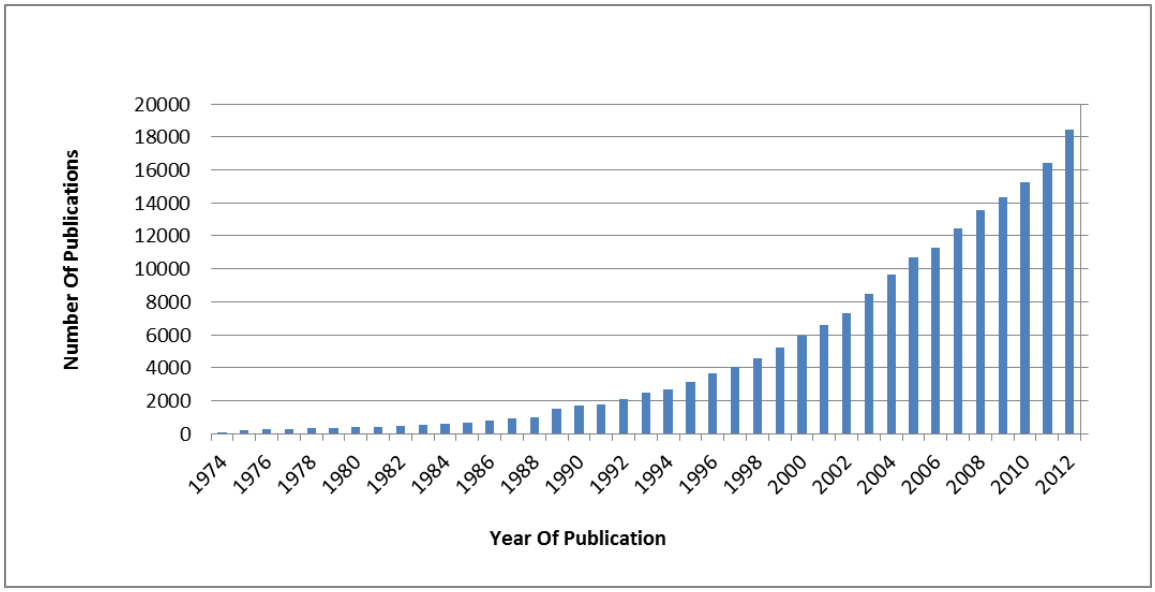

Figure 1: Pubmed Search; Quality of Life Articles per Year

3.2. Questionnaires

QoL is usually ascertained by a questionnaire that is completed by the subject or by an examiner[196]. Numerous health related QoL tools exist and most have numerical values for answers where scores can be totalled up and compared between subjects[196]. Items in questionnaires can be split into indicator and causal variables. Indicator variables do not necessarily alter QoL but reflect it, while causal variables in theory influence QoL[205]. Recognising the presence, absence and proportion of indicator or causal variables is important to establish as both act differently[205]. In questionnaires with separate domains, e.g. physical wellbeing, social wellbeing etc, subscale scores can be calculated[207].

Some questionnaires provide a generalised overview of quality of life and others are more specific in teasing out factors specific to a pathology and the complex impairments on wellbeing that can result[196]. General QoL questionnaires have the advantage of producing data that can be compared between different patient disease groups[196]. This also means that they may not be sensitive enough to recognise factors that are important in a particular patient group[196]. Disease specific questionnaires are tailored so that particular issues within a disease are recognised and reflected by the resultant scores[196]. These scores are usually more sensitive to changes in disease[196].

The choice of using a general or specific questionnaire should largely depends on the group of patients studied. In one study comparing general to disease specific questionnaires in

patients with Rheumatoid Arthritis (RA), all questionnaires were able to differentiate between severities of RA[206]. In another comparison study, a general questionnaire was a more valid measure of QoL than a disease specific tool in Asthma and was better at discriminating between different QoL domains[207]. On the other hand, a disease specific QoL score for Atrial Fibrillation was found to be more sensitive in detecting lower QoL than a generic tool[208].

It is advantageous for a questionnaire study to contain aspects of both a general and a disease specific questionnaire[196]. Some questionnaires have been designed with this in mind and alternatively some studies use both a general and a disease specific questionnaire[196].

3.2.1. Questionnaire Development

The creation of a questionnaire is a complex and time consuming process[205]. The European Organisation for Research and Treatment of Cancer's (EORTC) QoL group have developed many QoL questionnaires and have published guidelines for questionnaire development[209]. Below is a summary of the main points in the process[209]:

- The questions must be chosen after a thorough knowledge and understanding of the target population has been obtained: which can be achieved by reviewing past literature; and interviews with patients and clinicians.
- Once a series of questions have been chosen, the questionnaire will begin a testing procedure.
- A pre-test will be performed, testing the design of the questionnaire and questions. A review process with structured interviews will then follow. Preliminary scale structures can be hypothesised.
- A field test will be performed to assess the validity, reliability, acceptability and cross cultural application. For this a large multinational cohort of patients must be used.

3.2.1.1. Validity

The EORTC propose that the sample size needed for the validation of questionnaires is 10 subjects per question[209]. Questionnaires need to be valid in terms of the following[199]:

- Content: is the questionnaire sensitive to the relevant QoL domains of the tested population?

- Convergence: does the questionnaire correlate with other similar outcomes? While there is no gold standard of life quality in which to validate questionnaires, general questionnaires or a single global scale question are used for comparison[196,199]. In disease specific questionnaires, another specific questionnaire may be used, or new validation studies using general scales may need to be carried out[196].
- Discriminance: does the questionnaire distinguish between dissimilar constructs?

3.2.1.2. Reliability, Appropriateness and Responsiveness

Tests of reliability are also important. Can the questionnaire produce the same results when repeated? The inter-rater (observer) and test-retest reliability scores for questionnaires need to be considered[196]. While precise levels of reliability required are controversial, the EORTC state that a test-retest reliability of 0.70 is regarded as acceptable, while a reliability of 0.80 is regarded as good[209]. If the tool is required for patient monitoring, the reliability needs to be higher than this[209].

Also, how appropriate is the questionnaire to the study population? Is the time scale, format and wording of questions applicable to the study population?[196]. Furthermore, can the tool recognise clinically meaningful changes in QoL when they are present?[196].

3.2.1.3. Other Psychometric Issues

The ceiling effect may occur when the response to a question has a tendency to skew towards an extreme, this can be prevented by adapting the available responses to create more variability within the extremes[199].

It is recognised that patients adapt to changes in their physical wellbeing[199]. One study demonstrating this is of 160 breast cancer patients at least 5 years post-diagnosis[210]. Their QoL was compared to the QoL of a control group, in which no differences of QoL were found[210].

In studies using a pre and post-test design, subjects may initially over-estimate their wellbeing (response shift)[199]. This phenomena can be reduced by adding a retrospective pre-test after the post-test response has been created, thus ensuring that subjects complete both tests with the same internal cognitive standards[199]. This technique was tested by Howard et al, who applied the technique to 33 psychology students and their perceived knowledge on a particular class[211]. He found that there were significant differences between

the retrospective pre-test and the prospective pre-test, in which subjects over-estimated their knowledge in the prospective pretest[211]. The same findings were found in a similar study by Pohl[212].

3.3. Factors Influencing QoL

It is beyond the scope of this thesis to review the literature on the factors that generally influence QoL. Instead, the important influential factors will be mentioned. It is important to note that the research presented refers to life satisfaction, happiness or overall wellbeing, which influences QoL, but does not necessarily dictate it.

3.3.1. Population Factors

On a macroscopic level, economic and political factors are known to effect the general wellbeing of a population.

3.3.2. Economy

Examples of factors that are important in the wellbeing of a population are economic fluctuations, income inequality and unemployment[213].

Between 1991 and 2004, Ireland experienced an economic boom with a 70% increase in GNP and reduction in unemployment[214]. A study using population representative data from the Living in Ireland Survey looked at the responses to questions in different domains, finding a substantial increase in financial satisfaction and modest increases in work satisfaction and mental health as measured by the general health questionnaire (GHQ)[214]. Satisfaction related to housing, leisure activities and most importantly overall health were not affected[214].

After a review of the topic, one author concludes that income inequality will reduce the QoL of a population overall, particularly for the poor[215]. Subjects that are employed, over 40, with below average incomes and have a recent wage increase tend to have the highest life satisfaction ratings[215].

Unemployment is repeatedly shown to reduce the QoL of persons in countries with a higher GDP[213]. A longitudinal population based study asking people to rate their overall life satisfaction found that people who are eventually unemployed do not initially have poor life satisfaction before the unemployment event, but develop poor life satisfaction which is

maintained even if re-employment occurs[216]. This relationship is complex, with many factors such as health influencing unemployment and QoL[213].

3.3.2.1. Political and Cultural Factors

Studies monitoring the levels of life satisfaction comparing countries with and without political unrest have found that life satisfaction tends to increase in countries with low levels of corruption and high levels of law and order[213]. Furthermore, economic freedom is found to correlate with increased satisfaction in poor countries, while political freedom correlates more strongly in wealthier countries[213]. But both economic freedom and political freedom are thought to be associated with good life satisfaction in the population[213].

3.3.3. Individual Factors Influencing QoL

3.3.3.1. Wealth

Cross-sectional survey studies generally conclude that increasing wealth improves subjective wellbeing, but the very wealthy (selected from the Forbes list of most wealthy Americans) are not much happier than a control group of wealthy people in a similar area[213]. This effect is mediated by ones perception of comparative wealth[213].

Long term studies demonstrate that as income steadily increases however, this does not lead to an increase in satisfaction[213]. This is explained by an increase in material aspirations[213].

3.3.3.2. Age

Long term population based studies suggest that wellbeing follows a U shaped curve relative to age, with satisfaction bottoming out in middle age and increasing to the age of 65[213]. After the age of 65 life satisfaction steadily declines, mirroring the perceived reduction in health[213].

3.3.3.3. Gender

Females are usually reported to have higher life satisfaction ratings than males in population based surveys, but this finding is not consistent[215]. Age is an important moderator as middle age women report reduced overall happiness than males[213]. A meta-analysis of 300 studies concludes that older females have worse subjective wellbeing than males[217].

3.3.3.4. Marriage and Family Life

A literature review of cross-sectional studies concludes that wellbeing is higher in persons that are married than not married[218]. Longitudinal studies however suggest that while happiness is increased after marriage, this effect is not long lasting[219].

Subjects that become widowed demonstrate long term reduced life satisfaction ratings. A longitudinal study of 15 years suggests that widows have reduced life satisfaction ratings that never return to that of their pre-widowed state[220]. Divorce leads to a more temporary reduction in life satisfaction[205,213].

3.3.3.5. Health Factors

Physical health is an important factor in determining quality of life, from a patient or population perspective. In a population based survey study, physical health was deemed the most important factor that determined happiness[221].

The relationship between health and wellbeing is complex; an individual condition can effect varying and numerous QoL domains, but compounding this may be the presence of numerous conditions within the individual[222]. QoL after a cardiac event for example is impaired in domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, while domains affected due to peripheral arterial disease are mobility and pain[223]. In a recent multicentre study of 3000 primary care patients between the ages of 65 and 85 with multimorbid conditions, it was found that QoL was negatively correlated with increased disease severity and disease count[222]. This study took into account a large number of conditions, 45 in total, where previous literature only analysed 29 conditions[222]. Of these 45 conditions, 21 were found to impair quality of life[222]. Table 5 shows the top 16 conditions that impacted QoL, ranked by their effect on the EQ-VAS (a 100 point overall wellbeing visual analogue scale)[222].

Table 5: Medical Conditions that Significantly Reduce QoL According to Reductions in EQ-VAS Score[222]

Disease	Drop in EQ-VAS (total score 100)
Parkinson's disease	(-12.29)
Rheumatism/CPA	(-5.56)
Depression	(-5.33)
Obesity	(-4.33)
Cardiac insufficiency	(-4.19)
Neuropathies, asthma/COPD, osteoporosis, chronic low back pain, coronary heart disease, insomnia and urinary incontinence.	significant negative effects on HRQL

An inverse link between disease count and QoL has been shown in studies with younger populations[222]. Meta-analyses find moderate but consistent correlations between physical health and overall wellbeing; this finding is stronger in females than males[213].

3.3.3.6. Sleep

Lack of sleep is known to negatively influence the body and mind. In a study of 502 community residents, those with poor sleep were found to be impaired in various domains of wellbeing[224]. The relationship between sleep duration and health follows a U shaped curve[224]. One large scale epidemiological study associated low mood and social isolation to persons who on average achieved less than 7 hours and more than 9 hours of sleep in a 24 hour period[225]. This U shaped relationship between sleep duration and impaired health has been reproduced in many epidemiological studies[224]. A causal direction has not been established, but it is likely that the association between sleep and wellbeing is bi-directional[225].

3.3.3.7. Summary

Quality of life is a multidimensional concept with complex interrelationships between physical, psychological and social factors. In order to appreciate a person's quality of life in the context of epilepsy and meningioma, an understanding of these two conditions and the combination of these conditions is required.

Chapter 4: Epilepsy and Meningioma

4.1. Introduction

The epileptogenic potential of meningioma is well recognised. In 1935, Robert Groff published his series of 291 resected meningioma patients describing their association with epilepsy[226]. Of these patients, 114 experienced seizures of various type, frequency and prognosis[226]. Among his observations, he found that epilepsy often predated neurological impairment, that meningiomas of the parietal, frontal and temporal lobes were particularly epileptogenic, that seizures can develop after surgery, that surgery can relieve seizures and that seizures can recur after a long period of remission with no evidence of tumour recurrence[226]. Of those experiencing seizures, 50 died prematurely within the average follow up period of 4 years[226]. While the causes of death in these patients may not be seizure related, it is important to note that epilepsy has a significant effect on the outcome of meningioma[226].

4.2. Epidemiology

4.2.1. Epilepsy in Meningioma

Not many studies have focused on the incidence of epilepsy in meningioma[227]. In the literature, the proportion of patients with seizures as the first symptom ranges between 20 and 50%[227]. In Lieu et al.'s retrospective analysis of 222 surgically treated meningiomas, 59 (26.6%) presented with epilepsy and 30 (13%) presented postoperatively[227]. This data suggests that at least 40% of meningioma patients will develop seizures around the time of diagnosis and within a relatively short follow up period[§227]. Similar percentages of pre and postsurgical epilepsy have been found in other recent studies[228,229]. The majority of studies conducted between 1930 and 1980 find that the proportion of patients with epilepsy pre-operatively is greater than 60%[230,231]. The proportion of patients developing epilepsy post-operatively however, is comparable to that of recent studies[230,231]. One explanation for this is the increased availability of advanced imaging techniques after 1980, leading to an earlier diagnosis of meningioma and thus a reduced risk of developing seizures.

[§] Maximum follow up period for patients with epilepsy was 12 years and the minimum was 1 year in this study looking at the prognosis of meningioma patients[227].

4.2.2. Meningioma in Epilepsy

Brain tumours are responsible for 6-10% of all epilepsy cases and 12% of acquired epilepsy cases[232]. Meningiomas receive little mention in the epilepsy literature, whereas gliomas are frequently reported[104,109,110,233]. In one prospective population based study of epilepsy, brain tumours were found in 11% of cases: 71% of brain tumours were primary and at least 71% of the primary tumours were glioma[234]. Perhaps the reason meningiomas are not mentioned is they account for one fifth of intracranial tumours and are less epileptogenic than benign gliomas[235]. In one study of parietal tumours and epilepsy, meningiomas were found accountable for seizures in 14% of cases[236].

4.3. Associated Factors with Epilepsy

There are no gender differences associated with the occurrence of epilepsy in meningioma[227]. Preoperative epilepsy is more common in meningioma patients who are aged between 50 and 60, but this finding was not statistically significant in Lieu et al.'s study[227].

Location of the meningioma is important in the development of epilepsy, with an increased incidence associated with supratentorial tumours and more specifically the convexity, sphenoid wing parasagittal and falx regions[227,237]. The parietal lobe is most often quoted as the lobe most associated with epilepsy in meningiomas, but there is variation in the literature[227,237]. A recent 3D magnetic resonance imaging (MRI) study of 44 pre-surgical supra-tentorial meningioma patients found the premotor cortex of the frontal lobe to be associated with the highest incidence of epilepsy[238].

The histological type of meningioma is usually not associated with significant differences in epilepsy incidence[227,237]. Peri-tumour oedema is significantly associated with the development of epilepsy in Lieu et al.'s study[227]. Around 40% of patients with oedema developed epilepsy, as opposed to 20% of patients without oedema[227]. The MRI study by Hamasaki et al found that the absence of oedema was a significant finding for their non-epilepsy group[238]. Patients experiencing seizure freedom after surgery varies between 19% and 64%[227].

Factors associated with the development of seizures postoperatively include: pre-operative seizures, peritumoural and cerebral oedema, brain retraction, interruption of cortical veins, arterial damage and Simpson's grade of resection[227].

While informative, studies looking at the associated factors leading to epilepsy are limited. One recent retrospective study observed the seizure outcomes of 626 surgically resected supratentorial meningiomas and summarised the limitations of the literature in the following way[239]:

- Studies lacked a uniform population (infratentorial, paediatric, different grades)
- Lack of multivariate analysis

Their study had a uniform population and a multivariate analysis was performed. The factors significantly associated with preoperative seizures after multivariate analysis were Karnofsky Performance Score (KPS) <80, absence of headaches and vasogenic oedema. Less significant factors associated with pre-operative seizures were male gender and larger tumours. Significant factors for the continuation of post-operative seizures were uncontrolled pre-operative seizures, parasagittal and sphenoid wing tumours.

4.4. Pathophysiology

4.4.1. Epilepsy in Brain Tumours

The following are thought to influence the development of epilepsy in brain tumours[232,237]:

- disruption of neuronal connections and inhibition of local network regulation
- Neuronal, axonal and synaptic plasticity, i.e. neuronal generation, axon collateral sprouting and neosynaptogenesis
- impaired glial cell activity
- increased vascular permeability
- abnormal function of the blood brain barrier
- peritumoral oedema
- inflammation
- necrosis
- hemosiderin deposition
- disequilibrium of neurotransmitters, ions and amino acids

Some tumours vary in their basic epileptogenic actions[232]. Glioma for example are infiltrative, while meningiomas disturb the cortical surface[232]. The development of epilepsy in brain tumours is multifactorial[232].

4.4.2. Meningioma Specific Factors

Peritumoural brain iscahemia is one factor thought to be important in meningiomas and this would partly explain the correlation between oedma and the development of epilepsy[232,237]. It would also be expected that size of the tumour, degree of mass effect and necrosis and

the location of the tumour would correlate with the development and location of the epileptogenic foci[237]. As this is not always the case, it is clear that other factors are significant[237].

While denervation of surrounding cortex is a significant epileptogenic factor, meningiomas usually distort the surrounding cortex and influence an increase in connectivity[237]. Dysequilibrium of ions, neurotransmitters and amino acids is also thought to be influencial in meningioma and epileptogeneis[237].

Histological studies of peritumoural cortex provide further evidence to the epileptogenesis of meningiomas[237]. Significant differences in the levels of size, distribution and number of presynaptic neurones could lead to increased release of excitatory neurotransmitters[237].

4.5. Treatment

There is a desire to prevent seizures, they can lead to aspiration, brain injury, trauma and brain oedema[240]. In meningioma, anti-epileptic drugs (AEDs) are widely used in this regard but the evidence base behind this is poor.

4.5.1. Prophylaxis

Neurosurgery is known to promote seizures as a result of brain retraction, cortical irritation, hydrocephalus, oedema, or infection[241]. But despite this there is no data to suggest that all meningiomas should receive seizure prophylaxis around the time of surgery. In a recent systematic analysis of 698 supratentorial meningioma patients from 19 studies containing AED prophylaxis outcomes, no early or late seizure benefit was found between treated and non-treated populations[241]. This does not mean that patients should not receive prophylactic treatment. The analysis excluded patients with pre-operative seizures, a strong risk factor for developing post-operative seizures. Therefore, the use of prophylactic AEDs may be considered in cases where there is a high seizure risk[241].

4.5.2. Long Term Pharmacotherapy

Studies of seizure control and characteristics are few and limited[239]. One recently published study observed the seizure outcomes of 626 surgically resected supratentorial meningiomas[239]. Patients with seizures were treated with the following AEDs:

- Phenytoin 52%
- Levetiracetam 26%,
- Divalproex sodium 11%
- Carbamazepine 11%
- Lamotrigine 2%
- Phenobarbital 2%

Patients were followed up and their seizure frequency recorded with the Engel[242] classification:

- class I: seizure-free.
- class II: rare seizures.
- class III: meaningful seizures.
- class IV: no seizure improvement or worsening

The majority of patients were seizure free with AED treatment. The distribution of patients across Engel scores after 12 and 48 months is included in Table 6.

Table 6: Seizure Outcome Classified by Engel Score 12 and 24 Months Post Meningioma Resection[239]

Engel Score	12 Month (%)	48 Month(%)
1	82	90
2	5	3
3	7	0
4	5	7

As mentioned previously, adverse post-operative seizure prognosis is associated with uncontrolled pre-operative seizures, parasagittal and sphenoid wing tumours[239]. Choice of AED was not found to influence seizure outcomes[239].

Another retrospective study has observed that AED withdrawal in meningioma results in seizure recurrence for 9% of patients, which is less than that observed in non-tumour patients with epilepsy[243].

4.6. Prognosis

While mortality is not increased when epilepsy and meningioma occur concurrently, morbidity may be synergistically affected[80]. A recent study comparing neuro-cognitive function of meningioma patients to healthy controls, found that meningioma patients experienced significant deficits in all domains tested after an average follow up period of 3.4 years; domains tested were: executive functioning, verbal memory, information processing capacity, attention, psychomotor speed and working memory[244]. Patients that also had epilepsy, had significantly worse executive functioning and psychomotor functioning and this was attributed to higher epilepsy burden and the use of AED[244]. Another study also found that quality of life (QoL) was impaired in patients with meningioma and epilepsy, this will be discussed in the next section.

4.7. Epilepsy Meningioma and Quality of Life

Minimal research has been conducted on the quality of life of those with epilepsy due to meningioma[245]. To demonstrate this, a literature search was performed.

4.7.1. Literature Search

The following search terms were entered into PubMed (MEDLINE):

"(epilep* OR seizure*) AND (quality of life OR qol OR wellbeing OR health) AND (meningioma)"

This generated 11 results. Only three articles were relevant to the topic of QoL in meningioma due to epilepsy and written in English:

1. Seizure Control for Patients Undergoing Meningioma Surgery[239].
2. Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas[245].
3. Factors influencing morbidity and mortality after cranial meningioma surgery-a multivariate analysis[85].

4.7.2. Literature Review

Seizure Control for Patients Undergoing Meningioma Surgery[239]

This is a retrospective analysis of 626 post surgery meningioma patients, 84 of which presented with seizures. The authours found that patients with epilepsy were three times more likely to have a reduced KPS (<80). KPS is a 100 point measure of physical functioning. While physical functioning is an important element of quality of life, it does not correspond to overall QoL[246].

Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas[245]

Waagemans et al looked at the effect of cognitive defects and epilepsy on long term QoL in 89 low grade meningioma patients after neurosurgery. They found that QoL as measured by the SF-36 (an overall QoL instrument) was significantly impaired by cognitive dysfunction or AED use. The authours concluded that epilepsy reduced quality of life as a result of cognitive deficits via AEDs. This study was limited by a small sample size; AED use was found in only 23 patients and only 11 patients had seizures in year prior to participation. In addition to this, epilepsy's effect on QoL was not the primary outcome of the study.

Factors influencing morbidity and mortality after cranial meningioma surgery-a multivariate analysis[85]

This study performed a multivariate analysis on 385 post-surgical meningioma patients. Seizures were found to influence the post-operative KPS score, but had no bearing on QoL, which was only significantly impaired by cranial nerve disturbances.

4.7.3. Discussion

There is a lack of literature focussing on the impact of epilepsy and meningioma on QoL. Studies that mention both factors have a low sample size of participants with epilepsy, do not use an appropriate QoL tool, or look at too few epilepsy related variables. Within research establishing quality of life factors and meningioma, the main focus has been to establish quality of life after surgery and or radiotherapy by using a variety of self-reported and operator dependent questionnaires. These studies either do not measure seizure outcomes or use a tool that measures functioning, such as the KPS.

In summary, the role that epilepsy may have in influencing the QoL of meningioma patients is poorly understood and understudied. Clinically this is significant as many patients with

meningioma will develop epilepsy and QoL is an important factor when considering how to manage seizures. More specifically, it is important to know: whether or not AEDs should be commenced; what the treatment aims are; how aggressively should treatment be administered; and their impact on QoL. In addition to this, it is important that clinicians are able to counsel patients about the effects of meningioma and epilepsy on life. When considering the wider population a disease specific understanding of QoL is important so that inter-disease comparisons can be made for resource allocation.

An understanding of meningioma, epilepsy and QoL is also important for guiding research, particularly by identifying factors that are influential with QoL. Future studies will benefit by focusing on factors that are important to QoL in patients with meningioma or epilepsy.

Chapter 5: Methods

5.1. Aims

The overall aim of this thesis is to conduct an observational pilot study that examines the relationships between meningioma, epilepsy and quality of life (QoL). The aims of this study are:

1. To assess the impact of epilepsy on QoL in meningioma patients by comparing meningioma patients with epilepsy to those without.
2. To assess the additional impact of meningioma in patients with epilepsy by comparing meningioma patients with epilepsy to matched epilepsy patients without meningioma.
3. To assess the influence of patient characteristics on QoL in these groups.

5.2. Hypothesis

The primary hypothesis is that meningioma patients with epilepsy will have QoL scores that are more impaired than the scores of meningioma patients without epilepsy.

The secondary hypothesis is that meningioma patients with epilepsy will have QoL scores that are more impaired than the scores of epilepsy patients without meningioma.

5.3. Overview

This study was conducted at the Walton Centre NHS Foundation Trust between November 2012 and August 2013. Patients with meningioma and epilepsy were identified and assessed for study eligibility. Eligible patients were invited to participate by post and those that responded were included in the study. Study participants were then posted QoL questionnaires. Once a completed questionnaire was obtained, the case-notes of that participant were reviewed and when all a full dataset was obtained, the data analysis began.

5.4. Permissions and Ethical Approval

Approval from the Walton Centre NHS Foundation Trust Research and Development department was requested and obtained in October 2012. Full ethical approval was obtained from the NHS National Research Ethics Service (NRES) North West committee in November 2012 after completion of requested amendments to the patient information leaflets. Approval letters are included in appendix II.

5.5. Participants

5.5.1. Meningioma Patients With and Without Epilepsy

5.5.1.1. Selection

When selecting meningioma participants for inclusion, tumour grade, tumour location, time since surgery, aetiology of meningioma, diseases of cognition and the presence of other intracranial tumours were considered with the aim of reducing heterogeneity.

High grade meningiomas are rare and are more likely to impair QoL. Extracranial meningiomas were not of interest in this study and meningiomas of the posterior fossa are not likely to produce seizures. Surgery is known to impair quality of life and this is particularly true for intracranial surgery. In the vast majority of patients there is no known trigger or aetiological factor in the development of a meningioma. For a small proportion of patients, meningiomas are secondary to neurofibromatosis type 2 (NF2), which renders patients susceptible to multiple lesions. Finally, patients with severe cognitive difficulty may find it difficult to comprehend and answer questions accurately about QoL and patients with other intracranial tumours will also have a significantly impaired quality of life.

The following selection criteria were applied when constructing the meningioma sample.

Inclusion Criteria:

- Benign World Health Organisation (WHO) grade 1 meningioma
- Supratentorial meningioma
- Minimum 6 months post-op

Exclusion criteria

- WHO grade 2 or 3 meningioma
- Infratentorial meningioma
- Intracranial surgery occurring within 6 months of participation date
- Formally diagnosed NF2
- Formally diagnosed dementia or learning difficulties
- Other intracranial tumours that are not meningioma

Meningioma patients were separated into two groups by the presence of epilepsy: meningioma with epilepsy and meningioma without epilepsy. Patients were placed into the meningioma with epilepsy group if they experienced at least two seizure episodes, or one seizure episode for which anti-epileptic drug (AED) therapy was commenced. One seizure episode is defined as the occurrence of any number of seizures within a 24 hour period[7].

5.5.1.2. Recruitment

Meningioma patients who underwent surgical resection after January 2002 were identified by searching the hospital's pathology department's histopathology database. This resulted in the identification of 590 meningioma patients. The case notes of each patient were reviewed to ensure that the selection criteria were met. The histology records were also reviewed to ensure that patients diagnosed before the recent revisions of the WHO grading criteria would still be classified as grade I after the revision. Furthermore, patient details were checked against a central NHS database to obtain the most up to date postal details and alive/dead status.

At the end of this process 350 patients were suitable for inclusion. These patients were invited to participate.

5.5.2. Epilepsy without Meningioma

5.5.2.1. Selection

The epilepsy without meningioma group was matched to the meningioma group by sex, age (±5 years) and duration of disease (±3 years). The bracketed cut offs were deemed appropriate for balancing practicalities with robustness of matching.

With regards to patient selection: epilepsy classification, disorders of cognition, presence of tumours and intracranial surgery were considered.

Structural epilepsies as opposed to genetic or unknown causes of epilepsy are most comparable to epilepsy in meningioma. Disorders of cognition, the presence of intracranial tumours (including meningioma) and intracranial surgery were excluded. Lesions that are known to be benign, such as angiomas, were not excluded.

The definition for epilepsy was the same as that used in the meningioma group. The selection criteria for the epilepsy group were as follows.

Inclusion:

- Focal epilepsy
- Epilepsy of symptomatic and cryptogenic aetiology
- Matched by age, sex and duration of disease
- Meets requirements for epilepsy definition

Exclusion:

- Primary generalised seizures
- Known idiopathic epilepsy
- Intracranial surgery occurring within 6 months of screening for study
- Formally diagnosed dementia or learning difficulties
- Non-benign Intracranial tumours

5.5.2.2. Recruitment

To identify patients for the epilepsy without meningioma group, a bank of epilepsy patients was created by filtering the hospitals electronic clinic database for clinic codes and disease codes specific to epilepsy. These codes are based on the International Classification of Diseases (ICD)10. Meningioma patients from the meningioma with epilepsy and meningioma without epilepsy groups were then matched to several age, sex and disease duration epilepsy patients by filtering the epilepsy bank by these three characteristics. This process generated a list of possible matches, in which the case notes were reviewed until a suitable epilepsy participant that met the selection criteria was found.

When this process failed to identify a suitable participant, the bank was filtered again but for similar as opposed to equal ages (±5 years) and disease durations (±3 years). Difference in disease duration was considered to be more significant for influencing QoL and so the repetition of the filtering process was performed with a particular rank in mind. This rank is tabulated below (Table 7).

Some members of the epilepsy without meningioma group previously experienced a period of remission in which they had no seizures for a significant period of time (>10 years). For these patients, disease duration was taken from the year that epilepsy recurred.

Table 7: Match Ranking Guide for the Selection of Epilepsy without Meningioma Patients

Rank	Age (± years)	Disease Duration (± years)	Sex
1	0	0	Exact
2	1	0	Exact
3	2	0	Exact
4	3	0	Exact
5	4	0	Exact
6	5	0	Exact
7	0	1	Exact
8	1	1	Exact
9	2	1	Exact
10	3	1	Exact
11	4	1	Exact
12	5	1	Exact
13	0	2	Exact
14	1	2	Exact
15	2	2	Exact
16	3	2	Exact
17	4	2	Exact
18	5	2	Exact
19	0	3	Exact
20	1	3	Exact
21	2	3	Exact
22	3	3	Exact
23	4	3	Exact
24	5	3	Exact

When the list of matched epilepsy without meningioma patients was created, their details were also cross checked against the central NHS database for recent addresses and live/dead status.

5.6. Outcome Measures

5.6.1. QoL Questionnaires

Three questionnaires provided the quality of life data for this study. It was decided that a mixture of general and disease specific measures were used. Many questionnaires were considered, but the following three were chosen for their ease of application and scoring, their widespread use and their use in meningioma and epilepsy studies. All questionnaires are included in appendix IV.

5.6.1.1. SF-36

The short form 36 (SF-36) is a 36 item general QoL measure that has been widely used in numerous disease populations, including that of meningioma and epilepsy[245]. It has undergone numerous validation studies and has been validated for use as a self-administrated postal questionnaire in the United Kingdom (UK)[247]. The SF-36 can be administered in 5-10 minutes[248]. The output of the SF-36 is organised into 8 subscales which are summarised by two general scores, one for physical health and another for mental health. This is shown in Table 8.

Table 8: SF-36 Subscale Categories and Summary Scores

Subscales				Summary Score
Physical Functioning (PF)	Role Physical (RP)	Bodily Pain (BP)	General Health (GH)	**Physical Health Summary (PCS)**
Vitality (VT)	Social Functioning (SF)	Role Emotional (RE)	Mental Health (MH)	**Mental Health Summary (MCS)**

The SF-36 provides scoring software that transforms subscale and summary scores so that a mean of 50 and standard deviation of 10 is representative of normal QoL[248]. The algorithm behind these transformations uses data from a healthy US population to define normal QoL.

For this study, minimally important changes have been defined as a difference of 3.0 points in PCS and 4.6 points in MCS[249]. These figures are based on mean QoL changes seen within epilepsy patients over a period of time[249]. Minimally important changes in other conditions can range from 0.5 to 5.0 in PCS and 2.5 to 6.6 for MCS, with more severe conditions requiring larger changes[250].

5.6.1.2. FACT-BR

The Functional Assessment of Cancer Therapy-Brain questionnaire (FACT-BR) is a disease specific questionnaire. It can be considered in two parts: the FACT-G, which is a general tool within the context of cancer and the FACT-BR which is specific to brain cancer patients. The only difference in these forms is the addition of a brain cancer subscale (BRCS) to the FACT-BR. The FACT-BR is split into 5 subscales that lead to one summary score. The FACT-G is split into 4 subscales that form one summary score. This is demonstrated in Table 9.

Table 9: FACT-BR Subscale Categories and Summary Scores

Subscales					Summary Scores
Physical Wellbeing (PWB)	Social/Family Wellbeing (SWB)	Emotional Wellbeing (EWB)	Functional Wellbeing (FWB)	NA[a]	**FACT-G Total**
Physical Wellbeing (PWB)	Social/Family Wellbeing (SWB)	Emotional Wellbeing (EWB)	Functional Wellbeing (FWB)	Brain Cancer (BRCS)	**FACT-BR Total**

[a]*BRCS not used for FACT-G*

Both versions of the form can be completed in 10-15 minutes. The FACT-BR and FACT-G have been used in meningioma previously and both are validated as self-administered tools[88,251].

On the FACT-BR, no healthy normal scores are available, but in patients with primary brain cancer the mean FACT-BR score is 136 (SD = 26). In this study, a meaningful difference for the FACT-BR total score has been defined as a minimum of 9.2 in the total score[252]. Recommended minimal changes specific to the FACT-BR are not available, so this value was created on the information provided by Ringash J et al on estimating important differences in brain cancer patients[252]. Recommended changes for subscales have been estimated in brain cancer patients as 5-7 for BRCS and 2-3 for all other subscales[253].

The normal score of the FACT-G has been defined as 80.1 (SD = 18.1) with reference to a healthy US population[254]. A minimally important change on FACT-G has been defined as 3 to 7 points in patients with a primary brain tumour[251].

5.6.1.3. AEP

The Liverpool Adverse Events Profile (AEP) is designed to detect common central nervous system side effects related to anti-epileptic medications[255]. Anti-epileptic drugs are known

to influence the QoL of patients and studies in meningioma suggest that this also may be the case for meningioma patients[245]. Each individual item on the AEP can be considered as an output, or the scores can be summated into one summary score. The AEP is a validated tool that is suitable for self-administration[256].

The mean total AEP score in epilepsy patients is usually between 37 to 39[257,258]. In this study, an overall change of 11 points on the AEP is defined as clinically significant[245]. This figure is based on clinical change in patients with temporal lobe epilepsy.

5.6.2. Missing Data

The FACT-BR categorises items into subscale scores by adding each item within the subscale. If less than 50% of items within a subscale are missing, the following formula can be used to create a prorated subscale score:

Prorated subscale score = ([Sum of item scores] x [N of items in subscale]) ÷ [N of items answered]

If more than 50% of items within a subscale are missing, the subscale and thus the total scores cannot be calculated.

The SF-36 is more sophisticated in the handling of missing data. The physical functioning subscale score is estimated by a model that utilises item response theory when missing data are present[248]. This IRT based model did not improve the missing data estimation for the remaining subscales. Instead, a subscale score is estimated by taking the mean of the subscale scores and inserting this into the missing item. If a subscale score cannot be estimated, a total summary score can still be calculated with the use of a regression model and the remaining scales. To calculate PCS, the PF subscale and a total of 7 subscales must be present. For MCS, the MH subscale and a total of 7 subscales must be present.

Participants with computed total scores on the SF-36 and FACT-BR will be put forward for analysis.

The AEP is a simple questionnaire with no subscales. When an item is missing on the AEP, simple mean imputation on a group by group basis was used to replace the missing item. For example, missing items from cases within the meningioma with epilepsy group are replaced by the average score of an item within the meningioma with epilepsy group. A maximum of three missing items per case was tolerated for inclusion into the analysis.

5.6.3. Clinical characteristics

Patient demographics and clinical factors potentially influence quality of life. Details related to demographics, comorbidities, the meningioma and epilepsy were collected in this study to account for confounding factors and to provide insight into their factors that have influence on QoL. These variables and the intended collection style are tabulated in Table 10 below.

Table 10: Variables Considered for Data Collection and Data Input Style

Category	Independent Variable	Data Input
Demographics	Age	Years
	Sex	Male or Female
	Employment Status	As Employment Questionnaire
Comorbidities	# Comorbidities	Number
	Named Comorbidity	Free-text
Meningioma	Time since Surgery	Number
	Tumour Location	Free-text
	Lobe Affected	Free-text
	Tumour Recurrence	Yes or No
	Simpson Resection	Grade 1-5
	Radiotherapy	Yes or No
	# Meningioma Symptoms	Number
	Named Meningioma Symptoms	Free-text
Epilepsy	Time since first Seizure	Years
	Time since first AED	Years
	First AED	Free-text
	Current AEDs	Free-text
	# AEDs	Number
	Seizure Frequency	As Epilepsy Questionnaire
	Seizure Type	Focal / Dyscognitive / Bilateral
	Cause of Epilepsy	Free-text

Seizure frequency, AED use and employment status was obtained from patients directly via supplementary questions placed on the end of the AEP. These are included in appendix IV. All other variables were collected from the patient notes.

5.7. Points of Contact

Three documents were posted to eligible patients as a first contact:

- A cover sheet summarising the study and the purpose of the postal contact
- A detailed patient information sheet explaining the study in simple terms (specific to each patient group)
- Consent form

These forms are included in appendix III. Patients were given a pre-paid envelope and 3 weeks to return their consent form. In the case of non-responders, a telephone call was made to ensure the correct address had been used so that further effort can be made in maximising participation numbers.

Once a consent form was received, the three questionnaires and a supplementary sheet were sent to participants and a prepaid envelope was provided.

5.8. Data Analysis

All questionnaire data and data relating to patient characteristics were inserted into excel spread sheets. When data collection was complete the questionnaires were scored and all data were transferred to a statistical software package. SPSS version 20 was used to perform all statistical analyses.

The analysis was split into three parts: descriptive statistics; quality of life mean score comparisons; and quality of life regression analysis. The dependent variables in this study were the total scores and subscale scores of the questionnaires. Independent variables were all the clinical characteristics stated previously.

Students t-tests were used to compare means and chi squared and Fisher's exact t-tests were used to compare frequencies. Significance was set at the $p = 0.05$ level for all analyses. Levenes test for equal variances was used where appropriate.

5.8.1. Descriptive Statistics

The differences in patient characteristics and response rates were identified and appropriate statistical tests applied to look for significant differences between the three patient groups. The null hypothesis for each of these tests is that there is no difference in characteristic between groups.

Patient groups were compared in the following manner:

1. Meningioma with epilepsy versus meningioma without epilepsy
2. Meningioma with epilepsy versus epilepsy without meningioma

Only the statistical details of significant results are fully reported.

5.8.2. QoL Mean Score Comparisons

The SF-36, FACT-BR and AEP measure QoL on ranked Likert scales. This is ordinal data but it was assumed to be continuous and each ordered point was assumed to be equidistant. These assumptions are believed to be robust in the presence of large sample size[259].

A preliminary data analysis was performed to identify cases with missing data, to assess the reliability of the questionnaires and to decide if parametric techniques can be applied to the dataset for the comparison of means.

After this, the mean scores of each subscale and summary measure were compared between groups in the same pairsspecified for the descriptive statistics analysis. Only the significant statistical results are reported.

5.8.3. Regression Analysis

Univariate regression analysis were performed between all independent variables and all the questionnaire summary scores as an exploratory analysis. Multiple hierarchical linear regression models were created for two pooled groups and for each dependent variable, as demonstrated in Table 11. Eight regression models were created in total. The dependent variables were assumed to be continuous.

Table 11: Group and Questionnaire Plan for Regression Analysis

	Groups	
	Meningioma without Epilepsy and Meningioma with Epilepsy	**Meningioma with Epilepsy and Epilepsy without Meningioma**
Dependent variables	PCS	PCS
	MCS	MCS
	FACT-BR TOTAL	FACT-G
	AEP	AEP

Independent variables inserted into the multiple regression models were chosen on the basis of the univariate analysis, Pearson correlations and theoretical considerations. More details are included in the results chapter.

Chapter 6: Results

6.1. Descriptive Statistics

6.1.1. Responders

The first patients were identified for inclusion in March 2013 and the last questionnaire was received by July of the same year. Table 12 summarises the response rates in the study. The epilepsy without meningiomagroup was significantly worse at responding than the meningioma with epilepsy group (X^2 (1, n = 486) = 24.31, p < 0.001) and the meningioma with epilepsy group were significantly worse at responding than the meningioma without epilepsy group (X^2 (1, n = 350) = 3.90, p = 0.048).

Table 12: Participant Response Rate

	Groups							
	Meningioma Without Epilepsy		Meningioma with Epilepsy		Epilepsy without Meningioma		Total	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total Eligible	211	-	139	-	347	-	697	-
Non-Responder	80	37.90%	72	51.80%	260	74.90%	412	59.10%
Drop Out After Consent	22	10.40%	11	7.90%	23	6.60%	56	8.00%
Study Participant	109	51.70%	56	40.30%	64	18.40%	229	32.90%

6.1.2. Demographics

Table 13 summarises the demographics of each group.

6.1.2.1. Age

The mean age of the study population was 59.9 (± 12.2) years. For the meningioma without epilepsy and meningioma with epilepsy group, the mean age was 60.3 (± 12.0) and 61.2 (± 11.2) respectively. The mean age in the epilepsy without meningiomagroup was 57.9 (± 13.2). There is no statistically significant difference between the mean age of the meningioma with epilepsy group compared to the meningioma without epilepsy group and the epilepsy without meningioma group (p > 0.05).

6.1.2.2. Gender

The majority of participants were female (80.8%). In the meningioma without epilepsy group and epilepsy without meningioma group the proportion of female participants was 85.3% and 81.2% respectively. The proportion of females was lowest in the meningioma with epilepsy group (71.4%). The differences in gender between the meningioma with epilepsy group and the other groups are not significant ($p > 0.05$).

6.1.2.3. Employment

The majority of participants across all groups were retired (43%). Thirty-two percent of participants were employed and 17% of participants were unemployed. There was no significant difference in employment status between the meningioma with epilepsy and the other groups ($p > 0.05$).

Table 13: Group Demographics

		Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		Total (n=229)	
Characteristics		**Mean**		**Mean**		**Mean**		**Mean**	
Age		60.33		61.20		57.92		59.87	
Characteristics		**Meningioma**		**Meningioma with Epilepsy**		**Epilepsy without Meningioma**		**Total**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Female	93	85.30%	40	71.40%	52	81.20%	185	80.80%
	Male	16	14.70%	16	28.60%	12	18.80%	44	19.20%
Employment	Full Time	21	19.30%	11	19.60%	15	23.40%	47	20.50%
	Part Time	17	15.60%	6	10.70%	4	6.20%	27	11.80%
	Unemployed[a]	3	2.8%	0	0.0%	1	1.6%	4	1.7%
	Unemployed[b]	0	0.0%	1	1.8%	0	0.0%	1	0.4%
	Unemployed[c]	12	11.0%	9	16.1%	13	20.3%	34	14.8%
	Carer	3	2.80%	0	0.00%	4	6.20%	7	3.10%
	Retired	49	45.00%	25	44.60%	25	39.10%	99	43.20%
	Student	1	0.90%	2	3.60%	0	0.00%	3	1.30%
	No Answer	3	2.80%	2	3.60%	2	3.10%	7	3.10%

[a]*Unemployed and seeking employment*
[b]*Unemoployed and not seeking employment*
[c]*Unemployed due to disability*

6.1.3. Meningioma Variables

These are summarised in Table 15.

6.1.3.1. Years since Operation

The mean number of years between participation and surgery was 4.68 years (±2.71). In the meningioma with epilepsy group, the mean number of years was 4.85 (±2.85) and this is compared to 4.59 years (± 2.65) in the meningioma without epilepsy group. This difference is not significant ($p > 0.05$). These points are illustrated by the boxplot below (Figure 2).

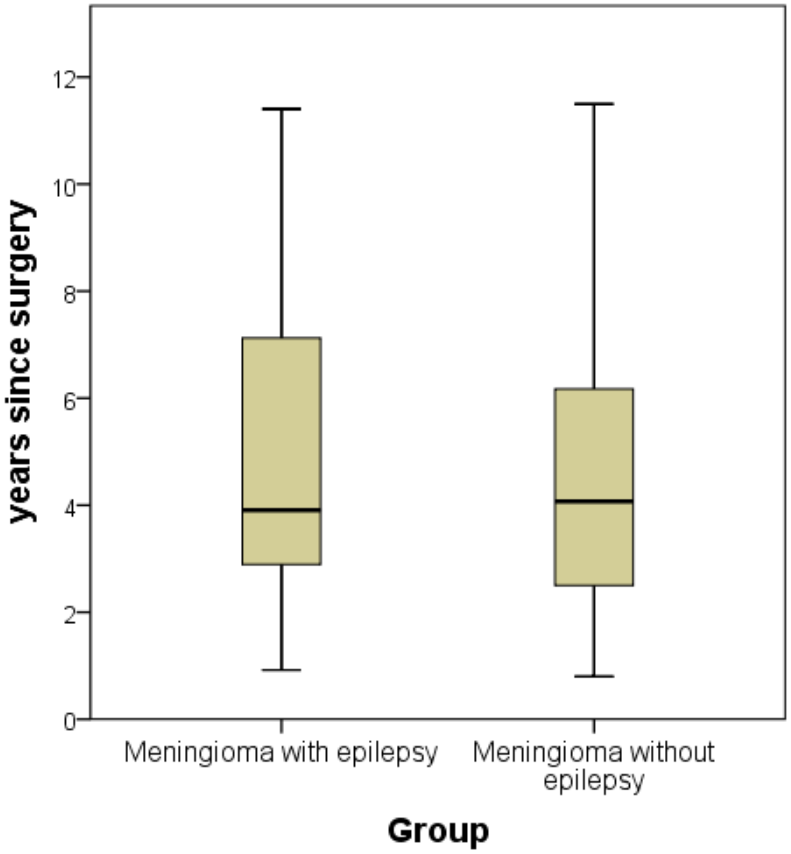

Figure 2: Boxplot of Years since Surgery for Meningioma Groups

6.1.3.2. Simpson's Grade of Resection

The meningioma with epilepsy group were more likely to have achieved a grade one resection (43.6%), a higher proportion than the meningioma without epilepsy group (26.9%). The meningioma without epilepsy group were most likely to have achieved a grade 2 resection (43.5%), which was achieved in 30.9% patients within the meningioma with epilepsy group. These differences are not statistically significant ($p > 0.05$).

6.1.3.3. Current Symptoms Related to Meningioma and the Resection

In the meningioma without epilepsy group, 45.0% of patients were symptom free whilst 33.9% experienced just one symptom. Epilepsy was not included as a symptom in this analysis. In the meningioma with epilepsy group 42.9.0% of patients were symptom free whilst 46.4% experienced just one symptom. This is tabulated in Table 14 and further demonstrated in Figure 3. The differences in complication number between groups are not statistically significant ($p > 0.05$).

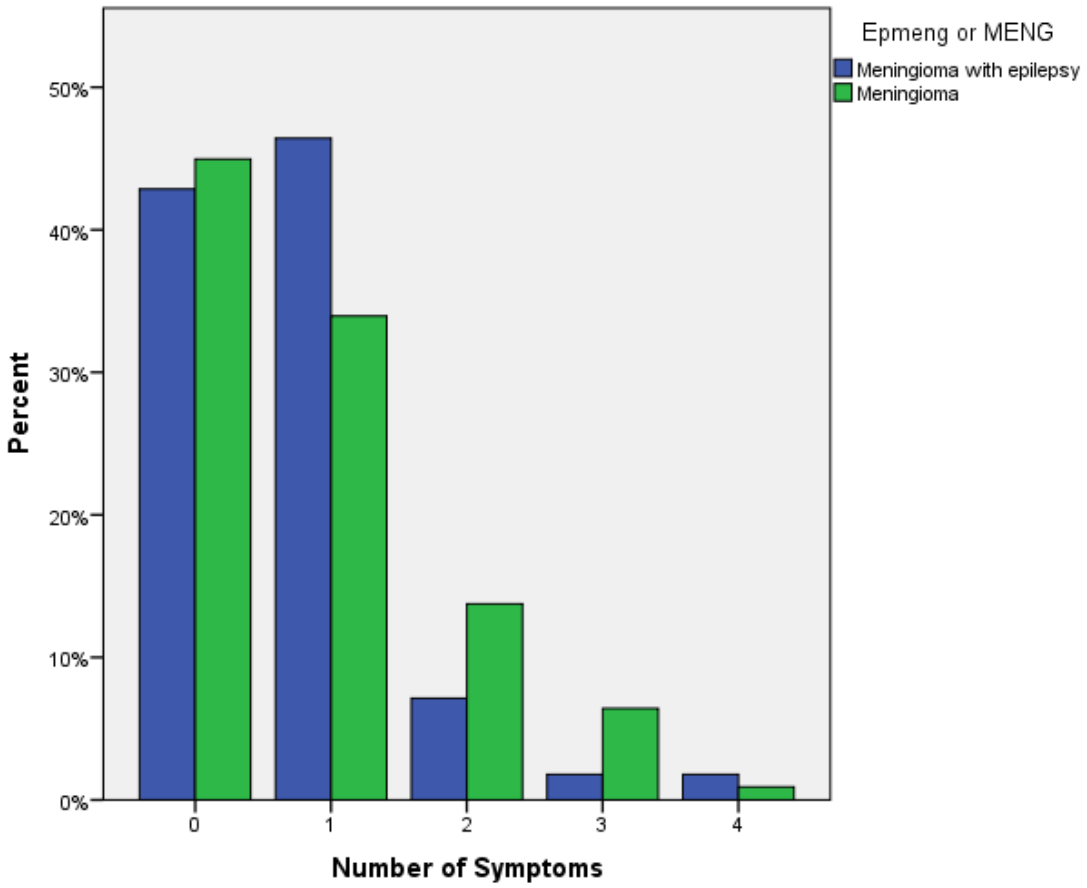

Figure 3: Number of Current Symptoms due to Meningioma or Meningioma Resection

The most frequently occurring symptoms in the meningioma without epilepsy group were related to vision (26.6%), headaches (11%) and cognitive/emotional difficulties (9.2%). In the meningioma with epilepsy group, the most frequent symptoms were motor/sensory (14.3%) cognitive/emotional (14.3%) and visual (8.9%). These distributions are tabulated below. The differences in the distribution of individual symptoms between groups are non-significant ($p > 0.05$), with exception to visual symptoms (X^2 (1, n = 165) = 6.03, p = 0.014).

Table 14: Symptoms Secondary to Meningioma or Meningioma Resection

		Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		Total (n=165)	
		Count	%	Count	%	Count	%
Visual[a]		29	26.60%	5	8.90%	34	20.60%
Cognitive/Emotional		10	9.20%	8	14.30%	18	10.90%
Headache		12	11.00%	3	5.40%	15	9.10%
Motor/Sensory		7	6.40%	8	14.30%	15	9.10%
Infection		6	5.50%	5	8.90%	11	6.70%
Cranial Nerve		9	8.30%	1	1.80%	10	6.10%
CSF problems		5	4.60%	4	7.10%	9	5.50%
Balance/Co-ordination		5	4.60%	1	1.80%	6	3.60%
Cosmetic		3	2.80%	2	3.60%	5	3.00%
Neuroendocrine		3	2.80%	0	0.00%	3	1.80%
Resus[b]		0	0.00%	2	3.60%	2	1.20%
Scar Pain		2	1.80%	0	0.00%	2	1.20%
PE[bc]		0	0.00%	1	1.80%	1	0.60%
Haemorrhage		1	0.90%	0	0.00%	1	0.60%
Tinnitus		0	0.00%	1	1.80%	1	0.60%
Number of Symptoms	0	49	45.00%	24	42.90%	73	44.20%
	1	37	33.90%	26	46.40%	63	38.20%
	2	15	13.80%	4	7.10%	19	11.50%
	3	7	6.40%	1	1.80%	8	4.80%
	4	1	0.90%	1	1.80%	2	1.20%

[a]*Difference is statistically significant*
[b]*Not current symptom, but deemed significant enough to have potential implications for current health.*
[c]*Pulmonary Embolism*

6.1.3.4. Meningioma Location

In the meningioma without epilepsy group the most frequent location of the meningioma was parafalcine/parasagittal (24.8%) and convexity (22.0%). In the meningioma with epilepsy group, the most frequent locations were also parafalcine/parasagittal (30.4%) and convexity (28.6%). The difference in tentorial meningiomas between the meningioma with epilepsy (0.0%) and meningioma without epilepsy group (9.2%)was significant (X^2 (1, n = 165) = 3.98, p = 0.046).

6.1.3.5. Lobe Effected

The lobe most commonly encroached in the meningioma without epilepsy group was the frontal lobe (41.3%) followed by the parietal lobe (11.9%). For the meningioma with epilepsy group, the lobe most commonly encroached was again the frontal (55.4%) and parietal lobes (16.1%). A total of 8 cases had a tumour which abutted two lobes. In these

cases, each lobe was counted separately. There is no statistical difference in the lobe encroached between the meningioma without epilepsy and meningioma with epilepsy groups ($p > 0.05$).

6.1.3.6. Recurrent Meningioma

The present tumour was a recurrent meningiomain 8.9% and 7.3% of the meningioma with epilepsy group and the meningioma without epilepsy group respectively. This difference is not significant ($p > 0.05$). The mean number of years since the first meningioma resection for these patients was 9 (±7) for the meningioma without epilepsy group and 12 (±6) for the meningioma with epilepsy group. The difference between these values is not significant ($p > 0.05$).

6.1.3.7. Radiotherapy

Radiotherapy was delivered in 11.9% of cases in the meningioma without epilepsy group and in 8.9% of cases in the meningioma with epilepsy group. The mean number of years since the completion of radiotherapy is 5(±3) and 2(±1) in the meningioma with epilepsy and meningioma without epilepsy groups respectively. None of these differences are significant ($p > 0.05$). This is tabulated below in Table 15; as are the remainder of the meningioma variables.

Table 15: Summary Table of Meningioma related Variables

		Meningioma without epilepsy (n=109)		Meningioma with Epilepsy (n=56)		Total (n=165)	
Characteristics		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years since surgery		4.59	2.65	4.86	2.85	4.68	2.72
# Meningioma Symptoms		0.84	0.95	0.73	0.82	0.81	0.91
		Count	**Percent**	**Count**	**Percent**	**Count**	**Percent**
Simpson's grade	1	29	26.90%	24	43.60%	53	32.50%
	2	47	43.50%	17	30.90%	64	39.30%
	3	6	5.60%	5	9.10%	11	6.70%
	4	26	24.10%	9	16.40%	35	21.50%
Meningioma location	Convexity	24	22.00%	16	28.60%	40	24.20%
	Intraventricular	1	0.90%	0	0.00%	1	0.60%
	Parafalcine	27	24.80%	17	30.40%	44	26.70%
	Skull base	22	20.20%	11	19.60%	33	20.00%
	Skull base[a]	6	5.50%	0	0.00%	6	3.60%
	Sphenoid Wing	19	17.40%	12	21.40%	31	18.80%
	Tentorial	10	9.20%	0	0.00%	10	6.10%
Lobe	Frontal	45	41.30%	31	55.40%	76	46.10%
	Occipital	11	10.10%	2	3.60%	13	7.90%
	parietal	13	11.90%	9	16.10%	22	13.30%
	Temporal	12	11.00%	7	12.50%	19	11.50%
	Not Stated	32	29.40%	11	19.60%	43	26.10%
Recurrent Meningioma		8	7.30%	5	8.90%	13	7.90%
Radiotherapy		13	11.90%	5	8.90%	18	10.90%

[a]**encroaching towards posterior fossa**

6.1.4. Epilepsy Variables

6.1.4.1. Epilepsy Cause

In the meningioma with epilepsy group, epilepsy can be classified as secondary to meningioma (Table 16). For the epilepsy without meningioma group, the aetiology of epilepsy varied. In 41 (64%) cases the aetiology was unknown. In 23 (36%) cases however, a cause of epilepsy was identified. The most common known aetiology was stroke (20.3% of structural cases).

Table 16: Aetiology of Epilepsy in the Epilepsy without Meningioma Group

Aetiology	Count	Percentage %
Unknown	41	64.1%
Stroke	13	20.3%
Mesial Temporal Lobe Sclerosis	2	3.1%
Hippocampal Sclerosis	1	1.6%
Arteriovenous Malformation	1	1.6%
Cavernoma	1	1.6%
Epidermoid Tumour	1	1.6%
Acoustic Neuroma	1	1.6%
Encephalitis	1	1.6%
Other Structural[a]	2	3.1%

[a]Aetiology not mentioned in notes

6.1.4.2. Seizure Onset

The average time between seizure onset and study participation for the 56 meningioma patients with epilepsy was 5.59 (± 3.8) years. This is compared to the average of 6.25 (±4.6) years in the epilepsy without meningioma group. The range of seizure onset is considerably larger in the epilepsy without meningioma group (28.0 years versus 15.5). The difference in means is not statistically significant (p = >0.05).

6.1.4.3. Years on AED

The meningioma with epilepsy group have been taking anti-epileptic drugs (AEDs) for an average of 5 (±4) years and this is compared to the epilepsy without meningioma group who have been taking AEDs for an average of 6 (±6) years. The difference in means is not statistically significant (p = > 0.05).

6.1.4.4. Seizure Frequency

Only 7 (12.5%) participants in the meningioma with epilepsy group experienced a seizure in the previous 6 months, compared to 39 (60.9%) participants in the control group. The distribution of seizure frequencies is summarised in Table 17.

Table 17: Seizure Frequency of Meningioma with Epilepsy and Epilepsy without Meningioma Groups

	Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)	
Seizure Frequency in Previous 6 Months	**Count**	**Percentage**	**Count**	**Percentage**
0	49	87.50%	39	60.90%
1	2	3.60%	6	9.40%
2 - 3	4	7.10%	6	9.40%
4 - 5	0	0.00%	2	3.10%
6 - 9	0	0.00%	5	7.80%
10+	1	1.80%	6	9.40%

When comparing seizure frequencies, the difference in proportion of participants without seizures is significant (X^2 (1, n = 120) = 9.46, p = 0.02).

6.1.4.5. Seizure Type

In both groups, bilateral convulsive seizures have occurred in the majority of cases. This is shown in Table 18. The "Focal" row is representative of participants in which only focal seizures occur. The "Dyscognitive" row is representative of patients that have dyscognitive seizures, may have focal seizures, but do not have bilateral convulsive seizures. The "Bilateral Convulsive" row is representative of participants in which bilateral convulsive seizures occur, and focal or dyscognitive seizures may occur.

Table 18: Distribution of Seizure Type in the Meningioma with Epilepsy and Epilepsy without Meningioma Groups

	Groups					
	Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		Total (n=120)	
Most Severe Seizure	**Count**	**Percentage**	**Count**	**Percentage**	**Count**	**Percentage**
Focal	9	16.10%	4	6.30%	13	10.80%
Dyscognitive	4	7.10%	17	26.60%	21	17.50%
Bilateral Convulsive	33	58.90%	42	65.60%	75	62.50%
Not Known	10	17.90%	1	1.60%	11	9.20%

When assessing the differences of each individual seizure type, the proportion of participants with dyscognitive seizures significantly differed between the groups (X^2 (1, n = 120) = 6.51, p = 0.011).

6.1.4.6. First Drug

The most frequent first drug prescribed was Phenytoin (50.0%) in the meningioma with epilepsy group and lamotrigine in the epilepsy without meningioma group (37.7%). The proportions of first drug prescribed between groups is tabulated below (Table 19).

Table 19: First AED; Meningioma with Epilepsy and Epilepsy without Meningioma

	Group					
	Meningioma with Epilepsy (n=56)		Epilepsy without meningioma (n=64)		Total (n=120)	
First Drug	Count	Percentage	Count	Percentage	Count	Percentage
Carbamazepine	12	21.4%	16	26.2%	28	23.9%
Gabapentin	1	1.8%	0	0.0%	1	0.9%
Lamotrigine	3	5.4%	23	37.7%	26	22.2%
Levetiracetam	5	8.9%	5	8.2%	10	8.5%
Oxcarbemazepine	1	1.8%	1	1.6%	2	1.7%
Phenytoin	28	50.0%	7	11.5%	35	29.9%
Sodium Valproate	4	7.1%	8	13.1%	12	10.3%
Phenobarbitone	0	0.0%	1	1.6%	1	0.9%
Not Stated	2	3.6%	0	0.0%	2	1.7%

When looking at the difference of proportions between each drug, only lamotrigine ($X^2(1, n = 120) = 14.70$, $p < 0.001$) and Phenytoin (X^2 (1, n = 120) = 20.21, $p < 0.001$) differed significantly.

6.1.4.7. Number of Current AEDs

For the meningioma with epilepsy group the average number of AEDs being taken was 0.68 (±0.69). In the epilepsy without meningioma group, the average number of AEDs being taken was 1.20 (±0.60). Despite the apparent similarity in these means, there is a statistical difference in the mean number of AEDs for each group (t (118) = 4.47, $p < .001$). This is tabulated below (Table 20).

Table 20: Number of Current AEDs Meningioma with Epilepsy and Epilepsy without Meningioma Groups

	Group					
	Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		Total (n=120)	
Number of AEDS	Count	Percentage	Count	Percentage	Count	Percentage
0	24	42.90%	5	7.80%	29	29.25%
1	27	48.20%	42	65.60%	69	89.70%
2	4	7.10%	16	25.00%	20	28.55%
3	1	1.80%	1	1.60%	2	2.50%

6.1.4.8. Current AED

In the meningioma with epilepsy group 32 participants took a total of 40 AEDs, the most common of which were sodium valproate (15.9%) and phenytoin (15.9%). In the epilepsy without meningioma group 59 patients took a total of 77 AEDs and the most commonly prescribed drugs were lamotrigine (25.6%) and levetiracetam (25.6%). All the prescribed AEDs for each group is summarised in Table 21.

Table 21: Current AEDs taken by the Meningioma with Epilepsy and Epilepsy without Meningioma Groups

	Group					
	Meningioma with Epilepsy (n=56)		**Epilepsy without Meningioma (n=64)**		**Total (n=120)**	
Current AED	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**
Lamotrigine	8	12.7%	21	25.6%	29	20.0%
Levetiracetam	4	6.3%	21	25.6%	25	17.2%
Sodium Valproate	10	15.9%	9	11.0%	19	13.1%
Carbamazepine	5	7.9%	12	14.6%	17	11.7%
Phenytoin	10	15.9%	5	6.1%	15	10.3%
Gabapentin	1	1.6%	2	2.4%	3	2.1%
Zonisamide	0	0.0%	2	2.4%	2	1.4%
Oxcarbemazepine	1	1.6%	0	0.0%	1	0.7%
Phenobarbitone	0	0.0%	1	1.2%	1	0.7%
Lacosamide	0	0.0%	1	1.2%	1	0.7%
Pregablin	0	0.0%	1	1.2%	1	0.7%
Topiramate	0	0.0%	1	1.2%	1	0.7%
Acetozalamide	0	0.0%	1	1.2%	1	0.7%
Clobazam	1	1.6%	0	0.0%	1	0.7%

The differences in current AED were only significant for levetiracetam ($X^2(1, n = 120) = 10.43, p = 0.001$). It is used more often as a second line drug in the epilepsy without meningioma group and it is particularly effective in treating drug resistant focal epilepsy[260].

6.1.5. Comorbidities

6.1.5.1. Number of Comorbidities

The total number of medical and surgical comorbidities was collected for all three participant groups. In each group, the mean number of comorbid conditions was 2 (±2). The differences between these means are not significant when comparing the meningioma with epilepsy to the meningioma without epilepsy group and meningioma with epilepsy to the epilepsy without meningioma group ($p > 0.05$). Below is a bar chart summarising these findings (Figure 4).

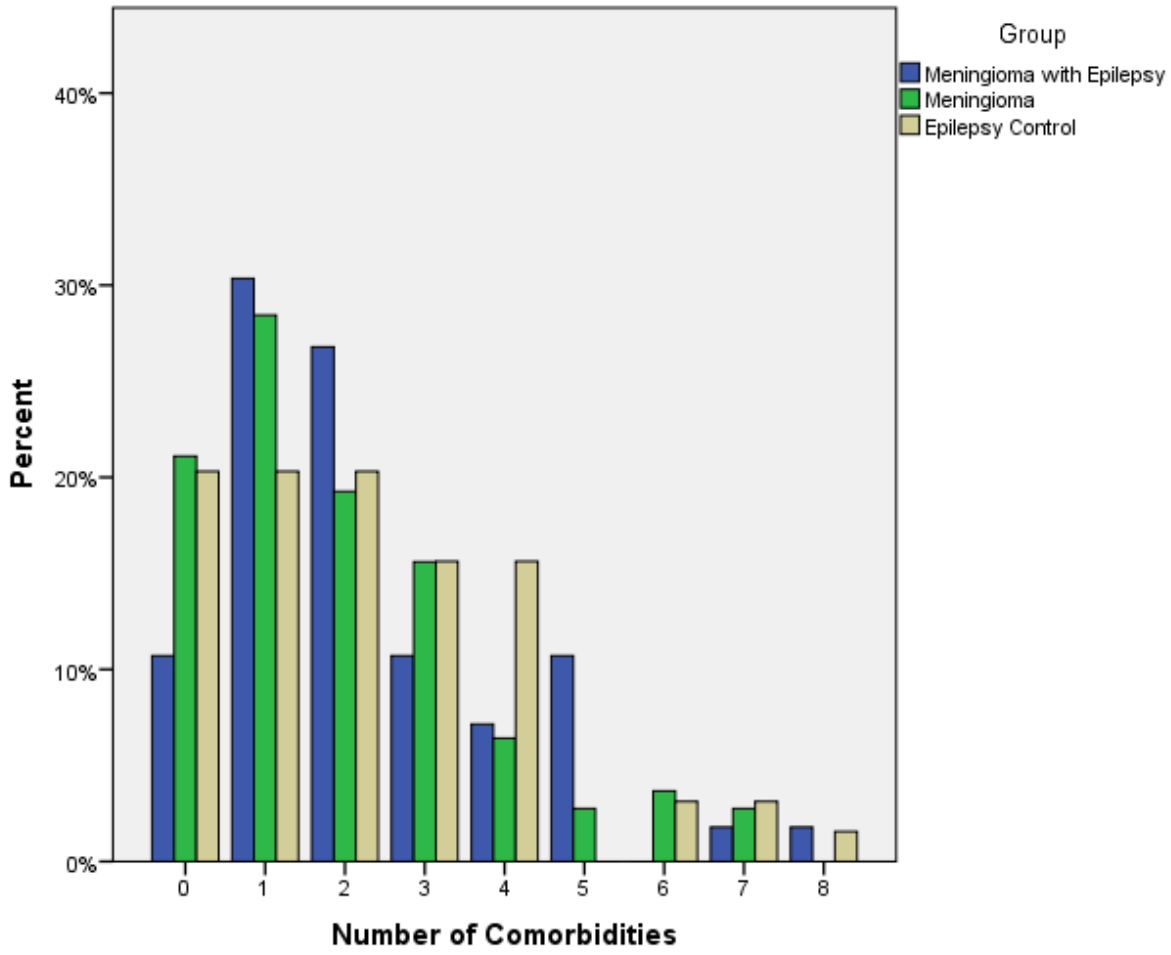

Figure 4: Proportion of Number of Comorbidities by Participant Group

6.1.5.2. Named Comorbidities

In the meningioma with epilepsy group, there were 58 comorbidities in 56 patients. The most prevalent comorbidity with 25% of participants affected was hypertension. This was followed by arthritis (12.5%), diabetes (12.5%) and thyroid disorders (12.5%). In the meningioma without epilepsy group, there were 209 comorbidities in 109 patients. The most prevalent comorbidity was hypertension, which was present in 23.9% of participants. Cancers (23.9%), depression (10.1%) arthritis (9.2%) and thyroid disorders (9.2%) most frequently occur after hypertension. In the epilepsy without meningioma group there were 143 comorbidities in 64 participants. Hypertension is again most prevalent with 14 (25%) participants exhibiting this comorbidity. Stroke (18.8%), depression (15.6%) and ischaemic heart disease (14.1%) were the next most prevalent.

There was no significant difference with the distribution of any individual medical or surgical comorbidity between the meningioma with epilepsy and the meningioma without epilepsy group.

When comparing comorbidity between the meningioma with epilepsy and the epilepsy without meningioma group, stroke differed significantly (X^2 p = 0.022). All other variables were non-significant. ($X^2(1, n = 120) = 5.29$, $p = 0.022$).

6.2. Quality of Life Mean Scores

6.2.1. Preliminary data analysis

6.2.1.1. Missing Data Analysis

In total there were 81 cases (35.4%) with missing items in a questionnaire (Table 22). Only 14 questionnaires (2%) could not be included in the quality of life (QoL) analysis: 7 from the SF-36, 4 from the FACT-BR questionnaire and 3 from the AEP (Table 23).

Table 22: Cases with Missing Data in All Groups

	Group							
	Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		Total (n=229)	
Questionnaires with Missing Data	n	%	n	%	n	%	n	%
None	69	63.30%	36	64.30%	43	67.20%	148	64.60%
1	31	28.40%	18	32.10%	12	18.80%	61	26.60%
2	8	7.30%	2	3.60%	6	9.40%	16	7.00%
3	1	0.90%	0	0.00%	3	4.70%	4	1.70%

Table 23: Number of Cases Excluded from Analysis by Questionnaire and Group

	Group							
	Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		Total (n=229)	
Questionnaire	n	%	n	%	n	%	n	%
SF-36	2	1.83%	1	1.79%	4	6.25%	7	3.06%
FACT-BR	2	1.83%	0	0.00%	2	3.13%	4	1.75%
AEP	2	1.83%	1	1.79%	0	0.00%	3	1.31%
Total	6	5.50%	2	3.57%	6	9.38%	14	6.11%

There was no significant difference in the number of questionnaires with missing data, or the proportion of cases put forward for analysis between the meningioma with epilepsy and meningioma without epilepsy group or epilepsy without meningioma group ($p > 0.05$). When looking at patient characteristics, patients with missing data are older than responders (Table 24). This difference is highly significant (t (227) = 3.75, $p < 0.001$).

Table 24: Demographics of Participants with Missing Data

	Missing Data Present?			
	No Missing Data		Missing Data	
Characteristics	**Mean**	**SD**	**Mean**	**SD**
AGE	57.7	12.4	63.8	10.7

		No Missing Data		Missing Data	
Characteristics		**n**	**%**	**n**	**%**
Gender	Female	119	80.40%	66	81.50%
	Male	29	19.60%	15	18.50%
Employment	Full Time	33	22.30%	14	17.30%
	Part Time	24	16.20%	3	3.70%
	Unemployed[a]	4	2.7%	1	1.20%
	Unemployed[b]	20	13.50%	14	17.30%
	Carer	5	3.40%	2	2.50%
	Retired	57	38.50%	42	51.90%
	Student	3	2.00%	0	0.00%
	No Answer	2	1.40%	5	6.20%

[a]Unemployed
[b]Unemployed due to disability

6.2.1.2. Reliability

To determine the reliability of the questionnaires, their internal consistency was assessed with the Cronbachs Alpha tool[261]. This tool produces a coefficient ranging from 0 to 1 representing the reliability of summated scales within a questionnaire. A coefficient score of greater than 0.70 is deemed an acceptable level of reliability. All summated scales in the three questionnaires had an α coefficient greater than 0.70, confirming the reliability of these questionnaires (tables 25-27).

Table 25: Cronbachs Alpha Coefficients for SF-36

	SF-36		
	Scale	**Cronbachs Alpha**	**Items in Scale**
Subscales	GH	0.88	5
	PF	0.96	10
	RP	0.97	4
	BP	0.89	2
	VT	0.87	4
	SF	0.91	2
	RE	0.95	3
	MH	0.77	5
Total Scores	PCS	0.89	4
	MCS	0.91	4

Table 26: Cronbachs Alpha Coefficients for FACT-BR

FACT-BR			
	Scale	**Cronbachs Alpha**	**Items in Scale**
Subscales	PWB	0.89	7
	SWB	0.88	7
	EWB	0.82	6
	FWB	0.91	7
	BRCS	0.89	20
Total Scores	FACT-G	0.87	4
	FACT-BR	0.84	5

Table 27: Cronbachs Alpha Coefficient for AEP

AEP		
Scale	**Cronbachs Alpha**	**Items in Scale**
AEP	0.92	19

6.2.1.3. Normality Testing

T-tests and multiple regression analyses require that the dependent variable is normally distributed for inferences to be reliable and accurate. Normality testing was performed in each group and for each dependent variable with q-q plots, histograms and Kolmogorov-Smirnov and Shapiro-Wilk tests.

The q-q plots showed that data was normally distributed. Non-normality seems most pronounced in the Kolmogorov-Smirnov and Shapiro-Wilk tests. These tests have reduced power with smaller sample sizes and are highly sensitive to extreme values. Their results are usually a supplement to the visual plots[262].

A $\log_{10}$ transformation was attempted but this did not improve the appearance of the plots, nor did it improve the outcomes of the Kolmogorov-Smirnov and Shapiro-Wilk tests.

According to the central limit theorem, when sample data is taken from a population which is approximately normal, the sampling data should be normal also[262]. Furthermore, when sample sizes are greater than 40, a slight violation of normal distribution is not problematic and parametric testing can still be used[262]. All groups have sample sizes that are greater than 40.

While the data for each dependent variable does not follow a perfect normal distribution, it could be argued that parametric testing was still appropriate in this dataset.

6.2.2. QoL Scores

6.2.2.1. Meningioma without Epilepsy and Meningioma with Epilepsy

The mean QoL scores for the meningioma without epilepsy and meningioma with epilepsy groups were compared and independent samples t-tests completed. The mean scores from each questionnaire are shown in tables 28, 29 and 30, and box plots of the summary scores are shown in figures 5, 6 and 7. It is evident that for all outcome measures except general health (GH), QoL is worse in the meningioma with epilepsy group when compared to the meningioma without epilepsy group. With exception to the AEP, a lower score equates to worse QoL.

The difference in means was significant for the FACT-BR summary score (t (92.9) = -2.55, p = 0.012) and the BRCS subscale score (t (161) = -3.14, p = 0.002). No other summary or subscale score means differed significantly.

Table 28: SF-36 Summary and Subscale Scores Meningioma Groups

		Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		
Score	**Domain**	**Mean**	**SD**	**Mean**	**SD**	**Difference in Mean**
Subscale	PF	46.8	11.6	44.5	13.0	-2.4
	RP	46.2	11.5	44.0	12.0	-2.3
	BP	48.6	11.2	48.8	10.7	+0.2
	GH	49.5	11.3	46.3	12.4	-3.2
	VT	49.0	11.3	47.6	10.6	-1.4
	SF	47.9	11.0	44.1	13.7	-3.8
	RE	46.9	11.8	44.0	12.2	-2.9
	MH	49.0	11.2	48.2	11.3	-0.8
Summary	PCS	47.5	11.2	45.8	11.2	-1.7
	MCS	48.9	11.4	46.8	11.7	-2.0

Note: No statistically significant differences in means

Table 29: FACT-BR Summary and Subscale Scores Meningioma Groups

		Meningioma without epilepsy (n=109)		Meningioma with Epilepsy (n=56)		
Score	**Domain**	**Mean**	**SD**	**Mean**	**SD**	**Difference in Mean**
Subscale	PWB	22.9	5.5	21.2	6.2	-1.8
	SWB	22.4	5.7	20.3	7.0	-2.1
	EWB	19.5	4.5	18.6	5.2	-0.9
	FWB	20.5	6.7	19.1	7.7	-1.4
	BRCS	60.1	14.1	52.6	14.8	-7.4**
Summary	TOTAL	146.1	29.6	131.7	35.9	-14.4*

* ***p = < 0.05*** *****p = <0.01***

Table 30: AEP Summary Scores of Meningioma Groups

	Meningioma without Epilepsy (n=109)		Meningioma with Epilepsy (n=56)		
Questionnaire	**Mean**	**SD**	**Mean**	**SD**	**Difference in Mean**
AEP	36.1	10.4	39.4	13.7	+3.3

Note: Difference in mean is not significant

Each item of the AEP was compared between groups with students t-tests. Patients in the meningioma with epilepsy group were significantly more likely to report the presence of shaky hands (t (76.5) = -3.57, $p < 0.001$). The proportion of patients with scores above 45 in the meningioma with epilepsy group (32.1%) and the meningioma without epilepsy group (22.0%) did not differ significantly (X^2 (1, n = 165) = 2.00, $p < 0.221$).

6.2.2.2. Meningioma with Epilepsy and Epilepsy without Meningioma

The mean QoL scores for the meningioma with epilepsy and epilepsy without meningioma group were compared and an independent samples t-test applied to each (Tables 31-33). All summary scores indicated worse functioning in the epilepsy without meningioma group, as were all subscales scores except PF on the SF-36 (Table 31) and SWB on FACT-BR (Table 32). None of these differences were significant at the $p = 0.05$ level. These scores are presented in figures 5, 6 and 7. The differences in item means for the AEP were also not significant. The proportion of epilepsy without meningioma patients with a score over 45 was 37.5%, which does not significantly differ from the 32% of patients with a score over 45 in the meningioma with epilepsy group (X^2 (1, $n = 120$) = 0.178, $p < 0.673$).

Table 31: SF-36 Summary and Subscale Scores Epilepsy Groups

		Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		
	Domain	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**Difference in Mean**
Subscale	PF	44.5	13.0	44.8	13.3	+0.3
	RP	44.0	12.0	42.7	12.3	-1.3
	BP	48.8	10.7	47.6	11.8	-1.2
	GH	46.3	12.4	44.1	13.9	-2.2
	VT	47.6	10.6	43.7	12.3	-3.8
	SF	44.1	13.7	42.7	13.0	-1.4
	RE	44.0	12.2	41.7	14.3	-2.3
	MH	48.2	11.3	43.9	12.0	-4.3
Summary	PCS	45.8	11.2	45.6	11.9	-0.2
	MCS	46.8	11.7	42.8	12.8	-4.1

Note: No significant differences in means

Table 32: FACT-G Summary and Subscale Scores Epilepsy Groups

		Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		
	Domain	**Mean**	**SD**	**Mean**	**SD**	**Difference in Mean**
Subscale	PWB	21.2	6.2	20.4	6.9	-0.8
	SWB	20.3	7.1	20.6	6.0	+0.3
	EWB	18.6	5.2	16.7	5.7	-1.8
	FWB	19.1	7.7	18.1	7.7	-1.0
Summary	FACTG	79.1	22.9	75.8	23.2	-3.3

Note: No significant differences in means

Table 33: AEP Summary Scores of Epilepsy Groups

	Meningioma with Epilepsy (n=56)		Epilepsy without Meningioma (n=64)		
Score	**Mean**	**SD**	**Mean**	**SD**	**Difference in Mean**
AEP	39.4	13.7	40.8	11.3	+1.4

Note: No statistically significant difference in mean

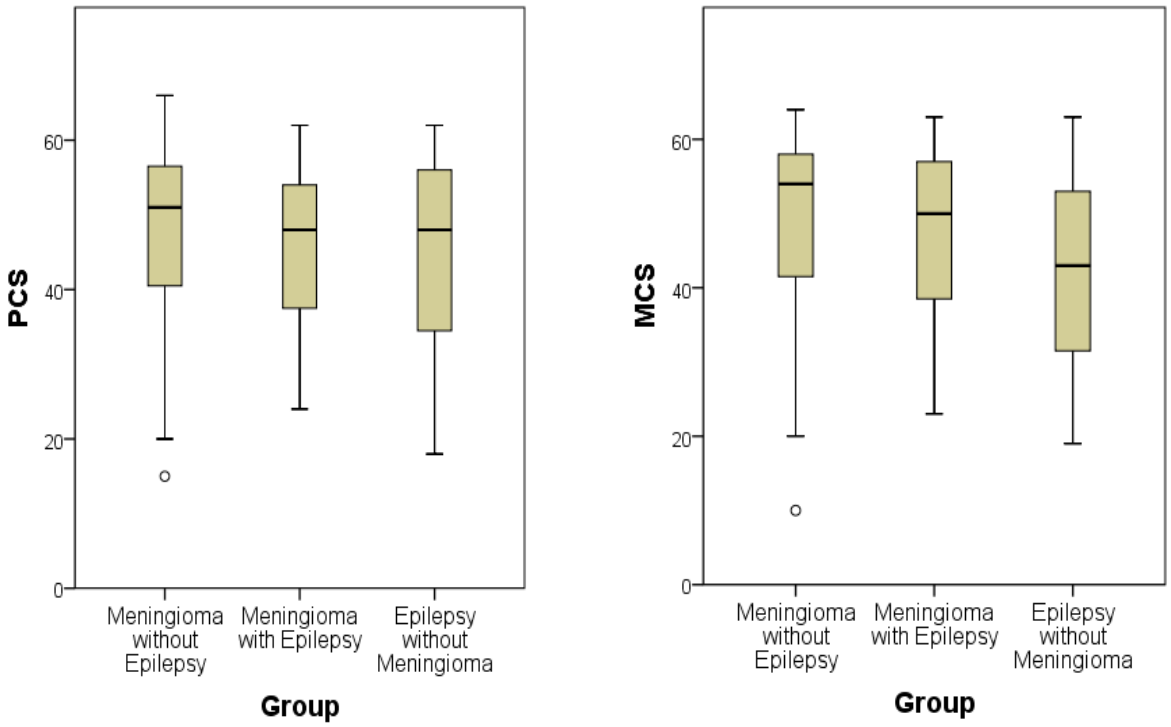

Figure 5: Boxplots of SF-36 Scores for all Participant Groups

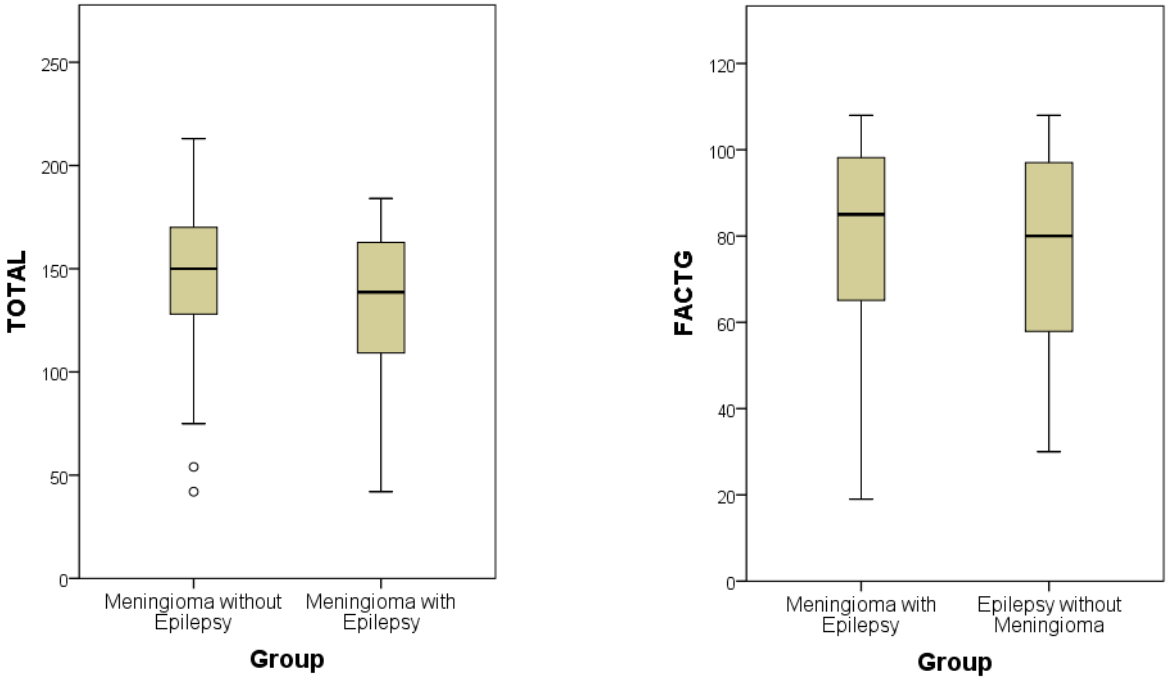

Figure 6: Boxplots of FACT Total and FACT G

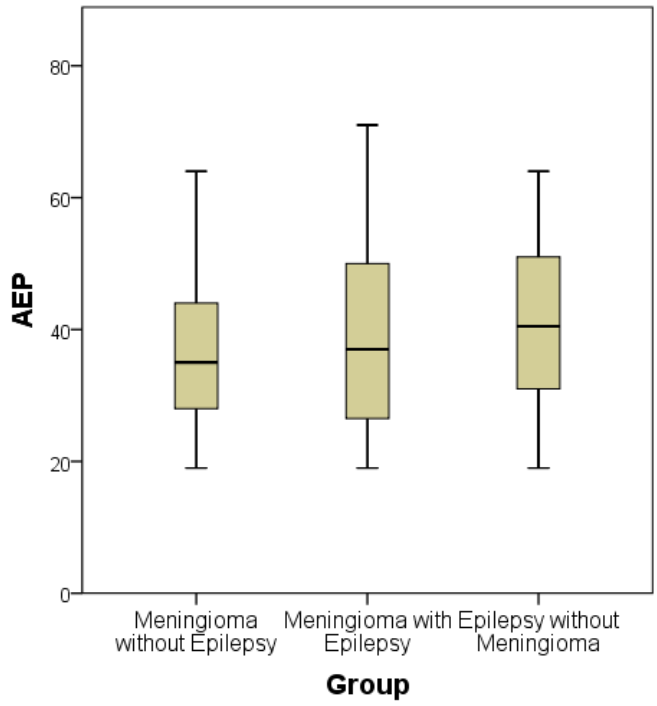

Figure 7: Boxplot of AEP scores for all Participant Groups

6.2.3. Outliers

Box and whisker plots with the dependent variable on the y axis were used to identify outliers (figures 5 to 7). Three outliers were found, all in the meningioma without epilepsy group. Each case was an outlier for different questionnaires: one physical component summary (PCS); one mental component summary (MCS) and FACT-BR Total; and one FACT-BR Total. All had quality of life scores well below the interquartile range for their respective questionnaires.

No specific reason could be found to explain the low scores of these participants, but two were unemployed due to disability; all had comorbidities; and all had significant symptoms resulting from their meningioma or resection. Of the three cases, two had visual problems; two had problems with their motor or sensory function; and all three had problems with either headache, cognition/emotion or cranial nerves (Table 34).

Table 34: Characteristics of Outliers in the Meningioma without Epilepsy Group

		Outliers			Outlier Group (n=3)	Meningioma without Epilepsy Group (n=109)
Characteristic		**1**	**2**	**3**	**Mean or Mode**	**Mean or Mode**
Age		48	66	58	57	60.3
Gender		Male	Female	Female	Female (66.6%)	Female (85.3%)
Employment		Unemployed	Retired	Unemployed	Unemployed (66.6%)	Retired (45%)
Years Since Surgery		4	2	9	5	5
Simpson's Grade		1	2	1	1 (66.6%)	2 (43.5%)
Tumour Location		Tentorial	Skull Base	Tentorial	Tentorial (66.6%)	Parafalcine/Parasagittal (24.8%)
# Meningioma Symptoms		2	2	3	2	0.73
# Comorbidities		2	3	1	2	2
Score	PCS	44	***15***[a]	30	30	47
	MCS	***10***[a]	59	20	29	49
	FACT-BR	***42***[a]	146	***54***[a]	81	146
	LAEP	49	29	64	47	49

[a] ***Outlying scores***

In all cases, QoL was found to be particularly impaired in other subscales and summary scores reducing the possibility of an isolated error. Therefore, these scores are felt to represent a truly impaired score. The QoL and subscale scores for the three outliers are tabulated below.

No justification can be made for the removal of these outliers on the basis of erroneous data. As these are three cases in a sample of over 100 it is unlikely that their inclusion will significantly alter the results or conclusions of this study. It was decided not to remove these cases from the analysis.

To observe the effect of this decision, t-tests of questionnaire scores between the meningioma with epilepsy and meningioma without epilepsy group were compared with and without the outliers. As would be expected, the meningioma without epilepsy group would have improved mean QoL scores after the removal of outliers. However, no differences in outcome were observed by removing these cases, with exception to the "TOTAL" score of the FACT-BR. When removing outliers, the difference in means between the meningioma without epilepsy and meningioma with epilepsy group changes from being significant (t (92.9) = -2.55, p = 0.012) to very significant (t (86.4) = -3.09, p = 0.003) (two sample t-test p = 0.004).

6.3. Regression Analysis

There are numerous assumptions that should be met for a multiple linear regression analysis[263]. Each regression model was assessed for the following:

1. Normal distribution of the dependent variable residuals
2. Homoscedasticity
3. Multicollinearity
4. Linearity of dependent and independent variables
5. Independence of observations

A histogram and standardised p-p plot of the four dependent variables in each group was assessed and found to be normally distributed. Scatter plots of the standardised residual for each dependent variable in each group was assessed and found to be homoscedastic. Multicollinearity was avoided by producing a Pearson correlation table and by outright eliminating any independent variables with a high correlation (> 0.8). No variables had a Pearson correlation that was greater than 0.8 but some variables had significant correlations greater than 0.6 (Table 35 and Table 36). This influenced the insertion of independent variables into the multiple regression analysis.

Table 35: Variables with Correlations Greater than 0.6 in the Meningioma Groups

Meningioma without Epilepsy and Meningioma with Epilepsy		
Correlating Variables		**Correlation (R)**
Age	Retired	0.647*
Employed	Retired	-0.689*
Current AED Use	Epilepsy Meningioma Group	0.698*

***p* < 0.001**

Table 36: Variables with Correlations Greater than 0.6 in the Epilepsy Groups

Meningioma with Epilepsy and Epilepsy without Meningioma		
Correlating Variables		**Correlation (R)**
Age	Retired	0.626*
Employed	Retired	-0.616*
Epilepsy without meningioma	Cryptogenic Epilepsy	0.674*
Year on AED	Years Since Seizure Onset	0.732*
Lamotrigine	2nd and 3rd Generation Drug	0.635*
Any Seizure Prior 6 Months	1-3 Seizures prior 6 Months	-0.697*
Any Seizure Prior 6 Months	> 4 Seizures prior 6 Months	-0.603*

***p* < 0.001**

Scatterplots of each independent variable and each dependent variable showed evidence of a linear relationship in all counts. After each multiple regression model was produced, the absence of multicollinearity was confirmed by the variance inflation factor (<3) and tolerance (>0.3) of the final model. Independence of observations was assessed and confirmed after the production of each model with the Durbin-Watson statistic (>1.5 and < 2.5).

6.3.1. Correlating Variables

Some variables of particular interest were found to significantly correlate with one another, but did not have correlations greater than 0.6. They are listed in Table 37 and Table 38.

Table 37: Correlating Variables of Interest Meningioma Groups

Meningioma without Epilepsy and Meningioma with Epilepsy		
Correlating Variables		**Correlation (R)**
Depression	Unemployment	0.261***
Depression	No. Comorbidities	0.177*

***p* < 0.05**
****p* < 0.001**

Table 38: Correlating Variables of Interest Epilepsy Groups

Meningioma with Epilepsy and Epilepsy without Meningioma		
Correlating Variables		**Correlation (R)**
Depression	Years Since Seizure Onset	0.281**
Depression	Neoplasm	0.177*
Depression	No. Comorbidities	0.184*

***p* < 0.05**
****p* < 0.01**

6.3.2. Univariate Regression Analysis

The number of participants should substantially outnumber the number of independent variables in a multiple regression analysis. A minimum number of 5 participants per variable is usually tolerated but at least 10 participants per variable should be attempted[264].

A selection process was undertaken to select independent variables of interest that correlate with the dependent variables but not the independent variables (Table 34 and Table 35). Simple linear regression was performed to identify variables that predict the dependent variables in the meningioma (meningioma with epilepsy and meningioma without epilepsy) and the epilepsy groups (meningioma with epilepsy and epilepsy without meningioma).

Eight sets of analysis with all dependent and independent variables were performed in the format shown in Table 10. The results of this analysis are presented in appendix V. Significantly predictive variables are presented below (Tables 39 to 46). Certain variables were recoded for simplification or to account for their low distribution in the dataset:

- "Employed full time" and "Employed part time" were recoded into "Employed".
- "Unemployed and seeking employment", "Unemployed and not seeking employment" and "Unemployed due to disability" were recoded into one "Unemployed" variable.
- "Number of AEDs" was coded as a binary "current AED use" for the meningioma groups.
- Named current AEDs were also coded into "1st generation" or "2nd-3rd generation" AED.
- Seizure frequency was coded into: "0 Seizures prior 6 month", "Any Seizure Prior 6 Months", "1-3 Seizures Prior 6 Months" and "4+ Seizures Prior 6 Months". "Any Seizure Prior 6 Months" is equal to "No Seizure Prior 6 Months" but the direction of the relationship is inverted.

Table 39: Univariate Analysis; Significant Predictors of PCS Meningioma Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.123	-0.359	0.000[a]
# Comorbidities	0.122	-0.357	0.000[a]
# Meningioma Symptoms	0.114	-0.345	0.000[a]
Employed	0.101	0.327	0.000[a]
Recurrence (Meningioma)	0.043	-0.221	0.005
Motor Sensory	0.040	-0.216	0.006
Neuropathy	0.038	-0.210	0.007
Neoplasm	0.032	-0.195	0.013
Depression	0.031	-0.193	0.014
Cognitive/Emotional	0.029	-0.186	0.018
Hypertension	0.025	-0.175	0.026
Radiotherapy	0.023	-0.171	0.030
Arthritis	0.023	-0.170	0.031
Diabetes M	0.019	-0.160	0.042
Stroke	0.019	-0.159	0.043
Age	0.019	-0.157	0.046

Note: Table organised by magnitude of Beta
[a]p < 0.001

Table 40: Univariate Analysis; Significant Predictors of MCS Meningioma Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.180	-0.431	0.000[a]
# Meningioma Symptoms	0.094	-0.316	0.000[a]
Age	0.087	0.304	0.000[a]
Depression	0.072	-0.279	0.000[a]
Cranial Nerve	0.051	-0.238	0.002
Retired	0.049	0.234	0.003
Resus	0.033	-0.196	0.012
Student	0.028	-0.186	0.018
Employed	0.022	0.169	0.032
Current AED Use	0.021	-0.164	0.037

Note: Table organised by magnitude of Beta
[a]p < 0.001

Table 41: Univariate Analysis; Significant Predictors of FACT-BR Meningioma Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.218	-0.472	0.000[a]
# Meningioma Symptoms	0.153	-0.398	0.000[a]
Current AED Use	0.066	-0.268	0.001
0 Seizures Prior 6 Months	0.060	0.257	0.001
First Generation	0.054	-0.246	0.002
Employed	0.051	0.239	0.002
Resus	0.046	-0.228	0.004
Depression	0.041	0.217	0.006
Meningioma Group	0.038	0.210	0.007
Motor Sensory	0.038	-0.209	0.008
Current Phenytoin	0.036	-0.206	0.009
Recurrence (Meningioma)	0.036	-0.205	0.009
Cranial Nerve	0.032	-0.196	0.013
Parietal Lobe	0.022	0.169	0.032
First Phenytoin	0.020	-0.160	0.042

Note: Table organised by magnitude of Beta
[a]p < 0.001

Table 42: Univariate Analysis; Significant Predictors of AEP Meningioma Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.191	0.443	0.000[a]
# Meningioma Symptoms	0.119	0.353	0.000[a]
0 Seizure[b]	0.093	-0.313	0.000[a]
Depression	0.072	-0.280	0.000[a]
1-3 Seizures[b]	0.063	0.262	0.001
Recurrence (Meningioma)	0.055	0.247	0.001
Current Levetiracetam	0.053	0.242	0.002
# Comorbidities	0.041	-0.217	0.006
Current AED Use	0.039	0.211	0.007
Age	0.038	-0.209	0.008
Cranial Nerve	0.036	0.204	0.009
2nd 3rd Generation AED	0.029	0.186	0.018
Current Clobazam	0.027	0.181	0.021
4+ Seizures[b]	0.027	0.181	0.021
Headache	0.023	0.169	0.031
Diabetes M	0.022	-0.168	0.033
Tinnitus	0.022	0.167	0.033
1st Generation AED	0.022	0.167	0.034
Retired	0.021	-0.165	0.036
Cognitive/Emotional	0.019	0.158	0.044
Current Phenytoin	0.019	0.157	0.046

Note: Table organised by magnitude of Beta
[a]p < 0.001
[b] Prior 6 Months

Table 43: Univariate Analysis; Significant Predictors of PCS Epilepsy Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
# Comorbidities	0.186	-0.440	0.000[a]
Unemployed	0.123	-0.359	0.000[a]
Employed	0.101	0.327	0.000[a]
Recurrence (Meningioma)	0.062	-0.265	0.004
Arthritis	0.058	-0.258	0.005
Age	0.041	-0.222	0.017
0 Seizure[b]	0.039	0.217	0.020
Neuropathy	0.039	-0.217	0.020
Diabetes M	0.036	-0.211	0.023
Neoplasm	0.034	-0.205	0.028
Motor Sensory	0.032	-0.201	0.031
First Lamotrigine	0.030	0.195	0.037
Hypertension	0.026	-0.187	0.046

Note: Table organised by magnitude of Beta
[a]p < 0.001
[b]Prior 6 Months

Table 44: Univariate Analysis; Significant Predictors of MCS Epilepsy Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.180	-0.431	0.000[a]
# AED	0.094	-0.320	0.000[a]
2nd 3rd Generation AED	0.089	-0.312	0.001
Current Levetiracetam	0.079	-0.295	0.001
4+ Seizures[b]	0.053	-0.248	0.008
Retired	0.041	0.221	0.017
0 Seizures[b]	0.039	0.217	0.020
Depression	0.038	-0.215	0.021
Neoplasm	0.033	-0.204	0.029
Employed	0.022	0.169	0.032
Current Pregablin	0.030	-0.195	0.036
Epidermoid Tumour	0.027	-0.188	0.044

Note: Table organised by magnitude of Beta
[a]p < 0.001
[b]Prior 6 Months

Table 45: Univariate Analysis; Significant Predictors of FACT-G Epilepsy Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.218	-0.472	0.000[a]
0 Seizures[b]	0.120	0.357	0.000[a]
# AED	0.101	-0.330	0.000[a]
Current Levetiracetam	0.090	-0.313	0.001
Current AED Use	0.078	-0.293	0.001
2nd 3rd Generation AED	0.074	-0.287	0.002
Employed	0.051	0.239	0.002
4+ Seizures[b]	0.049	-0.239	0.009
# Comorbidities	0.048	-0.237	0.009
1-3 Seizures[b]	0.043	-0.227	0.013
Resus	0.035	-0.209	0.023
Cranial Nerve	0.028	-0.191	0.037
Current Pregablin	0.028	-0.191	0.038
Recurrence (Meningioma)	0.026	-0.185	0.044

Note: Table organised by magnitude of Beta
[a]p < 0.001
[b]Prior 6 Months

Table 46: Univariate Analysis; Significant Predictors of AEP Epilepsy Groups

Independent Variables	Adjusted R Squared (R^2)	Beta (β)	Significance (p)
Unemployed	0.191	0.443	0.000[a]
0 Seizure[b]	0.124	-0.363	0.000[a]
# AED	0.114	0.349	0.000[a]
Current Levetiracetam	0.094	0.319	0.000[a]
2nd 3rd Generation AED	0.088	0.309	0.001
# Comorbidities	0.070	0.279	0.002
Recurrence (Meningioma)	0.057	0.254	0.005
Parietal Lobe	0.054	-0.249	0.006
4+ Seizures[b]	0.052	0.244	0.007
1-3 Seizures[b]	0.045	0.230	0.012
Cranial Nerve	0.032	0.199	0.030
Diabetes M	0.027	0.189	0.040

Note: Table organised by magnitude of Beta
[a]p < 0.01
[b]Prior 6 Months

On the basis of the results from the Univariate regression analysis and Pearson correlation tables, independent variables were chosen for input into the multiple regression analysis. The variables were arranged into four blocks on the basis of a theoretical hierarchy. The chosen variables are shown in tables 47 and 48. The independent variables within each regression are unique to each group, but not the dependent variables.

Table 47: Independent Variables for Regression - Meningioma Groups

Meningioma without Epilepsy and Meningioma with Epilepsy Groups (n = 165)	
Block	**Independent Variables**
1: Demographics	Age Female[a] Unemployed[a]
2: Comorbidities	Number of Comorbidities Arthritis[a] Depression[a] Diabetes Mellitus[a] Neoplasm[a]
3: Meningioma	Number of Meningioma Symptoms Motor/Sensory[a] Cranial Nerve[a] Recurrence (of meningioma)[a]
4: Epilepsy	Meningioma with Epilepsy[a] Any Seizure Prior 6 Months[a] Current AED Use[a]

[a]***Binary Variables***

Table 48: Independent Variables for Regression - Epilepsy Groups

Meningioma with Epilepsy and Epilepsy without Meningioma (n = 120)	
Block	**Independent Variable**
1: Demographics	Age Unemployed[a] Female[a]
2: Comorbidities	Number of Comorbidities Depression[a] Diabetes Mellitus[a] Neoplasm[a] Stroke[a]
4: Meningioma	Cranial Nerve[a] Cognitive Emotional[a]
3: Epilepsy	Epilepsy without meningioma[a] 1-3 Seizures prior 6 Months[a] > 4 Seizures prior 6 months[a] Levetiracetam[a] Number of AEDS

[a]***Binary Variables***

Each block was inserted separately into a hierarchical model, so that model 1 would consist of block 1, model 2 would consist of block 1 and block 2, model 3 would consist of blocks 1 to 3 and model 4 would consist of blocks 1 to 4.

6.3.3. Multiple Regression Results: Meningioma with Epilepsy and Meningioma without Epilepsy

6.3.3.1. Regression Overview

All regression analyses created models that accounted for variance in the four dependent variables. The models with the greatest explained variance for each regression analysis and the independent variables that significantly contributed to predicting the dependent variable are summarised below. For all regression equations, the block 1 was significant in explaining variance (F (p = < 0.05) and F change (p = < 0.05).

6.3.3.2. SF-36: Physical Component Summary

For PCS, model 3 accounted for 32.9% of the variance in PCS (adjusted R^2 = 0.329, F (12,149) = 7.589, p < 0.001). The addition of blocks 2 (R^2 change = 0.09, p = 0.003) and 3 (R^2 change 0.10, p < 0.001) were significant. The insertion of block 4 into the model did not explain any further variance in PCS (R^2 change = 0.003, p =0.866). It reduced the adjusted R^2 value (adjusted R^2 = 0.319, F (15,146) = 6.027, p < 0.001).

Numerous variables significantly and negatively predicted PCS in model 3. They are as follows: increasing age (β = -0.203, p = 0.004), unemployment (β = -0.289, p < 0.001), arthritis (β = -0.142, p = 0.036), diabetes mellitus (β = -0.147, p = 0.029), the presence of a neoplasm (β = -0.172, p = 0.010), increasing number of meningioma symptoms (β = -0.231, p = 0.003) and meningioma recurrence (β = -0.141, p = 0.044).

The full regression model is shown in Table 49.

Table 49: Hierarchical Regression model SF-36 PCS Meningioma with Epilepsy and Meningioma without Epilepsy

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.175***	0.191***		0.241***	0.088*		0.329***	0.101***		.319***	.003	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	64.507	4.684		65.217	4.592		67.835	4.419		68.106	4.558	
	Age	-0.237	0.070	-0.248**	-0.191	0.069	-0.200*	-0.194	0.066	-0.203**	-0.193	0.067	-0.202**
	Female	-1.578	2.031	-0.056	-1.766	1.972	-0.062	-1.883	1.854	-0.066	-2.011	1.907	-0.071
	Unemployed	-12.725	2.268	-0.412**	-11.810	2.269	-0.382***	-8.917	2.237	-0.289***	-8.845	2.286	-0.286***
2	# Comorbidities				-0.774	0.437	-0.123	-0.602	0.426	-0.096	-0.558	0.437	-0.089
	Arthritis				-4.594	2.564	-0.126	-5.151	2.436	-0.142*	-5.145	2.468	-0.141*
	Depression				-4.005	2.764	-0.104	-2.403	2.641	-0.062	-2.342	2.669	-0.061
	Diabetes Mellitis				-5.528	2.980	-0.130	-6.247	2.834	-0.147*	-5.834	2.934	-0.137*
	Neoplasm				-5.000	1.932	-0.181*	-4.759	1.829	-0.172*	-4.735	1.854	-0.171*
3	# Menin. Symptoms							-2.826	0.943	-0.231**	-2.888	0.957	-0.236**
	Motor/Sensory							-4.397	2.777	-0.111	-3.952	2.882	-0.100
	Cranial Nerve							-1.616	3.402	-0.035	-1.910	3.466	-0.041
	Recurrence							-5.772	2.838	-0.141	-5.583	2.876	-0.136
4	Meningioma with Epilepsy										-1.886	2.243	-0.080
	Any Seizure Prior 6 Months										-0.452	4.152	-0.008
	Current AED										1.446	2.780	0.052

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.3.3. SF-36: Mental Component Summary

Model two accounted for 25.4% of the variance in MCS (adjusted R^2 = 0.254, $F(8,153)$ = 7.867, p = 0.000). Only the insertion of block 2 was significant (R^2 change = 0.055, p = 0.043).

Independent variables that significantly predicted MCS in model 2 were age (β = 0.214, p = 0.003), unemployment (β = -0.348, p = 0.000) and depression (β = -0.166, p = 0.021). As a whole, model 3 and model 4 did not significantly add to the amount of variance in MCS, but the number of meningioma symptoms (β = -0.171, p = 0.035) and the use of AEDs (β = -0.202, p = 0.048) significantly contributed to MCS in these models.

The full regression model is shown in Table 50.

Table 50: Hierarchical Regression Model SF-36 MCS Meningioma with Epilepsy and Meningioma without Epilepsy

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.222***	0.237***		0.254***	0.055*		0.279***	0.042		0.279***	0.042	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	35.266	4.679		37.335	4.682		39.871	4.712		41.599	4.793	
	Age	0.214	0.070	0.218**	0.210	0.070	0.214**	0.193	0.071	0.194**	0.182	0.071	0.185*
	Female	2.231	2.029	0.076	2.242	2.011	0.077	2.172	1.977	0.074	1.464	2.006	0.050
	Unemployed	-12.220	2.266	-0.385***	-11.060	2.314	-0.348***	-9.559	2.386	-0.301***	-9.091	2.405	-0.286***
2	Number of Comorbidities				-0.604	0.446	-0.094	-0.413	0.454	-0.064	-0.438	0.459	-0.068
	Arthritis				1.345	2.614	0.036	1.345	2.598	0.036	1.686	2.596	0.045
	Depression				-6.570	2.818	-0.166*	-6.350	2.816	-0.160*	-6.797	2.807	-0.172*
	Diabetes Mellitis				-5.740	3.039	-0.131	-6.024	3.022	-0.137*	-6.519	3.086	-0.149
	Neoplasm				1.049	1.970	0.037	1.235	1.951	0.043	0.922	1.950	0.032
3	# Menin. Symptoms							-2.144	1.005	-0.171*	-2.087	1.007	-0.166*
	Motor/Sensory							-0.552	2.962	-0.014	-1.071	3.031	-0.026
	Cranial Nerve							-3.519	3.628	-0.074	-3.983	3.645	-0.084
	Recurrence							0.719	3.026	0.017	0.133	3.025	0.003
4	Meningioma with Epilepsy										1.653	2.359	0.068
	Any Seizure Prior 6 Months										1.970	4.366	0.035
	Current AED										-5.827	2.924	-0.202*

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.3.4. FACT-BR

Model 4 accounted for 40.6% of variance on the FACT-BR Total scores (adjusted R^2 = 0.406, F(15,145) = 8.296, p = 0.000). The addition of each block was significant: block 2 (R^2 change = 0.063, p = 0.021), block 3 (R^2 change = 0.101, p = 0.000) and block 4 (R^2 change = 0.064, p = 0.001).

In model four, the β scores for independent variables that significantly predicted FACT-BR Total were as follows: unemployment (β = -0.312, p = 0.000), depression (β = -0.152, p = 0.019), diabetes mellitus (β = -0.147, p = 0.024) number of meningioma symptoms (β = -0.234, p = 0.001) and current AED (β = -0.218, p = 0.020).

The full regression model is shown in Table 51.

Table 51: Hierarchical Regression Model FACT-BR Meningioma with Epilepsy and Meningioma without Epilepsy

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.219***	0.233***		0.260***	0.063*		0.349***	0.101***		0.406***	0.064**	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	0.061	0.198	0.022	141.876	13.203		150.287	12.748		156.192	12.440	
	Age	8.008	5.679	0.099	0.095	0.198	0.034	0.092	0.191	0.033	0.097	0.183	0.035
	Female	-43.585	6.621	-0.470	7.983	5.595	0.098	7.642	5.249	0.094	4.748	5.111	0.058
	Unemployed	0.061	0.198	0.022***	-40.298	6.697	-0.435***	-33.244	6.576	-0.359***	-28.881	6.381	-0.312***
2	Number of Comorbidities				-1.619	1.302	-0.086	-1.475	1.250	-0.079	-1.745	1.215	-0.093
	Arthritis				-1.082	7.579	-0.010	-2.872	7.204	-0.026	-1.019	6.917	-0.009
	Depression				-19.796	7.860	-0.177*	-15.719	7.500	-0.141*	-16.983	7.185	-0.152*
	Diabetes Mellitis				-18.956	8.563	-0.154*	-20.193	8.117	-0.164*	-18.191	7.965	-0.147*
	Neoplasm				-3.582	5.554	-0.045	-2.823	5.244	-0.035	-4.955	5.040	-0.062
3	# Menin. Symptoms							-8.981	2.739	-0.243**	-8.636	2.638	-0.234**
	Motor/Sensory							-13.707	7.712	-0.123	-15.498	7.595	-0.139*
	Cranial Nerve							-7.717	9.958	-0.055	-11.740	9.601	-0.083
	Recurrence							-7.303	8.178	-0.061	-9.000	7.854	-0.076
4	Meningioma with Epilepsy										1.686	6.080	0.025
	Any Seizure Prior 6 Months										-16.623	11.333	-0.105
	Current AED										-17.705	7.501	-0.218*

p <0.05
****p<0.01***
*****p<0.001***

6.3.3.5. AEP

Model 4 accounted for 31.2% of the variance on AEP scores (adjusted R^2 = 0.312, F(5,149) = 5.954, p = 0.000). The addition of block 2 did not significantly explain more variance on AEP (R^2 change = 0.036, p = 0.218). The addition of blocks 3 and four were significant (R^2 change = 0.074, p = 0.004 and R^2 change = 0.078, p = 0.001).

The independent variables that significantly predicted AEP scores in model four were as follows: unemployment (β = 0.246, p = 0.001), diabetes mellitus (β = 0.147, p = 0.034), recurrence of meningioma (β = 0.160, p = 0.023), any seizure in prior 6 months (β = 0.187, p = 0.014) and current AED (β = 0.220, p = 0.027).

The full model is shown in Table 52.

Table 52: Hierarchical Regression Model AEP Meningioma with Epilepsy and Meningioma without Epilepsy

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.173***	0.188***		0.183***	0.036		0.242***	0.074**		0.312***	0.078***	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	38.755	5.273		38.273	5.361		35.566	5.289		34.305	5.149	
	Age	-0.067	0.079	-0.062	-0.066	0.080	-0.061	-0.056	0.079	-0.052	-0.065	0.076	-0.060
	Female	-0.435	2.263	-0.014	-0.212	2.275	-0.007	-0.128	2.192	-0.004	0.640	2.125	0.020
	Unemployed	14.589	2.559	0.416***	13.494	2.639	0.384***	10.369	2.675	0.295***	8.643	2.584	0.246***
2	Number of Comorbidities				-0.145	0.512	-0.020	-0.346	0.510	-0.048	-0.111	0.495	-0.016
	Arthritis				-2.261	2.997	-0.055	-2.041	2.920	-0.049	-3.261	2.797	-0.079
	Depression				4.639	3.130	0.109	3.436	3.058	0.081	3.931	2.923	0.092
	Diabetes Mellitus				7.433	3.484	0.153*	8.150	3.394	0.168*	7.135	3.326	0.147*
	Neoplasm				-0.371	2.259	-0.012	-0.397	2.191	-0.013	0.602	2.101	0.019
3	# Menin. Symptoms							2.279	1.126	0.164*	1.925	1.081	0.139
	Motor/Sensory							3.535	3.223	0.081	5.234	3.165	0.120
	Cranial Nerve							4.650	4.080	0.088	6.310	3.929	0.120
	Recurrence							6.831	3.399	0.146*	7.476	3.257	0.160*
4	Meningioma with Epilepsy										-2.777	2.537	-0.104
	Any Seizure Prior 6 Months										11.654	4.701	0.187*
	Current AED										6.932	3.108	0.220*

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.4. Multiple Regression Results: Meningioma with Epilepsy and Epilepsy without Meningioma

6.3.4.1. Regression Overview

Each hierarchical regression analyses produced a model that significantly accounted for a proportion of variance in the dependent variables. A summary of the main findings is included below. For all regression equations, block 1 was significant in explaining variance (*F* and *F* change $p = < 0.05$).

6.3.4.2. SF-36: Physical Component Summary

Model 2 significantly accounted for 33.2% of the variance in PCS (adjusted $R^2 = 0.332$, $F(8,077) = 7.0$, $p = 0.000$). The addition of block 3 (R^2 change = 0.025, $p = 0.123$) and block 4 (R^2 change = 0.023, $p = 0.556$) were not statistically significant.

Two variables significantly and negatively predicted a lower PCS score in model 2. These were unemployment ($\beta = -0.415$, $p < 0.001$) and the number of comorbidities ($\beta = -0.357$, $p < 0.001$). These variables remained significant in the other models. Cognitive/emotional symptoms due to the meningioma became a significant predictor of reduced PCS when the epilepsy block was added ($\beta = -0.172$, $p = 0.043$). No other variables were significant.

The full model is presented in Table 53.

Table 53: Hierarchical Regression model SF-36 PCS Meningioma with Epilepsy and Epilepsy without Meningioma

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.229***	0.250***		0.332***	0.129**		0.346***	0.025		0.359***	0.023	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	67.110	5.216		61.249	5.074		60.411	5.043		60.285	5.409	
	Age	-0.309	0.079	-0.333***	-0.132	0.085	-0.142	-0.109	0.085	-0.118	-0.126	0.087	-0.136
	Female	-0.535	2.246	-0.020	0.508	2.117	0.019	0.387	2.098	0.014	0.861	2.152	0.032
	Unemployed	-13.178	2.450	-0.459***	-11.935	2.355	-0.415***	-11.747	2.369	-0.409***	-11.075	2.610	-0.386***
2	# Comorbidities				-2.243	0.618	-0.357***	-2.307	0.613	-0.368***	-2.083	0.652	-0.332**
	Depression				-1.604	2.769	-0.047	-1.734	2.741	-0.051	-1.550	2.787	-0.045
	Diabetes Mellitus				-5.750	3.459	-0.134	-3.443	3.679	-0.080	-2.071	3.916	-0.048
	Neoplasm				0.652	3.350	0.017	1.817	3.382	0.048	1.760	3.594	0.047
	Stroke				-0.228	2.911	-0.006	-0.782	2.900	-0.022	-0.769	3.028	-0.021
3	Cognitive/Emotional							-7.443	3.864	-0.155	-8.248	4.029	-0.172*
	Cranial Nerve							-8.984	10.146	-0.073	-13.157	10.504	-0.106
4	Epilepsy without Meningioma										-0.551	2.128	-0.024
	Levetiracetam										-3.903	2.818	-0.138
	1-3 Seizures Prior 6 Months										-1.960	3.034	-0.061
	4+ Seizures Prior 6 months										-3.409	3.450	-0.097
	# AEDS										2.000	1.762	0.121

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.4.3. SF-36: Mental Component Summary

Model 2 accounted for 24.1% of the variance in MCS (adjusted R^2 = 0.241, F (8,106) = 5.532, p < 0.001). The addition of block 3 was insignificant (R^2 change = 0.009, p = 0.531), as was the addition of block 4 (R^2 change = 0.056, p = 0.134).

Numerous variables significantly predicted impairment in MCS scores. These were unemployment (β = -0.303, p = 0.001), depression (β = -0.202, p = 0.021), diabetes mellitus (β = -0.178, p = 0.042) and stroke (β = -0.236, p = 0.007). MCS scores were significantly and positively predicted by increasing age (β = 0.262, p = 0.008).

The full regression model is included in Table 54.

Table 54: Hierarchial Regression SF-36 MCS Meningioma with Epilepsy and Epilepsy without Meningioma

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.127***	0.150***		0.241***	0.145**		0.236***	0.009		0.262***	0.056	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	40.924	5.951		34.644	5.794		35.213	5.841		39.154	6.126	
	Age	0.091	0.090	0.092	0.261	0.097	0.262**	0.243	0.098	0.245*	0.233	0.098	0.234*
	Female	0.724	2.563	0.025	1.516	2.418	0.052	1.663	2.430	0.057	1.363	2.437	0.047
	Unemployed	-10.990	2.795	-0.357***	-9.324	2.690	-0.303***	-8.920	2.743	-0.290**	-7.295	2.956	-0.237*
2	# Comorbidities				-0.790	0.706	-0.118	-0.744	0.709	-0.111	-0.862	0.738	-0.128
	Depression				-7.402	3.162	-0.202*	-7.374	3.174	-0.202*	-7.315	3.157	-0.200*
	Diabetes Mellitus				-8.141	3.950	-0.178*	-8.025	4.261	-0.175	-5.986	4.435	-0.131
	Neoplasm				-3.051	3.826	-0.076	-3.832	3.916	-0.095	-3.396	4.071	-0.084
	Stroke				-9.197	3.325	-0.236*	-8.788	3.359	-0.226**	-7.880	3.429	-0.203*
3	Cognitive/Emotional										1.237	4.564	0.024
	Cranial Nerve										-10.839	11.897	-0.082
4	Epilepsy without Meningioma										0.282	2.410	0.011
	Levetiracetam										-3.644	3.192	-0.120
	1-3 Seizures Prior 6 Months										1.493	3.436	0.043
	4+ Seizures Prior 6 Months										-0.209	3.907	-0.006
	# AEDS										-2.970	1.996	-0.168

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.4.4. FACT-BR: General

Model 4 accounted for 35.8% of the variance on FACT-G (adjusted R^2 = 0.358, F (15,103) = 5.391, p < 0.001). The addition of block's 2 (R^2 change = 0.118, p = 0.003) and 4 (R^2 change = 0.105, p = 0.003) were significant.

Being unemployed (β = -0.293, p = 0.000), a past history of stroke (β = -0.234, p = 0.005) and current use of levetiracetam (β = -0.230, p = 0.017) all significantly and negatively predicted FACT-G.

The full regression model is included below (Table 55).

Table 55: : Hierarchical Regression FACT-G Meningioma with Epilepsy and Epilepsy without Meningioma

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.183***	0.204***		0.273***	0.118**		0.273***	0.012		0.358	0.105**	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	90.402	10.536		79.411	10.387		78.101	10.455		84.215	10.518	
	Age	-0.138	0.159	-0.074	0.182	0.173	0.098	0.213	0.176	0.115	0.179	0.168	0.097
	Female	0.644	4.503	0.012	1.792	4.298	0.033	1.831	4.302	0.034	1.970	4.115	0.037
	Unemployed	-26.521	4.917	-0.465***	-25.059	4.794	-0.440***	-24.622	4.870	-0.432***	-16.706	5.071	-0.293***
2	# Comorbidities				-2.543	1.269	-0.204*	-2.615	1.271	-0.210*	-2.046	1.258	-0.164
	Depression				-6.793	5.744	-0.099	-7.096	5.747	-0.103	-7.261	5.457	-0.105
	Diabetes Mellitus				-14.536	7.191	-0.168*	-11.115	7.685	-0.128	-5.407	7.638	-0.062
	Neoplasm				1.363	6.950	0.018	2.632	7.060	0.035	-0.574	7.008	-0.008
	Stroke				-14.652	5.872	-0.206*	-15.363	5.917	-0.216*	-16.614	5.794	-0.234**
3	Cognitive/Emotional							-9.125	7.579	-0.100	-14.716	7.397	-0.161
	Cranial Nerve							-17.685	21.266	-0.071	-33.351	20.584	-0.133
4	Epilepsy without Meningioma										4.750	4.120	0.104
	Levetiracetam										-12.894	5.338	-0.230*
	1-3 Seizures Prior 6 Months										-11.316	5.870	-0.177
	4+ Seizures Prior 6 Months										-5.357	6.722	-0.075
	# AEDS										-4.136	3.415	-0.124

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.4.5. AEP

Model 4 accounted for 31.9% of the variance on AEP score (adjusted R^2 = 0.319, F (15,103) = 4.691 p < 0.001). The addition of block 2 (R^2 change = 0.128, p = 0.003) and block 4 (R^2 change = 0.124, p = 0.001) were significant. The addition of block 3 reduced the accounted for variance in the model (Table 56).

Variables that significantly predicted increased AEP scores were increasing number of comorbidities (β = 0.295, p = 0.006) and levetiracetam (β = 0.194, p = 0.051). Unemployment was significant in all models, but only marginally significant in model 4 (β = 0.182, p = 0.051).

Table 56: Hierarchical Regression AEP Meningioma with Epilepsy and Epilepsy without Meningioma

		Model 1			Model 2			Model 3			Model 4		
		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change		R^2	R^2 Change	
		0.122***	0.144***		0.220***	0.128**		0.216***	0.009		0.319***	0.124***	
Block	**Variables**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**	**B**	**Std. Error**	**Beta**
1	(Constant)	35.064	5.977		42.189	5.896		42.607	5.950		37.981	5.986	
	Age	0.039	0.090	0.038	-0.163	0.098	-0.161	-0.171	0.100	-0.169	-0.150	0.095	-0.148
	Female	0.463	2.530	0.016	-0.594	2.413	-0.020	-0.651	2.422	-0.022	-0.574	2.297	-0.020
	Unemployed	11.941	2.771	.386***	10.511	2.699	0.340***	10.139	2.749	0.328***	5.589	2.832	0.181
2	# Comorbidities				2.141	0.709	0.318**	2.162	0.713	0.321**	1.948	0.699	0.290**
	Depression				4.707	3.220	0.126	4.829	3.231	0.129	4.846	3.043	0.130
	Diabetes Mellitus				7.551	4.028	0.161	5.750	4.319	0.123	2.445	4.255	0.052
	Neoplasm				-2.012	3.894	-0.049	-2.391	3.969	-0.058	-0.731	3.903	-0.018
	Stroke				1.845	3.290	0.048	2.043	3.323	0.053	2.427	3.230	0.063
3	Cognitive/Emotional							3.188	4.265	0.064	6.551	4.124	0.132
	Cranial Nerve							11.635	11.971	0.086	20.008	11.488	0.147
4	Epilepsy without Meningioma										-2.762	2.305	-0.111
	Levetiracetam										6.293	2.979	0.207*
	1-3 Seizures Prior 6 Months										5.555	3.274	0.161
	4+ Seizures Prior 6 Months										2.665	3.752	0.069
	# AEDS										3.537	1.908	0.195

**** p <0.05***
*****p<0.01***
******p<0.001***

6.3.5. Post Hoc Analysis: AED Subgroup

In the univariate and multivariate analysis of QoL in the meningioma groups, AEDs consistently predicted impaired QoL scores except for the physical summary score of the SF-36. This raised the question, should meningioma patients receiving AEDs be treated as a separate group with specific QoL issues?

Independent samples t-tests were used to compare scores between AED treated and non AED treated meningioma patients. All tests, except for PCS, suggested that QoL was significantly more impaired in AED treated populations. The differences in MCS and FACT-BR are clinically meaningful (Table 57).

These results should be interpreted with caution however as post hoc analyses inflate the risk of type one error.

Table 57: Post Hoc QoL Comparisons by AED use in the Meningioma Groups

	No AED		AED		
	Mean	Std. Deviation	Mean	Std. Deviation	Difference In Mean
PCS	46.88	11.17	46.94	11.45	+0.06
MCS	49.11	10.98	44.19	12.98	-4.92*
TOTAL	145.5	29.19	123.71	39.36	-21.79***
AEP	36.03	10.57	42.06	14.72	-6.03**

p < 0.05
****p < 0.01***
*****p < 0.001***

Chapter 7: Discussion

7.1. Introduction

Quality of life (QoL) is increasingly being recognised as an important outcome measure that influences clinical decisions and policy making[265,266]. This is especially true for benign meningioma, as life expectancy is not impaired in the majority of these cases and disease burden can be high[80].

The relationships between meningioma and QoL, and between epilepsy and QoL, are well understood and there is a substantial literature base for these topics[94,188]. The relationship between meningioma patients with epilepsy and quality of life however, is not well understood and there is a lack of literature on this subject[245].

This study aimed to evaluate the impact that epilepsy would have on the quality of life of patients with benign meningioma. The QoL scores of meningioma patients with epilepsy were compared to the scores of meningioma patients without epilepsy and epilepsy patients without meningioma. Factors that were predictive of QoL were also identified.

The main hypothesis was that meningioma patients with epilepsy would have a worse QoL than meningioma patients without epilepsy. The secondary hypothesis was that patients with meningioma and epilepsy would also have a worse QoL than patients with epilepsy but no meningioma.

7.2. Sample Population

In total 229 patients participated in this study: 109 had a meningioma but no epilepsy; 56 had meningioma and epilepsy; and 64 had epilepsy without a meningioma. The mean age of participants was 60 (±12), the majority were female (81%) and many were retired (43%).

Meningioma patients without epilepsy were most likely to respond to invitation and take part in this study (51.7%), followed by meningioma patients with epilepsy (40.3%) and epilepsy patients without meningioma (18.4%).

The characteristics of all meningioma patients (with or without epilepsy) were representative of a post-resection meningioma population. Both groups were comparable, with exceptions to the significantly increased proportion of patients with tentorial

meningiomas and visual complications in the meningioma without epilepsy group. Patients with varying lengths of follow up were included in the study.

Due to the matching process, the demographics of the epilepsy without meningioma group are not entirely representative of an epilepsy population. Furthermore, the severity of epilepsy in this group is less than would be expected from patients attending a tertiary centre and more closely resembles a sample of patients from general practice[267]. Despite this, epilepsy in the epilepsy without meningioma group is significantly more burdensome than epilepsy in meningioma with epilepsy patients, with an increased number of seizures and anti-epileptic drugs (AEDs) and an increased proportion of dyscognitive seizures. In both groups, patients with seizures were also medicated with at least 1 AED.

7.3. Primary Outcome: The impact of epilepsy on the quality of life of meningioma.

When comparing the mean QoL scores of the meningioma with epilepsy and meningioma without epilepsy groups, the meningioma with epilepsy group had consistently reduced QoL scores. These differences however, are only statistically significant when measured by the FACT-BR. On the SF-36 and the AEP, these differences were not statistically or clinically significant. A discussion of the main findings from each QoL measure is included below.

With exception to bodily pain, all subscale and summary scores of the SF-36 were reduced in the meningioma with epilepsy group, particularly in the subscales of general health, social functioning and emotional role. This resulted in a particularly reduced mental component summary (MCS) score. However, none of these differences in subscale or summary score were statistically significant. In addition to this, the differences in summary scores were not clinically significant.

Disease specific QoL measures are more sensitive than general QoL measures at detecting differences of QoL within the same populations of patients. Since the SF-36 is a general QoL measure, this could have accounted for the statistically and clinically insignificant differences observed. It has been highlighted by previous research that scores on the SF-36 are not particularly sensitive in detecting QoL differences between milder severities of epilepsy[91]. As mentioned earlier, the severity of epilepsy secondary to the meningioma in this study was very mild with the vast majority of patients in seizure remission.

Other studies using the SF-36 have found mean QoL scores to be significantly impaired in brain tumour patients with epilepsy. In these studies however, comparisons were made with a healthy control group. While in the present study, all meningioma patients regardless of epilepsy status had lower SF-36 scores than would be expected in a normal population and indeed, the SF-36 scores of meningioma patients with epilepsy were lower again, it is not appropriate to attach any significance to this.

Meningioma patients with epilepsy were impaired in all of the subscale and summated scores of the FACT-BR when compared to the meningioma without epilepsy group. The biggest differences were seen in the domains of physical wellbeing, social wellbeing and brain tumour related wellbeing. Only the differences in the brain tumour related wellbeing

were significant, the other scores narrowly escaped significance. This resulted in a total score that was statistically different between groups.

The brain tumour subscale contains two seizure related questions, namely “I have seizures” and “I am worried about seizures”. The possibility of the FACT-BR being over-sensitive to epilepsy on account of these two questions was entertained, but since they account for only 10% of the subscale score, this was felt to be highly unlikely. Furthermore, seizure worry and the presence of seizures are reasonable determinants of QoL[268]. No studies have used the FACT-BR to assess the impact of epilepsy on quality of life and so the epilepsy sensitivity of the FACT-BR in other studies cannot be commented upon.

The brain tumour subscale mostly contains questions related to cognition and mood, which can be impaired in patients with epilepsy[269]. On the SF-36, mental health was almost significantly impaired. Both of these findings may imply that cognitive and emotional wellbeing is mostly impaired in meningioma patients with epilepsy.

The AEP is intended to identify adverse drug reactions and despite the use of AEDs in the meningioma with epilepsy sample, the AEP also failed to detect a statistically or clinically significant difference in total score[257]. There was no strong evidence of the occurrence of adverse drug reactions. Scores above 45 are normally associated with AED toxicity and the proportion of patients in this range did not differ significantly between groups[270]. The mean of most individual items of the AEP were lower in the meningioma with epilepsy group but the only the difference in “shaky hands” was significant.

Assuming that AEP scores should be more impaired in the meningioma with epilepsy group, the explanation for an insignificant difference on AEP could be the low AED burden in the epilepsy with meningioma group. Alternatively, meningioma symptoms could be accounting for impaired AEP scores. However, since only the proportion of visual symptoms secondary to the meningioma are significant, and AEP scores are worse in the meningioma with epilepsy group, this seems unlikely.

The regression analysis provides a more conclusive explanation for the small difference on SF-36 scores. AEDs were consistently found to significantly predict impaired QoL scores both in the univariate and multiple regression analysis for all questionnaires except for the physical component summary (PCS) of the SF-36. When considered as a group in the

multiple regression analysis, epilepsy related variables accounted for significant increases in variance for the FACT-BR and the AEP, but individually, only AEDs were consistently significant. This suggests that QoL is more impaired in patients that take AEDs. Since there is a substantial proportion of patients in the meningioma with epilepsy group that are not taking AEDs, it is likely that the effect of AEDs in this study has been diluted when comparing means.

As a proof of concept and to guide further research, the meningioma with epilepsy and meningioma without epilepsy groups were re-categorised by current AED use. In doing this, all the total scores except PCS and the majority of subscale scores were significantly impaired in the meningioma group receiving AEDs. These differences were statistically and clinically significant. However, the dangers of attaching too much importance to a post-hoc subgroup analysis is understood and these findings will be interpreted solely as a point of interest.

Multiple regression cannot determine whether AEDs are the causal factor of impaired QoL or whether they represent similar, related underlying constructs, such as seizure frequency, which is significantly correlated to the use of AEDs in this sample and known to reduce QoL in epilepsy patients.

The regression analysis has also highlighted the importance of demographics, comorbidities and the effect of meningioma on QoL. These factors were more influential than the epilepsy variables in accounting for variance in QoL scores. This is not surprising as these groups represent numerous constructs that are known to impair QoL. Unemployment, diabetes mellitus and the number of meningioma symptoms were all consistently predictive of impaired QoL in all multiple regression analyses.

Depression is an important factor that is repeatedly shown to be associated with impaired QoL scores[188]. This is not surprising as the presence of depression can reduce QoL as an independent factor and also by enhancing the subjective perception of poor QoL[188]. In this study, depression was consistently predictive of reduced QoL in all univariate analysis but was not found to be predictive in the multiple regression analysis. This indicates that in this sample of meningioma patients, depression was complimentary to other factors in reducing QoL. In epilepsy and meningioma studies, depression is usually found to be associated with

various epilepsy and meningioma related factors, but in the present study only unemployment and the number of comorbidities were significantly correlated with depression[85,188]. This is probably because clinical depression was identified from the notes, while in other studies, the level of depression in each participant has been considered by the use of a scale[188]. It is assumed that the latter method is more sensitive at detecting current mood disequilibrium.

Few studies have focused on the individual factors that influence QoL in meningioma patients. One study found that extent of resection and tumour size was predictive of impaired QoL in a multivariate analysis, but the effects of individual meningioma attributed symptoms were not. While this latter point contrasts the findings of the present study, it is reasonable to assume that individual meningioma symptoms are not as powerful in predicting QoL as the combined effect of such symptoms, which is evident in this study.

QoL has been tested numerous times between patient groups in this study increasing the risk of family-wise type I error. This has implications for the significant FACT-BR result as it resulted in the only significant difference in mean QoL score. There are other findings from this study that argue against this result being a type I error. Despite not reaching significance, the SF-36, AEP and remaining FACT scores consistently demonstrated a trend similar to the FACT-BR and the regression analysis showed that epilepsy factors are important determinants of QoL. In addition and as discussed previously, there are potential reasons for the lack of significance on the SF-36 and AEP.

7.3.1. Comparisons with other Research

The findings in this study are supported somewhat by the limited literature surrounding meningioma, epilepsy and QoL. A similar study concluded that QoL scores were reduced in a meningioma with epilepsy population as a result of AED and their effects on cognition[245]. This study used the SF-36, but the mean scores of their populations were compared to the scores of a healthy control group and so no comment can be made as to whether the small difference in QoL score due to epilepsy in meningioma in the present study is a common finding.

Another study using the SF-36 but in a glioma population, also concluded that AED use impaired cognitive function but increased seizure frequency reduced QoL. This latter point

was not supported by the present study or the previous study mentioned. In the glioma study, QoL comparisons were made with a healthy control group.

In epilepsy populations, AEDs are repeatedly shown to impair the QoL of study participants[188]. This finding is also evident in patients with a relatively low epilepsy burden, such as in patients with remission but who prefer to remain in receipt of an AED[188]. Increased seizure frequency and severity of seizure is also known to impair QoL in epilepsy, but in the present study these variables were not strong enough to be significant.

7.4. Secondary Outcome: The Influence of meningioma on the quality of life of epilepsy

When comparing the QoL scores of the epilepsy without meningioma and the meningioma with epilepsy group, subscale and summary scores were consistently, but not significantly, worse in the epilepsy without meningioma group. On the SF-36, QoL was reduced in the epilepsy without meningioma group for all summary and subscale scores, but only the difference in mental health subscale was significant. The differences in summary scores were statistically and clinically non-significant.

A shortened version of the FACT-BR was used to compare quality of life in the meningioma with epilepsy and epilepsy without meningioma groups. All subscale and summary scores were lower in the epilepsy without meningioma group compared to the meningioma with epilepsy group, but none of these differences were statistically significant. Of the four subscales, emotional wellbeing had the biggest difference in score.

The total AEP scores in the epilepsy without meningioma group were larger than the total scores observed in the meningioma with epilepsy group and similarly to the above, these differences were not statistically or clinically significant. When interpreting the individual item scores, the majority of item means had higher scores in the epilepsy without meningioma group, but there was no statistically significant differences in individual item score.

These findings suggest that patients with meningioma and epilepsy have QoL that is equivalent patients with epilepsy but no meningioma. This is despite the severity of epilepsy being mild in the epilepsy without meningioma group. If QoL was more impaired in the meningioma with epilepsy group, this should have been reflected on the FACT-BR scores. Instead this measure also demonstrated that QoL is slightly impaired in the epilepsy without meningioma group.

Both groups differ significantly in terms of epilepsy severity and it may be hypothesised that differences in QoL should have significantly impaired QoL in the control group. One explanation for this not being shown, could be a lack of sensitivity to milder differences in epilepsy severity, particularly on the SF-36 and FACT-BR, both of which are not epilepsy specific measures. This explanation is supported by another study using the SF-36 in an

epilepsy population. It was found that when comparing patients with and without seizures, patients that experienced at least one seizure a month had significantly impaired scores[271]. In the present study, less than 20% of patients in the epilepsy without meningioma group experienced 6 or more seizures in 6 months.

On the AEP, seizure frequency alone cannot explain the insignificant findings. Instead the mild severity of epilepsy in the control group and an overall lack of adverse drug reactions could have explained this.

The effect of the meningioma could be reducing the difference in QoL. In other words, assuming that epilepsy severity is important in determining QoL differences in these groups, the difference in QoL due to epilepsy severity in the epilepsy without meningioma group could be reduced by the effect of meningioma in the meningioma with epilepsy group.

The findings from the regression analysis help to interpret the above findings. Increased seizure frequency, increased number of AEDs and the use of levetiracetam were found to significantly predict impaired QoL scores in the univariate analysis for all QoL measures. However in the multiple regression analysis only levetiracetam remained significant and this was only shown on FACT-G and AEP. The role of levetiracetam in predicting impaired QoL could be explained by its association with increased epilepsy severity[260]. Grouped epilepsy variables in a multiple regression analysis significantly add to the amount of accounted variance on the FACT-BR and the AEP, but this is not the case for the SF-36 confirming that this measure is not particularly sensitive at detecting differences in QoL due to epilepsy.

When considering meningioma related variables in the QoL of the meningioma with epilepsy and epilepsy without meningioma groups, two variables were significant in the univariate analysis: cognitive/emotional symptoms in PCS and cranial nerve symptoms on FACT-G and AEP. In the univariate analysis, these factors were the least significant identified predictors of their respective questionnaire. In the multiple regression analysis, only cognitive/emotional symptoms were predictive. Furthermore, this variable only became predictive after the epilepsy block of variables were entered into the regression model, indicating that the presence of cognitive/emotional symptoms is only significant in the context of epilepsy related factors in this model. Furthermore, the addition of the meningioma block of variables was insignificant for all models. This regression model could

be criticised for only containing two meningioma related variables, but these were the only variables that significantly predicted any dependent variable. All other variables were found to be poor predictors. Epilepsy related variables were more powerful in predicting the dependent variable as individual and grouped independent variables in the multiple regression analyses.

Overall, demographics and comorbidities were more consistent and superior in predicting impaired QoL than epilepsy or meningioma variables. Unemployment was consistently a predictive factor of impaired Qol in both the univariate and multiple regression analysis. Increased numbers of comorbidities, depression, diabetes mellitus and stroke were also found to be influential in the multiple regression. Number of comorbidities and unemployment have been shown in previous studies to impair QoL[188].

In the multiple regression analysis of the meningioma patients, depression was found to be predictive in the univariate but not the multiple regression analysis. In the multiple regression analyses of the epilepsy populations in this study, depression has a more significant role. This cannot be attributed to epilepsy related variables, such as AED use, as the correlation between them is not strong. Depression is significantly correlated with unemployment and the number of comorbidities in this sample, a finding similar in the meningioma regression analysis.

7.5. Conclusion

The primary hypothesis of this study was that meningioma patients with epilepsy have impaired quality of life when compared to meningioma patients without epilepsy. There is sufficient evidence to accept this hypothesis. QoL is consistently impaired in all summary measures and most subscales, and on the FACT-BR the difference in QoL was statistically significant and clinically meaningful. It is important to note however that this impairment in QoL is mild, and this is evident in the lack of a statistical or clinically significance difference on the SF-36 or the AEP. This mild impairment in QoL may reflect the mild severity of epilepsy in meningioma patients.

There is strong evidence that AEDs are strongly associated with impaired QoL in meningioma patients. Furthermore, there is limited evidence that subjective cognitive wellbeing is most impaired by epilepsy in meningioma.

To summarise the main points of the secondary outcome, the QoL of meningioma with epilepsy and epilepsy without meningioma patients is roughly equivalent. There is some evidence to suggest that epilepsy patients overall have more impaired QoL than do meningioma patients with epilepsy. However, in this sample, the influence of other underlying patient characterisitcs, such as employment and disease status, were far more powerful predictors of impaired QoL. The secondary hypothesis for this research was that the QoL of meningioma patients with epilepsy would be worse than the QoL of epilepsy patients without meningioma. This has not been shown in this study and this hypothesis can be confidently rejected.

7.6. Limitations of the present study

The main challenge of this research was in successfully identifying and recruiting a sufficient number of meningioma patients with epilepsy. In the sample population, meningioma patients with epilepsy were a minority subgroup and furthermore these patients were less likely than meningioma patients without epilepsy to respond to invitation. Compounding this issue further is the relatively small proportion of meningioma patients with epilepsy that are medicated with AEDs or experience frequent seizures. Only 7 meningioma patients with epilepsy experienced seizures within the previous 6 months in the current study. This limited the ability of the regression analysis to predict QoL on the basis of seizure frequency.

The poor response rate of the epilepsy without meningioma group was a limitation in this study with the potential of producing selection bias and reducing the external validity of the study.

Another limitation lies in the use of the AEP as an epilepsy related questionnaire. In this study, the AEP was found to be insensitive in detecting a difference in epilepsy severities, even when the FACT-BR identified a significant difference. Perhaps a questionnaire more specific to the overall effects of epilepsy and QoL such as the QOLIE-31 would have provided more meaningful results[272].

The reliance upon paper notes and clinic letters in identifying recent comorbidities and patient characteristics is another limitation of this study. There is the potential that important QoL determining variables were not represented in the notes as a result of focused specialist consultations. It may be expected that this issue is more significant for the epilepsy without meningioma group, due to a lesser degree of regular follow up and inpatient care, but many patients were referred to clinics by their general practitioner, who usually provides an up to date summary of the patient's current and significant past medical history. For all groups this non representation of current medical status is probably equally as important and more variance could have been explained in the regression models if the most up to date clinical information was obtained.

The last limitation is the time period in which to conduct the study. Since there was a year to complete all research activities the analysis of QoL at numerous time points was not

feasible. Furthermore, the evaluation of cognitive dysfunction would have been a valuable addition to the study had there been enough time to administer cognitive assessments.

7.7. Recommendations for Future Research

Future studies have the opportunity to build upon the strengths and limitations of previous studies and the present study so that the quality of life of meningioma patients and meningioma patients with epilepsy can be better understood.

If obtainable, larger samples of meningioma patients with epilepsy will allow for a better consideration of the effect of seizures and individual AEDs. This potentially has substantial implications for clinical recommendations on drug choice and the aim of AED treatment.

The direct comparisons of meningioma patients with and without epilepsy were of great value in this study, as were the comparisons with an epilepsy without meningioma group, and these comparisons should be repeated. However, subgroups of epilepsy severity should be created, as QoL is not equivalent across all severities of epilepsy. In this study, patients on AEDs were particularly found to have reduced QoL. The addition of a matched healthy control group will also provide insight in how QoL differs between meningioma patients with epilepsy and the general population.

Furthermore, the use of a measure more sensitive than the AEP is highly recommended for any future projects in this area aiming to stratify by epilepsy severity.

Since QoL measures rely on a patient's subjective interpretation of their own quality of life the influence of personality on QoL scores needs clarification in epilepsy and meningioma patients. Furthermore, the impact of cognitive functioning on QoL and the accuracy of QoL reporting also needs clarification.

In addition to the variables considered in this study, comorbidity severity, marital status, race and tumour size should also be included in future studies.

The use of medical records from tertiary centres is essential and should be supplemented by data from the patients themselves and their general practitioner.

7.8. What this study adds

This is the largest focussed analysis of quality of life in epilepsy and meningioma performed so far. It is also the first study to have directly compared QoL in meningioma patients with and without epilepsy directly.

The results of this study add to the existing knowledge base that epilepsy impairs QoL in meningioma patients. This study also agrees with the evidence that AEDs are a significant factor in the reduction of QoL.

Most importantly, this study has found that the QoL of meningioma patients with epilepsy is reduced to a small extent when directly comparing meningioma patients with and without epilepsy. This is a novel finding that has not been reported elsewhere and may be a result of the mild epilepsy severity in meningioma patients.

In this study the comparison of QoL between meningioma patients with epilepsy and epilepsy patients without meningioma was novel. This comparison has suggested that QoL is comparable in these groups.

7.9. Concluding remarks and clinical context

The underlying aim for most clinicians is to maximise the quality of life of their patients. Given the comparatively mild severity of epilepsy in meningioma and the significant negative effect of AEDs on QoL, AEDs should not be prescribed too readily or aggressively in these patients. Even monotherapy in the meningioma patients was enough to reduce QoL and there was not much evidence of adverse drug reactions from the AEP. Furthermore, the detrimental effect of unemployment and comorbidities was large for all patient groups in this study. Careful consideration of these patient circumstances in addition to their primary health complaint will help the clinician to identify areas of improvement that will result in a meaningful benefit to the lives of their patients.

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Appendix I

NICE Guidelines for the Management of Epilepsy:

I.I. NICE guidance for treatment of focal, generalised and absence seizures

I.II. NICE guidance for treatment of myoclonic and tonic/atonic seizures

I.l. NICE guidance for treatment of focal, generalised and absence seizures[106]

Treatment of focal seizures in children, young people and adults.

First line treatment:

- carbamazepine, lamotrigine

Alternative first line treatment:

- levetiracetam, oxcarbazepine, sodium valproate

Adjunctive treatment (if first line treatment is not effective or tolerated):

- carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate.

Action if adjunctive treatment is not effective or tolerated:

- consider referral to tertiary services (where other AEDs may be tried)

Treatment of generalised tonic clonic seizures in children, young people and adults.

First line treatment:

- sodium valproate, lamotrigine (if sodium valproate is not suitable)

Alternative first line treatment:

- carbamazepine, oxcarbazepine

Adjunctive treatment (if first line treatment is not effective or tolerated):

- clobazam, lamotrigine, levetiracetam, sodium valproate, topiramate

(If the person also has absences or myoclonic seizures, or may have juvenile myoclonic epilepsy do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin)

Treatment of absence seizures in children, young people and adults.

First line treatment:

- ethosuximide, sodium valproate (offer first if additional tonic clonicseizures are likely)

Alternative first line treatment:

- lamotrigine

Adjunctive treatment (if first line treatment is not effective or tolerated):

- Try a combination of ethosuximide, lamotrigine or sodium valproate.

Action if adjunctive treatment is not effective or tolerated:

- consider referral to tertiary services (where other AEDs may be tried)

(Cautions: do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin)

I.Il. NICE guidance for treatment of myoclonic and tonic/atonic seizures[106]

Treatment of myoclonic seizures in children, young people and adults.

First line treatment:

- sodium valproate

Alternative first line treatment:

- levetiracetam, topiramate

Adjunctive treatment (if first line treatment is not effective or tolerated):

- levetiracetam, sodium valproate, topiramate

Action if adjunctive treatment is not effective or tolerated:

- consider referral to tertiary services (where other AEDs may be tried)

(Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin)

Treatment of tonic and atonic seizures in children, young people and adults.

First line treatment:

- sodium valproate

Adjunctive treatment (if first line treatment is not effective or tolerated):

- lamotrigine

Action if adjunctive treatment is not effective or tolerated:

- consider referral to tertiary services (where other AEDs may be tried)

(Cautions: do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin)

Appendix II

Ethical Approvals:

II.I. Confirmation of Favourable Ethical Opinion: NRES Committee North West – Cheshire

II.II. R+D Project Approval Letter: The Walton Centre

Health Research Authority
National Research Ethics Service

NRES Committee North West - Cheshire

HRA NRES Centre North West
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7816
Fax: 0161 625 7299

12 November 2012

Mr Matthew Tanti (md0u842e@student.liv.ac.uk)
The Clinical Sciences Centre
Longmoor Lane
Liverpool
L9 7AL

Dear Mr Tanti

Study title:	**The impact of epilepsy on the quality of life of patients with benign meningioma**
IRAS project number:	**113165**
REC reference:	**12/NW/0747**

Thank you for your letter of 06 November 2012, responding to the Committee's request for further information on the above research and submitting revised documentation including additional changes as listed below:

- Supplementary Questions form will only be sent to epileptic patients
- Supplementary Questions form has removed seizure type descriptions and thus will not ask about seizure type
- Supplementary Questions form has altered its question about seizure frequency for ease of use
- A question eliciting employment status has been added to the bottom of the LEAP questionnaire
- Participant's details and their research data will be archived for 15 years after study completion in accordance with recommendations from the R&D department of the Walton Centre
- General formatting and language improvements to documents

The further information and additional changes as above were considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		01 October 2012
Investigator CV	Mr Michael Jenkinson - 1	25 September 2012
Investigator CV	Mr Anthony Marson - 1	25 September 2012
Investigator CV	Mr Matthew Tanti - 1	19 September 2012
Other: Cover sheet	5	24 September 2012
Other: Patients Results Breakdown	3	24 September 2012
Other: Summary of protocol in non-technical language	6	06 November 2012
Other: Supplementary questions	10	06 November 2012
Participant Consent Form	4	25 September 2012
Participant Information Sheet: Epilepsy without Meningioma	5	05 November 2012
Participant Information Sheet: Meningioma without Epilepsy	5	05 November 2012
Participant Information Sheet: Meningioma with Epilepsy	5	05 November 2012
Protocol	15	05 November 2012
Questionnaire: Professor Anthony Marson		25 September 2012

Questionnaire: FACT-Br	4	16 November 2007
Questionnaire: Liverpool Adverse Events Profile (LEAP) and Employment Questionnaire	1	01 November 2012
Questionnaire: SF-36 Your Health and Well-Being		06 November 2012
REC application	3.4	29 September 2012
Response to Request for Further Information		06 November 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/NW/0747 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

pp

Mr Jonathan Deans
Chair

Email: nrescommittee.northwest-cheshire@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Dr Mike Morris mike.morris@thewaltoncentre.nhs.uk)
Mr Michael Jenkinson, The Walton Centre NHS Foundation Trust
jenkinmd@liverpool.ac.uk
Miss Rebecca McDonald, Research Governance offices
(Rebecca.mcdonald@thewaltoncentre.nhs.uk)

NRES Committee North West - Cheshire

Attendance at Sub-Committee of the REC meeting held by correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Jonathan Deans	Consultant ENT Surgeon	Yes	
Dr Sue Elves	Consultant Clinical Psychologist	Yes	

The Walton Centre NHS
NHS Foundation Trust

Excellence in Neuroscience

Date: 10th October 2012

Dear Mr Michael Jenkinson,

Study Title: Epilepsy Meningioma and Quality of Life Version 11: 23/09/2012

CSP ID: **REC Reference:** 12/NW/0747 **R&D Reference: RG042/12**

Thank you for providing all of the documentation for the above study.

I am pleased to inform you that the above study has been given full R&D approval and you may begin this at the Walton Centre NHS Foundation Trust. This has been granted for the duration of the REC approval for your study.

The list of documents reviewed and approved for use are as follows:

Document	Version	Date
Protocol	V11	23.09.2012
SSI Form	V3.4	Signed 29.09.12
Consent Form	V4	25.09.2012
PIS	V7	25.09.2012

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, Good Clinical Practice, Trust policies and procedures, and all applicable legislation including, but not limited to, the Data Protection Act, the Health and Safety at Work Act, Human Tissue Act, Medicines for Human Use (Clinical Trials) Act. As Principal Investigator you retain overall responsibility for compliance with these requirements by all members of the research team. The recruitment target is 4 patients for this study.

You must ensure that you read and understand the enclosed conditions of approval

Should you have any queries, or feel that we can be of assistance, please do not hesitate to contact a member of the R&D office on 0151 529 8854.

I would like to take this opportunity to wish you well with your research

Yours Sincerely,

pp Mike Horrell

Dr M. Steiger
Director of Research and Development

CONDITIONS FOR RESEARCH APPROVAL

This study is subject to external performance management of recruitment on time and to target. You are responsible for ensuring that recruitment targets are met. The Trust expects the first participant to be recruited within 30 days of receipt of R&D approval. The R&D department must be informed of the date on which the first participant is recruited. You may delegate this responsibility to the CTU or a responsible member of your research team. If there is a delay in starting recruitment, you must inform the R&D office and give a reason for this. You are also required to provide recruitment data to the R&D office upon request. This information will be used to inform performance targets, which will be reported to the Trust Board.

Note that for non-questionnaire type studies you are required to document patient participation in a clinical trial on the orange card in the patient casenotes. This is required to ensure that the Trust retains the case notes for the period of time required for research records. If you are unsure as to the requirement of this in relation to your trial please contact the R&D office prior to commencement.

All researchers involved in the study must have undertaken GCP training within the last two years. Please ensure that you provide the R&D office with evidence of this.

You must obtain R&D approval (or acknowledgement) for all amendments during the course of the study. You must not implement an amendment until this has been granted. You should submit all amendment documentation to the R&D office unless the study has been adopted onto the UKCRN portfolio. If the study has been adopted onto the UKCRN portfolio and has been processed through CSP, *all amendments must be submitted through the Lead CLRN. In such cases please do not send any amendments to the R&D office directly*. The Lead CLRN will inform us of any amendments and will supply us with the required documentation.

You must ensure that annual reports are submitted to the REC in a timely fashion, and a copy should also be sent to R&D. On completion of the study you must ensure that the End of Study Report is submitted to the REC, and a copy sent to R&D. More information on post-approval requirements is available from
http://www.nres.nhs.uk/applications/after-ethical-review/

You must inform the R&D office of any changes to the management of your project, any extensions to the study, and any changes in funding, if applicable.

The Trust may monitor the progress or audit the conduct of your study at any time. The Trust reserves the right to suspend or withdraw R&D approval if you do not adhere to the requirements outlined. You must abide by all determinations of the R&D office and accept their final authority.

The R&D office must be notified of any Serious Adverse Events (SAEs) which are probably or definitely related to the trial, and any Suspected Unexpected Serious Adverse Reactions (SUSARs), promptly.

Appendix III

Postal Invitation Pack:

The Walton Centre NHS
NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

The impact of epilepsy on the quality of life of patients with benign meningioma

Cover Sheet Version 5 Dated 24/09/2012

Date:

Dear

We are writing to you today in the hope that you will agree to be part of a study establishing the quality of life of meningioma and epilepsy patients. Willing participants will complete a series of questionnaires in the comfort of their own home, and will only be inconvenienced for half an hour. Participation is completely voluntary and will not affect the treatment you are currently receiving in any way.

If you are interested, could I direct your attention to the patient information leaflet inserted as part of this postal pack. It is essential that you read all the details on this form. If you decide that you would like to take part, all you have to do is fill in the consent form attached in this pack and post it via the pre-paid envelope provided. You have three weeks in which to do this.

If you do not want to participate, all you need to do is ignore this letter. You will be contacted at a later date by phone. This will be to ensure we have sent these forms to the right address.

If you have any queries, you can contact the research team using the details on page 3 of the patient information leaflet.

Thank you for your time.
We hope to hear from you soon.

Mr Michael Jenkinson
Consultant Neurosurgeon

Professor Anthony Marson
Professor of Neurology

Matthew Tanti
Postgraduate Researcher

The Walton Centre NHS
NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

The impact of epilepsy on the quality of life of patients with benign meningioma

Patient Information Leaflet; Meningioma without Epilepsy Version 5 Dated 05/11/2012

Why is this study needed?

Quality of Life (QoL) is a term that encompasses a person's wellbeing and happiness. Epilepsy is known to impair QoL but for people with meningioma, QoL is less well understood, particularly if they also have epilepsy. Understanding QoL is important when deciding between the best treatment options for patients.

How will the study answer its question?

QoL is influenced by the physical, mental and emotional health of a person. The best way of ascertaining QoL is to take such influences into account and this is effectively done with questionnaires that can be filled out in the convenience of one's home.

We will be sending participants 3 questionnaires; one which focusses on brain cancer (FACT-BR), another focussing on epilepsy and employment (LAEP and Employment) and another focussing on QoL more generally (SF-36).We will be sending these questionnaires to three groups of people. You are in the meningioma without epilepsy group. The other groups are:

- Meningioma with epilepsy.
- Epilepsy without meningioma.

The comparison of questionnaire results between the three groups will help us to understand what factors influence quality of life.

Why have I been asked to take part?

You have been asked to take part in this study because you are a patient who has previously had surgery for meningioma and has not suffered from epilepsy. Many meningioma patients do not suffer from epilepsy and their QoL scores are needed for comparisons with the epilepsy groups. Your QoL scores are very important to this study.

What will happen to me during the study?

If you would like to take part in this study, we ask that you complete and send the attached consent form back to the research group within 3 weeks. When the research group has received your consent form, you will then be sent the three questionnaires:

- FACT-BR
- LAEP and Employment
- SF-36

In total, the questionnaires will take between 10 and 30 minutes to complete and should be filled out on the same day. Participants are only required to complete one round of questionnaires.

The Walton Centre NHS
NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

You will have 3 weeks to return the completed questionnaires from the date you received them. You will not have to pay for postage as a prepaid envelope will be provided.

When the questionnaires have been returned, you will have completed the study and there is nothing more you need to do.

What are the risks or disadvantages of taking part?

If you take part, your only inconvenience will be in answering our questions and posting completed forms. As mentioned before, all postage will be prepaid and the questionnaires will only take around 30 minutes to complete.

There are no major risks associated with taking part in the study. The biggest risk is in the use of your identifiable personal information, i.e. your name and address. These details will be held securely and access to this information is strictly limited to members of the research team.

Some questionnaires will ask sensitive questions regarding your work, emotions and relationships with other people. There is a slight risk that some people may find these questions upsetting. If this is a problem, you are able to withdraw yourself from the study and stop answering questions. This is not anticipated to be a major problem for the majority of participants.

What are the benefits of taking part?

There is no direct benefit to you as a result of your participation in this study. Indirectly some may learn of the influences on QoL, and some may be pleased in knowing that their participation may help doctors and future patients.

What if there is a problem?

It is not anticipated that there will be problems for you if you participate in this study. If there are any concerns you can contact the research team directly or consider withdrawing yourself from the study.

Will my taking part in this study be kept confidential?

Your confidentiality is a priority in this study. Only the research team will be aware of your participation. Questionnaire results will be anonymised, so your name and address is not shown and a patient study number will be assigned to your questionnaire. A conversion table with your name, address and study number will be secured in a locked cupboard and office.

Electronic data will be stored on password protected and encrypted computers. This study will act in accordance with the data protection act 1998.

When the study has been fully completed, identifiable information (names and addresses) and study data will be archived. This is to allow for future use of the data in scientific articles and conferences and to comply with local research policies.

Do I have to take part, and can I change my mind?

Your participation in this study is completely voluntary. It is recommended that you participate only if you wish to. You can change your mind and withdraw from the study at any point without giving a reason. Withdrawal from the study will not affect the care you receive at present or in the future.

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Fazakerley
Liverpool
L9 7LJ

What will happen to the results of the study?

We aim to report the findings of this study through conferences and scientific journals. No identifiable information will be used when presenting results.

If you would like an explanation of our findings to be sent to you, please initial the relevant "YES" box on the consent form. We will then arrange for a results breakdown sheet to be sent to you.

Who is doing this research study?

This study is based at the Education Centre of Aintree University Hospital, which is next door to the Walton Centre NHS Foundation Trust for Neurology and Neurosurgery. It will be completed as part of a research degree project under the close supervision of senior professionals from the University of Liverpool and the Walton Centre.

Who has reviewed this research study?

This study has been approved by the North West Greater Manchester Cheshire REC and the Walton Centre internal research committee.

Contact details

If you would like to gain independent advice about participation in research, you can contact the Walton Centre Research and Development department:

- **Telephone:** 0151 529 5446
- **Email:** researchdevelopment@thewaltoncentre.nhs.uk

If you would like to speak to the research team, please do not hesitate to contact us via the following:

- **Telephone**: 0151 529 5468
- **Email:** matthew.tanti@thewaltoncentre.nhs.uk
- **Post:** Matthew Tanti
  Department of Neurological Science
  Clinical Sciences Centre for Research and Education
  Longmoor Lane
  Liverpool
  L7 9LJ

Thanks for your time.

Mr Michael Jenkinson
Consultant Neurosurgeon

Professor Anthony Marson
Professor of Neurology

Matthew Tanti
Postgraduate Researcher

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NHS Foundation Trust
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Fazakerley
Liverpool
L9 7LJ

The impact of epilepsy on the quality of life of patients with benign meningioma

Patient Information Leaflet; Meningioma with Epilepsy Version 5 Dated 05/11/2012

Why is this study needed?

Quality of Life (QoL) is a term that encompasses a person's wellbeing and happiness. Epilepsy is known to impair QoL but for people with meningioma, QoL is less well understood, particularly if they also have epilepsy. Understanding QoL is important when deciding between the best treatment options for patients.

How will the study answer its question?

QoL is influenced by the physical, mental and emotional health of a person. The best way of ascertaining QoL is to take such influences into account and this is effectively done with questionnaires that can be filled out in the convenience of one's home.

We will be sending participants 3 questionnaires; one which focusses on brain cancer (FACT-BR), another focussing on epilepsy and employment (LAEP and Employment) and another focussing on QoL more generally (SF-36). In addition, a set of supplementary questions will be sent to participants to establish how many seizures they have and what anti-epileptic medication they use.

We will be sending these questionnaires to three groups of people. You are in the meningioma with epilepsy group. The other groups are:

- Meningioma without epilepsy.
- Epilepsy without meningioma.

The comparison of questionnaire results between the three groups will help us to understand what factors influence quality of life.

Why have I been asked to take part?

You have been asked to take part in this study because you are a patient who has previously had surgery for meningioma and has suffered from epilepsy. Meningioma patients that suffer from epilepsy are very important to this study.

What will happen to me during the study?

If you would like to take part in this study, we ask that you complete and send the attached consent form back to the research group within 3 weeks. When the research group has received your consent form, you will then be sent the three questionnaires:

- FACT-BR
- LAEP and Employment
- SF-36

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Fazakerley
Liverpool
L9 7LJ

You will also be sent a set of supplementary epilepsy questions. In total, the questionnaires and supplementary questions will take between 10 and 30 minutes to complete and should be filled out on the same day. Participants are only required to complete one round of questionnaires.

You will have 3 weeks to return the completed questionnaires and supplementary question sheet from the date you received them. You will not have to pay for postage as a prepaid envelope will be provided.

When the questionnaires have been returned, you will have completed the study and there is nothing more you need to do.

What are the risks or disadvantages of taking part?

If you take part, your only inconvenience will be in answering our questions and posting completed forms. As mentioned before, all postage will be prepaid and the questionnaires will only take around 30 minutes to complete.

There are no major risks associated with taking part in the study. The biggest risk is in the use of your identifiable personal information, i.e. your name and address. These details will be held securely and access to this information is strictly limited to members of the research team.

Some questionnaires will ask sensitive questions regarding your work, emotions and relationships with other people. There is a slight risk that some people may find these questions upsetting. If this is a problem, you are able to withdraw yourself from the study and stop answering questions. This is not anticipated to be a major problem for the majority of participants.

What are the benefits of taking part?

There is no direct benefit to you as a result of your participation in this study. Indirectly some may learn of the influences on QoL, and some may be pleased in knowing that their participation may help doctors and future patients.

What if there is a problem?

It is not anticipated that there will be problems for you if you participate in this study. If there are any concerns you can contact the research team directly or consider withdrawing yourself from the study.

Will my taking part in this study be kept confidential?

Your confidentiality is a priority in this study. Only the research team will be aware of your participation. Questionnaire results will be anonymised, so your name and address is not shown and a patient study number will be assigned to your questionnaire. A conversion table with your name, address and study number will be secured in a locked cupboard and office.

Electronic data will be stored on password protected and encrypted computers. This study will act in accordance with the data protection act 1998.

When the study has been fully completed, identifiable information (names and addresses) and study data will be archived. This is to allow for future use of the data in scientific articles and conferences and to comply with local research policies.

Do I have to take part, and can I change my mind?

The Walton Centre NHS
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L9 7LJ

Your participation in this study is completely voluntary. It is recommended that you participate only if you wish to. You can change your mind and withdraw from the study at any point without giving a reason. Withdrawal from the study will not affect the care you receive at present or in the future.

What will happen to the results of the study?

We aim to report the findings of this study through conferences and scientific journals. No identifiable information will be used when presenting results.

If you would like an explanation of our findings to be sent to you, please initial the relevant "YES" box on the consent form. We will then arrange for a results breakdown sheet to be sent to you.

Who is doing this research study?

This study is based at the Education Centre of Aintree University Hospital, which is next door to the Walton Centre NHS Foundation Trust for Neurology and Neurosurgery. It will be completed as part of a research degree project under the close supervision of senior professionals from the University of Liverpool and the Walton Centre.

Who has reviewed this research study?

This study has been approved by the North West Greater Manchester Cheshire REC and the Walton Centre internal research committee.

Contact details

If you would like to gain independent advice about participation in research, you can contact the Walton Centre Research and Development department:

- **Telephone:** 0151 529 5446
- **Email:** researchdevelopment@thewaltoncentre.nhs.uk

If you would like to speak to the research team, please do not hesitate to contact us via the following:

- **Telephone**: 0151 529 5468
- **Email:** matthew.tanti@thewaltoncentre.nhs.uk
- **Post:** *Matthew Tanti*
  Department of Neurological Science
  Clinical Sciences Centre for Research and Education
  Longmoor Lane
  Liverpool
  L7 9LJ

Thanks for your time.

Mr Michael Jenkinson
Consultant Neurosurgeon

Professor Anthony Marson
Professor of Neurology

Matthew Tanti
Postgraduate Researcher

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L9 7LJ

The impact of epilepsy on the quality of life of patients with benign meningioma

Patient Information Leaflet; Epilepsy without Meningioma Version 5 Dated 05/11/2012

Why is this study needed?

Quality of Life (QoL) is a term that encompasses a person's wellbeing and happiness. Epilepsy is known to impair QoL but for people with meningioma, QoL is less well understood, particularly if they also have epilepsy. Understanding QoL is important when deciding between the best treatment options for patients.

How will the study answer its question?

QoL is influenced by the physical, mental and emotional health of a person. The best way of ascertaining QoL is to take such influences into account and this is effectively done with questionnaires that can be filled out in the convenience of one's home.

We will be sending you 3 questionnaires; one which focusses on the brain (FACT-BR), another focussing on epilepsy and employment (LAEP and Employment) and another focussing on QoL more generally (SF-36). In addition, a set of supplementary questions will be sent to participants to establish how many seizures they have and what anti-epileptic medication they use.

We will be sending these questionnaires to three groups of people. You are in the epilepsy without meningioma group. The other groups are:

- Meningioma with epilepsy.
- Meningioma without epilepsy.

The comparison of questionnaire results between the three groups will help us to understand what factors influence quality of life.

Why have I been asked to take part?

You have been asked to take part in this study because you are a patient who attends the epilepsy clinic and does not suffer from meningioma. Epilepsy patients are needed to provide comparative QoL scores, and so are very important to this study.

What will happen to me during the study?

If you would like to take part in this study, we ask that you complete and send the attached consent form back to the research group within 3 weeks. When the research group has received your consent form, you will then be sent the three questionnaires:

- FACT-BR
- LAEP and Employment
- SF-36

The Walton Centre NHS
NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

You will also be sent a set of supplementary epilepsy questions. In total, the questionnaires and supplementary questions will take between 10 and 30 minutes to complete and should be filled out on the same day. Participants are only required to complete one round of questionnaires.

You will have 3 weeks to return the completed questionnaires and supplementary question sheet from the date you received them. You will not have to pay for postage as a prepaid envelope will be provided.

When the questionnaires have been returned, you will have completed the study and there is nothing more you need to do.

What are the risks or disadvantages of taking part?

If you take part, your only inconvenience will be in answering our questions and posting completed forms. As mentioned before, all postage will be prepaid and the questionnaires will only take around 30 minutes to complete.

There are no major risks associated with taking part in the study. The biggest risk is in the use of your identifiable personal information, i.e. your name and address. These details will be held securely and access to this information is strictly limited to members of the research team.

Some questionnaires will ask sensitive questions regarding your work, emotions and relationships with other people. There is a slight risk that some people may find these questions upsetting. If this is a problem, you are able to withdraw yourself from the study and stop answering questions. This is not anticipated to be a major problem for the majority of participants.

What are the benefits of taking part?

There is no direct benefit to you as a result of your participation in this study. Indirectly some may learn of the influences on QoL, and some may be pleased in knowing that their participation may help doctors and future patients.

What if there is a problem?

It is not anticipated that there will be problems for you if you participate in this study. If there are any concerns you can contact the research team directly or consider withdrawing yourself from the study.

Will my taking part in this study be kept confidential?

Your confidentiality is a priority in this study. Only the research team will be aware of your participation. Questionnaire results will be anonymised, so your name and address is not shown and a patient study number will be assigned to your questionnaire. A conversion table with your name, address and study number will be secured in a locked cupboard and office.

Electronic data will be stored on password protected and encrypted computers. This study will act in accordance with the data protection act 1998.

When the study has been fully completed, identifiable information (names and addresses) and study data will be archived. This is to allow for future use of the data in scientific articles and conferences and to comply with local research policies.

The Walton Centre NHS
NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

Do I have to take part, and can I change my mind?

Your participation in this study is completely voluntary. It is recommended that you participate only if you wish to. You can change your mind and withdraw from the study at any point without giving a reason. Withdrawal from the study will not affect the care you receive at present or in the future.

What will happen to the results of the study?

We aim to report the findings of this study through conferences and scientific journals. No identifiable information will be used when presenting results.

If you would like an explanation of our findings to be sent to you, please initial the relevant "YES" box on the consent form. We will then arrange for a results breakdown sheet to be sent to you.

Who is doing this research study?

This study is based at the Education Centre of Aintree University Hospital, which is next door to the Walton Centre NHS Foundation Trust for Neurology and Neurosurgery. It will be completed as part of a research degree project under the close supervision of senior professionals from the University of Liverpool and the Walton Centre.

Who has reviewed this research study?

This study has been approved by the North West Greater Manchester Cheshire REC and the Walton Centre internal research committee.

Contact details

If you would like to gain independent advice about participation in research, you can contact the Walton Centre Research and Development department:

- **Telephone:** 0151 529 5446
- **Email:** researchdevelopment@thewaltoncentre.nhs.uk

If you would like to speak to the research team, please do not hesitate to contact us via the following:

- **Telephone**: 0151 529 5468
- **Email:** matthew.tanti@thewaltoncentre.nhs.uk
- **Post:** *Matthew Tanti*
  Department of Neurological Science
  Clinical Sciences Centre for Research and Education
  Longmoor Lane
  Liverpool
  L7 9LJ

Thanks for your time.

Mr Michael Jenkinson
Consultant Neurosurgeon

Professor Anthony Marson
Professor of Neurology

Matthew Tanti
Postgraduate Researcher

Appendix III.V.

The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

The impact of epilepsy on the quality of life of patients with benign meningioma

Consent Form Version 4 Dated 25/09/2012

Centre Name: **The Walton Centre**

Name of Investigator: **Matthew Tanti**

Patient's Name:

Patient's Date of Birth: |__|__|/|__|__|/|__|__|__|__|

	Please initial boxes	
1. I confirm I have read and understood the information leaflet (version 5 dated (05/11/2012) for the above study, and have had the opportunity to ask questions and have had these answered satisfactorily.		
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my care or legal rights being affected.		
3. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the research team, Regulatory Authorities, co-sponsors (Walton Centre NHS Foundation Trust and University of Liverpool), or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records for this purpose.		
4. **I agree to take part in the above study.**		
5. I would like to be informed of the results of the study (initial one box only).	**YES**	
	NO	

Name of Participant	**Signature**	**Date** (dd-mm-yyyy)
Matthew Tanti		
Researcher	**Signature**	**Date** (dd-mm-yyyy)

Appendix IV

Questionnaires:

IV.I. **Sf-36**

IV.II. **Fact-Br (For Fact-G discount "Additional Concerns")**

IV.III. **AEP with additional employment question**

IV.IV. **Supplementary Questions (Only for patients with epilepsy)**

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

FACT-Br (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

Liverpool Adverse Events Profile (LAEP) and Employment Questionnaire

During the **last four weeks**, have you had any of the problems listed below? For each item, if it has always or often been a problem, ring 4; if it has sometimes been a problem, ring 3; and so on.

Please be sure to answer every item.

	Never a problem	Rarely a problem	Sometimes a problem	Always or often a problem
Unsteadiness	1	2	3	4
Tiredness	1	2	3	4
Restlessness	1	2	3	4
Feelings of aggression	1	2	3	4
Nervousness and/or agitation	1	2	3	4
Headache	1	2	3	4
Hair loss	1	2	3	4
Problems with skin, e.g. acne, rash	1	2	3	4
Double or blurred vision	1	2	3	4
Upset stomach	1	2	3	4
Difficulty in concentrating	1	2	3	4
Trouble with mouth or gums	1	2	3	4
Shaky hands	1	2	3	4
Weight gain	1	2	3	4
Dizziness	1	2	3	4
Sleepiness	1	2	3	4
Depression	1	2	3	4
Memory problems	1	2	3	4
Disturbed sleep	1	2	3	4

Employment

Which statement best describes your current employment status? Please ring one answer.

Employed Full Time	A		Unable to Work due to Disability	E
Employed Part Time	B		Looking after Family	F
Unemployed, Looking for Work	C		Retired	G
Unemployed, not Looking for Work	D		Student	H

Supplementary Questions

Version 10 Dated 06/11/2012

Seizure Frequency

Over the past 6 months how many epileptic attacks have you had?
Please **tick** the appropriate box:

Number of Seizures in Past 6 Months	Tick
None	
One	
2-3	
4-5	
6-9	
10+	

Anti-epileptic medication

What anti-epileptic drugs (AEDs) do you currently take? If you are not prescribed AEDs just insert NA.

Drug	Name of Drug	Strength (e.g. 200mg)	Frequency (e.g. once a day)
1			
2			
3			
4			

Appendix V

Simple Linear Regression:

V.I. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Demographic and Comorbidity Variables

V.II. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Meningioma Variables

V.III. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Epilepsy Variables

V.IV. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma - Demographic and Comorbidity Variables

V.V. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Meningioma Variables

V.VI. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Epilepsy Variables 1 of 2

V.VII. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Epilepsy Variables 2 of 2

V.I. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Demographic and Comorbidity Variables

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-BR			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Demographics	Age	0.019	-0.157	0.046	0.087	0.304	0.000	0.008	0.119	0.133	0.038	-0.209	0.008
	Female	-0.001	-0.071	0.370	-0.002	0.064	0.415	0.001	0.086	0.275	-0.005	0.031	0.698
	Employed Full Time	0.064	0.265	0.001	0.025	0.177	0.025	0.027	0.182	0.021	0.026	-0.179	0.022
	Employed Part Time	0.014	0.142	0.071	-0.006	0.026	0.739	0.007	0.116	0.142	-0.006	-0.003	0.968
	Employed	0.101	0.327	0.000	0.022	0.169	0.032	0.051	0.239	0.002	0.017	-0.153	0.052
	Unemployed Looking	-0.006	-0.015	0.849	-0.006	-0.018	0.821	-0.005	0.028	0.720	-0.006	-0.010	0.895
	Unemployed not looking	-0.004	0.050	0.525	-0.002	0.068	0.393	-0.004	0.050	0.526	0.001	-0.083	0.296
	Unemployed due Disability	0.148	-0.392	0.000	0.218	-0.472	0.000	0.284	-0.537	0.000	0.245	0.500	0.000
	Unemployed	0.123	-.359	0.000	.180	-.431	0.000	0.218	-0.472	0.000	0.191	0.443	0.000
	Caring for Family	0.006	0.112	0.155	0.000	-0.082	0.301	-0.006	0.022	0.782	-0.006	-0.018	0.817
	Retired	0.008	-0.119	0.132	0.049	0.234	0.003	0.010	0.127	0.109	0.021	-0.165	0.036
	Student	0.014	0.141	0.074	0.028	-0.186	0.018	-0.001	-0.076	0.339	-0.006	-0.014	0.856
	Blank	-0.006	0.008	0.918	-0.006	-0.024	0.758	-0.006	-0.020	0.799	-0.006	-0.007	0.934
Comorbidities	Arthritis	0.023	-0.170	0.031	-0.004	0.049	0.532	-0.006	0.004	0.956	-0.004	-0.045	0.572
	Asthma	-0.006	-0.016	0.841	-0.001	0.070	0.376	-0.003	0.055	0.484	-0.006	0.016	0.836
	Cardio (electric)	-0.004	-0.049	0.537	-0.002	0.066	0.403	-0.005	-0.036	0.649	-0.006	0.025	0.750
	Depression	0.031	-0.193	0.014	0.072	-0.279	0.000	0.041	0.217	0.006	0.072	-0.280	0.000
	Diabetes M	0.019	-0.160	0.042	0.008	-0.117	0.138	0.013	0.140	0.076	0.022	-0.168	0.033
	Hypertension	0.025	-0.175	0.026	-0.001	0.073	0.357	-0.003	-0.058	0.466	-0.004	-0.049	0.537
	IHD	0.000	-0.078	0.324	0.001	-0.082	0.300	0.001	0.085	0.281	-0.003	-0.057	0.475
	Migraine	-0.006	0.009	0.907	-0.006	-0.010	0.896	-0.006	0.024	0.759	-0.006	-0.023	0.774
	Neoplasm	0.032	-0.195	0.013	-0.001	0.073	0.357	-0.006	0.007	0.926	-0.005	-0.033	0.682
	Neuropathy	0.038	-0.210	0.007	-0.003	-0.055	0.485	-0.003	0.060	0.448	-0.003	-0.060	0.450
	Stroke	0.019	-0.159	0.043	-0.005	-0.037	0.640	-0.006	-0.006	0.935	0.006	-0.109	0.167
	Thyroid	0.013	-0.137	0.081	-0.005	0.032	0.687	-0.004	0.042	0.597	-0.006	-0.012	0.881
	# Comorbidities	0.122	-0.357	0.000	0.003	-0.097	0.221	0.011	0.133	0.092	0.041	-0.217	0.006

V.II. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Meningioma Variables

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-BR			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Meningioma Variables	Years since Surgery	-0.006	0.027	0.731	-0.006	0.014	0.857	-0.005	0.033	0.677	-0.003	-0.053	0.501
	Simpsons Grade	-0.006	-0.004	0.957	-0.001	0.071	0.372	0.001	0.088	0.271	0.005	-0.104	0.190
	Recurrence	0.043	-0.221	0.005	0.008	-0.117	0.138	0.036	-0.205	0.009	0.055	0.247	0.001
	Radiotherapy	0.023	-0.171	0.030	-0.004	-0.051	0.516	0.011	-0.132	0.096	0.007	0.114	0.147
	Visual	-0.006	-0.021	0.794	0.008	-0.117	0.138	0.000	-0.079	0.319	-0.006	0.015	0.847
	Cognitive/Emotional	0.029	-0.186	0.018	0.013	-0.138	0.079	0.017	-0.152	0.054	0.019	0.158	0.044
	Headache	-0.002	-0.067	0.394	0.009	-0.122	0.123	0.011	-0.130	0.100	0.023	0.169	0.031
	Motor Sensory	0.040	-0.216	0.006	-0.003	-0.058	0.463	0.038	-0.209	0.008	0.015	0.145	0.065
	Infection	0.015	-0.145	0.066	-0.003	-0.057	0.468	0.011	-0.129	0.102	0.011	0.129	0.101
	Cranial Nerve	0.013	-0.140	0.076	0.051	-0.238	0.002	0.032	-0.196	0.013	0.036	0.204	0.009
	CSF	-0.002	-0.068	0.392	0.003	-0.097	0.217	0.009	-0.124	0.118	0.015	0.145	0.065
	Dizzy/Balance/Coordination	0.012	-0.133	0.092	-0.004	-0.043	0.589	0.004	-0.100	0.206	0.008	0.119	0.130
	Cosmetic	0.003	-0.094	0.233	-0.002	-0.068	0.391	-0.005	-0.040	0.615	-0.005	-0.037	0.639
	Neuroendocrine	0.005	-0.105	0.182	0.016	-0.150	0.057	0.004	-0.099	0.211	0.003	0.095	0.227
	Resus	0.013	-0.139	0.077	0.033	-0.196	0.012	0.046	-0.228	0.004	0.008	0.118	0.136
	Scar Pain	-0.006	0.016	0.838	-0.006	0.013	0.870	-0.003	0.060	0.450	-0.006	0.003	0.973
	PE	-0.002	-0.063	0.427	-0.003	0.061	0.443	-0.006	-0.002	0.977	0.002	-0.089	0.259
	Haemorrhage	0.006	-0.112	0.155	-0.006	-0.022	0.784	0.000	-0.081	0.308	0.014	0.140	0.075
	Tinnitus	-0.006	-0.013	0.866	-0.003	0.061	0.443	0.001	-0.085	0.282	0.022	0.167	0.033
	# Complications	0.114	-0.345	0.000	0.094	-0.316	0.000	0.153	-0.398	0.000	0.119	0.353	0.000
	Convexity	-0.006	-0.002	0.978	-0.003	0.061	0.440	-0.003	0.057	0.473	-0.006	-0.027	0.735
	Ventricular	-0.003	-0.056	0.481	0.006	-0.111	0.160	-0.001	-0.075	0.346	0.004	0.100	0.206
	Parasagital/Parafalcine	-0.004	0.051	0.518	0.000	0.078	0.325	-0.002	0.068	0.395	0.007	-0.117	0.139
	SkullBase	-0.006	-0.019	0.813	-0.006	-0.014	0.860	-0.005	-0.037	0.646	-0.006	0.008	0.921
	Skullbase postfossa	0.001	-0.086	0.277	0.007	-0.114	0.149	0.000	-0.082	0.304	0.008	0.119	0.130
	skullbase total	-0.003	-0.056	0.480	-0.002	-0.064	0.419	-0.002	-0.068	0.391	-0.003	0.061	0.444
	Sphenoid Wing	-0.006	0.022	0.784	-0.006	-0.017	0.834	-0.006	-0.015	0.852	-0.005	0.035	0.657
	Tentorial	-0.006	-0.009	0.910	-0.001	-0.075	0.341	-0.003	-0.057	0.474	-0.002	0.065	0.408
	Frontal Lobe	0.001	-0.084	0.288	-0.006	0.023	0.770	0.000	-0.078	0.324	-0.003	-0.054	0.497
	Occipital Lobe	-0.005	0.036	0.654	0.012	0.134	0.088	0.008	0.119	0.134	0.000	-0.080	0.311
	Parietal Lobe	0.008	0.121	0.126	-0.003	0.055	0.485	0.022	0.169	0.032	0.016	-0.149	0.058
	Temporal Lobe	-0.004	0.044	0.578	-0.006	-0.022	0.779	-0.004	-0.044	0.583	-0.006	0.018	0.823
	Lobe Unknown	0.002	-0.088	0.265	0.008	-0.118	0.134	0.005	-0.104	0.189	0.024	0.174	0.027

Significant Results are Highlighted.

V.III. Simple Linear Regression: Meningioma without Epilepsy and Meningioma with Epilepsy - Epilepsy Variables

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-BR			AEP		
		Adjusted R Squared (R2)	**Beta (β)**	**Significance (p)**	**Adjusted R Squared (R2)**	**Beta (β)**	**Significance (p)**	**Adjusted R Squared (R2)**	**Beta (β)**	**Significance (p)**	**Adjusted R Squared (R2)**	**Beta (β)**	**Significance (p)**
Epilepsy Variables	Ep with Meng OR Meng	-0.001	0.073	0.353	0.001	0.084	0.286	0.038	0.210	0.007	0.012	-0.134	0.090
	Years since Seizure	0.029	-0.216	0.104	0.002	-0.141	0.291	0.008	-0.159	0.233	-0.013	0.068	0.611
	Years on AED	0.024	-0.206	0.135	0.004	-0.150	0.278	0.012	-0.175	0.204	-0.011	0.091	0.513
	Current Carbamazepine	-0.002	-0.065	0.408	0.008	-0.118	0.136	0.009	-0.125	0.114	-0.005	0.039	0.618
	Current Gabapentin	-0.005	0.036	0.648	0.003	0.095	0.229	-0.003	0.061	0.445	0.007	-0.116	0.141
	Current Lamotrigine	-0.004	0.051	0.521	-0.004	-0.048	0.544	0.003	-0.094	0.235	0.011	0.132	0.093
	Current Levetiracetam	-0.006	-0.023	0.768	0.013	-0.138	0.081	0.016	-0.149	0.060	0.053	0.242	0.002
	Current Oxcarbazepine	0.010	-0.126	0.109	0.017	-0.152	0.053	0.014	-0.142	0.073	-0.001	0.073	0.357
	Current Phenytoin	-0.005	0.033	0.678	0.016	-0.147	0.061	0.036	-0.206	0.009	0.019	0.157	0.046
	Current Sodium Valproate	0.000	0.081	0.307	-0.004	0.050	0.528	-0.003	-0.060	0.448	-0.006	0.024	0.765
	Current Clobazam	-0.006	0.008	0.921	0.011	-0.132	0.095	0.013	-0.137	0.082	0.027	0.181	0.021
	First Carbamazepine	-0.005	-0.037	0.637	-0.002	-0.064	0.421	0.007	-0.117	0.139	-0.003	0.057	0.470
	First Gabapentin	-0.005	0.036	0.648	0.003	0.095	0.229	-0.003	0.061	0.445	0.007	-0.116	0.141
	First Lamotrigine	0.000	0.079	0.315	-0.001	0.074	0.351	0.002	0.091	0.251	0.007	-0.116	0.140
	First Levetiracetam	-0.006	0.002	0.982	-0.006	0.001	0.995	-0.005	0.035	0.660	-0.003	0.061	0.442
	First Oxcarbazepine	-0.006	0.008	0.921	-0.003	0.054	0.497	-0.006	0.002	0.980	-0.006	-0.002	0.985
	First Phenytoin	-0.003	-0.053	0.504	0.002	-0.090	0.252	0.020	-0.160	0.042	0.012	0.133	0.091
	First Sodium Valproate	-0.006	0.002	0.984	-0.006	-0.013	0.872	-0.002	-0.067	0.402	-0.005	-0.030	0.702
	First No Drug	-0.005	0.033	0.675	-0.002	0.068	0.389	0.023	0.170	0.031	0.004	-0.101	0.200
	# AED	-0.006	0.025	0.753	0.022	-0.168	0.032	0.069	-0.274	0.000	0.053	0.242	0.002
	Current AED Use	-0.006	0.002	0.980	0.021	-0.164	0.037	0.066	-0.268	0.001	0.039	0.211	0.007
	First Generation	-0.005	0.031	0.692	0.014	-0.141	0.074	0.054	-0.246	0.002	0.022	0.167	0.034
	Second/Third Generation	-0.006	-0.004	0.965	0.007	-0.115	0.145	0.016	-0.150	0.058	0.029	0.186	0.018
	Seizure 0	0.001	0.085	0.282	0.001	0.088	0.267	0.060	0.257	0.001	0.093	-0.313	0.000
	Seizure 1	-0.006	-0.014	0.860	0.004	0.101	0.202	-0.005	-0.040	0.614	0.010	0.127	0.107
	Seizure 2-3	0.005	-0.105	0.182	0.008	-0.120	0.128	0.051	-0.239	0.002	0.046	0.229	0.003
	Seizure 10+	-0.006	0.008	0.921	0.011	-0.132	0.095	0.013	-0.137	0.082	0.027	0.181	0.021
	1-3 Seizures	0.003	-0.095	0.230	-0.005	-0.040	0.614	0.042	-0.219	0.005	0.063	0.262	0.001
	4+ Seizures	-0.006	0.008	0.921	0.011	-0.132	0.095	0.013	-0.137	0.082	0.027	0.181	0.021
	Focal	-0.002	-0.065	0.410	-0.001	-0.072	0.365	-0.003	-0.058	0.461	0.004	0.099	0.209
	Dyscognitive	-0.006	-0.027	0.734	-0.006	-0.023	0.770	-0.006	-0.006	0.942	-0.006	-0.027	0.734
	Bilateral	-0.005	0.041	0.607	-0.006	0.006	0.939	0.002	-0.089	0.262	-0.003	0.058	0.461

Significant Results are Highlighted

V.IV. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma - Demographic and Comorbidity Variables

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-G			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Demographics	Age	0.041	-0.222	0.017	0.023	0.176	0.059	-0.007	0.043	0.645	-0.004	-0.063	0.493
	Female	-0.005	-0.059	0.530	-0.008	-0.024	0.802	-0.008	-0.023	0.800	-0.006	0.046	0.617
	Employed Full Time	0.134	0.376	0.000	0.011	0.140	0.136	0.066	0.271	0.003	0.071	-0.282	0.002
	Employed Part Time	0.016	0.157	0.094	-0.008	0.035	0.709	0.002	0.100	0.279	-0.008	-0.021	0.824
	Employed	0.182	0.434	0.000	0.013	0.148	0.115	0.085	0.305	0.000	0.063	-0.266	0.003
	Unemployed and looking	-0.008	0.035	0.707	-0.001	-0.089	0.344	-0.005	-0.058	0.533	-0.007	0.036	0.697
	Unemployed not looking	-0.004	0.068	0.470	0.001	0.101	0.282	0.001	0.098	0.287	0.004	-0.112	0.223
	Unemployed due Disability	0.168	-0.419	0.000	0.146	-0.392	0.000	0.214	-0.470	0.000	0.160	0.408	0.000
	Unemployed	0.137	-0.381	0.000	0.134	-0.376	0.000	0.209	-0.465	0.000	0.135	0.378	0.000
	Caring for Family	0.024	-0.180	0.054	0.021	-0.173	0.064	-0.006	-0.046	0.618	0.004	0.111	0.231
	Retired	-0.002	-0.081	0.390	0.041	0.221	0.017	0.004	0.110	0.235	0.004	-0.111	0.228
	Student	0.009	0.131	0.162	0.018	-0.164	0.080	0.009	-0.133	0.148	-0.008	-0.028	0.763
	Blank	-0.009	0.014	0.879	0.010	0.137	0.144	-0.005	0.057	0.535	-0.005	0.059	0.526
Comorbidities	Arthritis	0.058	-0.258	0.005	-0.007	0.044	0.640	0.002	-0.101	0.276	0.010	0.134	0.145
	Asthma	-0.003	0.074	0.432	-0.009	0.000	0.997	-0.008	0.027	0.772	-0.002	0.081	0.383
	Cardio (electric)	0.010	-0.138	0.142	-0.007	0.037	0.692	-0.006	0.050	0.587	-0.008	0.027	0.773
	Depression	0.020	-0.168	0.072	0.038	-0.215	0.021	0.015	-0.153	0.096	0.021	0.171	0.063
	Diabetes M	0.036	-0.211	0.023	0.005	-0.119	0.205	0.020	-0.168	0.067	0.027	0.189	0.040
	Hypertension	0.026	-0.187	0.046	-0.008	-0.021	0.820	0.000	-0.094	0.309	-0.001	0.089	0.338
	IHD	0.006	-0.123	0.189	-0.003	-0.075	0.426	0.009	-0.133	0.151	0.010	0.135	0.144
	Migraine	-0.007	0.038	0.688	-0.009	0.010	0.919	-0.006	-0.046	0.622	0.000	0.094	0.309
	Neoplasm	0.034	-0.205	0.028	0.033	-0.204	0.029	0.015	-0.153	0.096	0.014	0.149	0.105
	Neuropathy	0.039	-0.217	0.020	-0.009	-0.016	0.861	-0.004	-0.069	0.454	-0.006	0.053	0.566
	Stroke	-0.006	-0.049	0.601	0.019	-0.165	0.078	0.019	-0.165	0.073	-0.008	0.029	0.751
	Thyroid	-0.005	-0.065	0.492	0.000	0.091	0.332	0.003	0.106	0.252	-0.008	-0.014	0.884
	# Comorbidities	0.186	-0.440	0.000	0.011	-0.140	0.135	0.048	-0.237	0.009	0.070	0.279	0.002

Significant Results Are Highlighted

V.V. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Meningioma Variables

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-G			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Meningioma	Years since Surgery	0.012	-0.175	0.200	-0.006	-0.114	0.409	-0.010	-0.092	0.506	-0.011	-0.087	0.529
	Simpsons Grade	-0.014	-0.073	0.601	-0.011	0.090	0.520	-0.008	0.103	0.457	-0.012	-0.082	0.556
	Recurrence	0.062	-0.265	0.004	0.003	-0.109	0.246	0.026	-0.185	0.044	0.057	0.254	0.005
	Radiotherapy	0.013	-0.146	0.120	-0.009	0.016	0.868	0.001	-0.095	0.305	0.013	0.146	0.113
	Visual	-0.004	0.069	0.461	-0.006	0.057	0.544	-0.007	0.039	0.675	0.020	-0.168	0.068
	Cognitive/Emotional	-0.009	-0.010	0.917	-0.007	0.037	0.692	-0.006	0.051	0.580	-0.009	0.002	0.980
	Headache	-0.002	0.081	0.391	-0.009	-0.018	0.848	-0.008	-0.026	0.779	-0.007	0.037	0.689
	Motor Sensory	0.032	-0.201	0.031	-0.001	0.086	0.361	-0.003	-0.072	0.435	-0.006	0.054	0.562
	Infection	-0.001	-0.090	0.338	-0.009	0.012	0.897	0.004	-0.113	0.221	0.005	0.116	0.210
	Cranial Nerve	0.023	-0.177	0.059	0.019	-0.165	0.078	0.028	-0.191	0.037	0.032	0.199	0.030
	CSF	-0.007	-0.048	0.610	-0.001	0.086	0.363	-0.007	-0.033	0.718	-0.005	0.062	0.504
	Dizzy/Balance/Coordination	-0.007	-0.046	0.624	-0.006	0.056	0.555	-0.006	0.055	0.553	-0.006	0.051	0.582
	Cosmetic	-0.002	0.085	0.367	-0.009	-0.013	0.891	-0.007	-0.045	0.628	0.007	-0.123	0.183
	Resus	0.013	-0.147	0.118	0.024	-0.180	0.054	0.035	-0.209	0.023	0.001	0.099	0.286
	PE	-0.005	-0.062	0.507	0.000	0.094	0.320	-0.007	0.045	0.628	0.006	-0.120	0.194
	Tinnitus	-0.009	-0.005	0.954	0.000	0.094	0.320	-0.008	-0.013	0.890	0.018	0.162	0.078
	# Complications	0.008	-0.128	0.174	-0.005	0.058	0.539	0.004	-0.110	0.233	-0.004	0.066	0.474
	Convexity	-0.008	-0.032	0.735	0.021	0.173	0.064	-0.006	0.050	0.593	-0.002	-0.078	0.399
	Parasagittal/Parafalcine	-0.007	-0.041	0.663	-0.002	0.082	0.384	-0.005	0.058	0.529	-0.008	-0.032	0.731
	Skull base total	-0.008	0.028	0.767	-0.006	-0.050	0.596	-0.006	-0.046	0.622	-0.001	0.087	0.347
	Sphenoid Wing	-0.004	0.069	0.461	-0.008	0.025	0.794	-0.007	0.040	0.667	-0.006	-0.047	0.615
	Frontal Lobe	0.005	-0.117	0.214	-0.005	0.060	0.527	-0.007	-0.034	0.717	-0.006	0.054	0.558
	Occipital Lobe	0.002	0.102	0.276	-0.003	0.074	0.435	0.005	0.116	0.211	-0.001	-0.086	0.353
	Parietal Lobe	0.005	0.118	0.207	0.017	0.160	0.088	0.004	0.114	0.219	0.054	-0.249	0.006
	Temporal Lobe	-0.009	0.010	0.913	-0.006	-0.055	0.563	-0.004	-0.069	0.453	-0.008	0.026	0.780
	Lobe Unknown	-0.009	-0.003	0.972	-0.005	0.058	0.535	-0.007	0.042	0.649	-0.009	0.001	0.991

Significant Result Are Highlighted

V.VI. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Epilepsy Variables 1 of 2

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-G			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Epilepsy	Ep with Meng OR Meng	-0.009	-0.007	0.940	0.019	-0.165	0.078	-0.003	-0.071	0.441	-0.005	0.056	0.549
	Years since Seizure	0.004	-0.115	0.223	-0.009	-0.008	0.936	-0.008	-0.021	0.823	-0.009	0.002	0.982
	Years on AED	-0.003	-0.081	0.405	-0.002	0.086	0.374	-0.008	0.030	0.756	-0.008	-0.030	0.755
	Remitted Epilepsy	0.008	-0.128	0.173	-0.007	-0.047	0.616	-0.007	0.041	0.658	-0.008	-0.028	0.766
	Stroke	0.014	-0.150	0.111	0.019	-0.165	0.078	0.015	-0.154	0.094	-0.005	0.057	0.539
	MTLS	0.000	0.092	0.326	-0.007	-0.043	0.646	-0.007	0.040	0.667	-0.002	0.078	0.402
	Hippocampal Sclerosis	0.006	-0.119	0.203	0.002	-0.104	0.268	0.019	-0.166	0.070	0.023	0.177	0.054
	AVM	-0.007	-0.038	0.687	0.004	-0.112	0.234	-0.008	-0.030	0.749	0.001	0.095	0.302
	Cavernoma	-0.007	0.044	0.644	0.007	-0.127	0.176	0.013	-0.146	0.112	0.001	0.095	0.302
	Epidermoid Tumour	-0.008	0.019	0.840	0.027	-0.188	0.044	0.000	-0.090	0.331	-0.005	0.058	0.529
	Acoustic Neuroma	0.010	-0.136	0.148	-0.004	0.071	0.452	-0.004	0.069	0.453	-0.004	0.066	0.477
	Encephalitis	0.000	-0.095	0.312	0.016	-0.157	0.093	0.006	-0.118	0.201	0.002	0.103	0.265
	Not Stated	-0.007	-0.037	0.698	-0.006	0.057	0.543	-0.007	-0.036	0.695	-0.006	-0.054	0.558
	# AED	-0.008	-0.025	0.792	0.094	-0.320	0.000	0.101	-0.330	0.000	0.114	0.349	0.000
	Current AED Use	-0.001	0.091	0.334	0.082	-0.300	0.001	0.078	-0.293	0.001	0.042	0.225	0.014
	Current Carbamazepine	0.002	0.101	0.281	0.082	-0.045	0.633	-0.004	0.070	0.447	-0.005	-0.061	0.511
	Current Gabapentin	0.002	-0.104	0.267	0.003	0.110	0.240	-0.005	-0.062	0.501	-0.009	-0.006	0.947
	Current Lamotrigine	0.000	0.092	0.328	0.000	-0.093	0.323	-0.008	-0.009	0.924	0.010	0.134	0.146
	Current Levetiracetam	0.020	-0.169	0.071	0.079	-0.295	0.001	0.090	-0.313	0.001	0.094	0.319	0.000
	Current Oxcarbazepine	0.010	-0.136	0.148	0.012	-0.142	0.130	0.012	-0.142	0.123	-0.005	0.058	0.529
	Current Phenytoin	-0.005	0.061	0.519	-0.009	0.004	0.963	-0.001	-0.088	0.340	-0.007	0.040	0.666
	Current Sodium Valproate	-0.006	0.050	0.594	-0.008	0.026	0.781	-0.003	-0.072	0.435	-0.007	-0.040	0.664
	Current Phenobrbitone	-0.007	0.044	0.644	0.005	0.116	0.215	-0.002	0.079	0.393	-0.007	-0.038	0.680
	Current Lacosamide	0.006	-0.119	0.203	0.002	-0.104	0.268	0.019	-0.166	0.070	0.023	0.177	0.054
	Current Zonisamide	-0.007	-0.048	0.609	0.020	-0.170	0.070	-0.003	-0.073	0.427	0.015	0.151	0.100
	Current Pregablin	0.020	-0.168	0.072	0.030	-0.195	0.036	0.028	-0.191	0.038	0.013	0.147	0.110
	Current Clobazam	-0.008	0.019	0.840	0.006	-0.119	0.204	-0.002	-0.083	0.372	0.023	0.177	0.054
	First Generation	0.010	0.138	0.140	-0.009	-0.011	0.907	-0.005	-0.057	0.538	-0.007	-0.040	0.667
	Second/Third Generation	-0.001	-0.091	0.334	0.089	-0.312	0.001	0.074	-0.287	0.002	0.088	0.309	0.001

Significant Results are Highlighted

V.VII. Simple Linear Regression: Meningioma with Epilepsy and Epilepsy without Meningioma – Epilepsy Variables 2 of 2

	Independent Variables	SF-36 PCS			SF-36 MCS			FACT-G			AEP		
		Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)	Adjusted R Squared (R2)	Beta (β)	Significance (p)
Epilepsy	Cryptogenic	0.014	0.149	0.111	-0.006	0.050	0.593	0.005	0.118	0.202	0.001	0.100	0.281
	Seizure 1	0.003	-0.106	0.258	-0.008	-0.020	0.830	0.018	-0.162	0.079	0.015	0.151	0.101
	Seizure 2-3	-0.004	-0.066	0.483	-0.007	-0.037	0.691	0.013	-0.147	0.110	0.017	0.160	0.082
	Seizure 4-5	-0.009	-0.011	0.903	0.019	-0.165	0.078	0.008	-0.127	0.170	0.002	0.104	0.262
	Seizure 6-9	0.002	-0.106	0.259	0.015	-0.153	0.102	0.025	-0.182	0.048	0.023	0.178	0.053
	Seizure 10+	0.022	-0.176	0.061	0.002	-0.106	0.262	0.006	-0.118	0.200	0.016	0.156	0.089
	1-3 Seizures	0.007	-0.124	0.186	-0.007	-0.043	0.645	0.043	-0.227	0.013	0.045	0.230	0.012
	Seizure 0	0.039	0.217	0.020	0.039	0.217	0.020	0.120	0.357	0.000	0.124	-0.363	0.000
	4+ Seizures	0.017	-0.160	0.087	0.053	-0.248	0.008	0.049	-0.239	0.009	0.052	0.244	0.007
	Focal	-0.008	0.025	0.791	-0.006	0.054	0.569	0.001	0.098	0.289	-0.008	-0.026	0.781
	Dyscognitive	-0.009	0.012	0.903	0.005	-0.117	0.212	-0.008	-0.019	0.841	-0.004	0.066	0.477
	Bilateral	-0.003	0.079	0.400	-0.006	0.055	0.557	-0.008	0.021	0.825	-0.007	-0.043	0.644
	First Carbamazepine	-0.007	-0.038	0.690	-0.003	-0.078	0.409	-0.005	-0.058	0.533	-0.008	0.010	0.918
	First Gabapentin	-0.006	0.052	0.583	0.009	0.132	0.161	-0.006	0.055	0.553	0.014	-0.150	0.104
	First Lamotrigine	0.030	0.195	0.037	-0.009	-0.009	0.927	0.010	0.135	0.144	-0.009	-0.006	0.948
	First Levetiracetam	-0.007	-0.042	0.656	0.002	-0.103	0.275	-0.005	-0.059	0.525	-0.004	0.067	0.467
	First Oxcarbazepine	-0.008	0.019	0.840	-0.001	0.086	0.361	-0.005	0.055	0.552	-0.008	-0.012	0.896
	First Phenytoin	-0.009	-0.009	0.923	0.001	0.101	0.282	-0.009	0.006	0.946	-0.007	-0.036	0.699
	First Sodium Valproate	0.004	-0.114	0.226	0.000	-0.096	0.308	-0.007	-0.042	0.646	-0.004	0.067	0.467
	First No Drug	-0.008	0.022	0.814	-0.007	0.039	0.676	-0.006	-0.050	0.586	-0.003	-0.077	0.403
	First Phenobarbitone	-0.007	0.044	0.644	0.005	0.116	0.215	-0.002	0.079	0.393	-0.007	-0.038	0.680

Significant Results are Highlighted