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Depression in glioma

Alasdair G. Rooney

M.D.
The University of Edinburgh
2011
Declaration

This thesis is my own work, which I have composed, under the academic supervision of Dr. Robin Grant and Dr. Alan Carson.

It has not been submitted for any other degree or professional qualification.

Signed…………………………………………………………………

Dr. Alasdair Rooney

Date…………………………………………………………………….
Abstract

BACKGROUND

Few high-quality observational studies have been conducted to examine clinically relevant features of emotional distress and Major Depressive Disorder (MDD) in adults with primary cerebral glioma. Our knowledge of these important complications of glioma is currently poor.

AIMS

This thesis aims to answer a series of relevant clinical questions. I have studied: [1] the frequency, independent clinical associations and course of general emotional distress measured using the NCCN Distress Thermometer (DT); [2] the utility of three depression screening tools for identifying MDD; [3] the frequency, independent clinical associations and course of MDD in glioma; [4] current patterns of practice, and the apparent tolerability of antidepressant treatment of depression in glioma; and [5] barriers to the effective management of MDD in glioma.

METHODS

I conducted a prospective, twin-centre, observational cohort study. Adults with a new histological diagnosis of primary supratentorial glioma were enrolled and interviewed three times: shortly after starting radiotherapy (T1), three months later (T2) and six months later (T3). At each time point participants completed the DT, the Hospital Anxiety and Depression Scale (Depression subscale, HAD-D), the Patient Health Questionnaire-9 (PHQ-9) and the Structured Clinical Interview for DSM-IV MDD (SCID). Barriers to depression management were studied using questionnaires completed by the patient and their named GP.

RESULTS

During a two-year recruitment period, 223 patients were eligible and 155 provided useable data (57.4% male, mean age = 54.2 years, 85.8% high-grade glioma, 78.1% radical radiotherapy, 55.5% chemotherapy). [1] High distress (DT score ≥ 4/10) was consistently a frequent complication, occurring in between 36.4% ± 7.6% of patients at T1 to 33.7% ± 10.2% at T3. In a logistic regression analysis, high distress at T1 was independently associated with MDD, functional impairment and younger age (χ² for model = 39.882, p < 0.001, R Square = 0.312). Patients who reported high distress at T1 (median DT score = 8; IQR 7 - 9) remained highly distressed on follow-up (T2 median score = 8, IQR 6 - 8; T3 median score = 7, IQR 5 - 8). [2] As screening tools, the HAD-D and PHQ-9 showed good internal consistency (α = 0.769 - 0.862 at any time point). The HAD-D displayed the best
operating characteristics on ROC curve analysis. At a threshold of 7+, sensitivity = 0.933, specificity = 0.907 and Positive Predictive Value (PPV) = 0.56. A threshold of 8+ displayed similar PPV, however. [3] The cross-sectional prevalence of MDD was 13.5% ± 5.4% at T1, 14.8% ± 6.7% at T2 and 6.8% ± 5.8% at T3. Inter-rater diagnostic agreement was good (κ = 0.81, 95% CI 0.60 – 1.00). MDD was independently associated with a past history of depression (OR = 3.8, 95%CI 1.5 - 9.8), and with current functional impairment (OR = 3.6, 95%CI 1.4 - 9.4). MDD persisted for at least three months in 9/17 patients who could be followed up. [4] The frequency of antidepressant prescription was 8.4% ± 4.4% at T1, 7.4% ± 4.9% at T2 and 12.6% ± 6.9% at T3. Citalopram was the most frequent antidepressant choice. Antidepressant tolerability appeared to be good among patients who could be followed up. [5] Barriers to the management of depression included 78.4% of GPs regarding major depression as a normal reaction to having glioma, and 39.2% expressing a belief that major depression did not always require treatment. In addition, most patients expressed a degree of resistance to any kind of future depression treatment.

DISCUSSION

This is the largest cohort study of depression in consecutively presenting adults with glioma, and the first to utilise criterion standard structured interview diagnoses in a longitudinal design. There is a degree of theoretical uncertainty about the nosological validity of MDD in glioma, although the clinical relevance of this uncertainty can be debated. Methodological limitations to the presented study include an absence of alternative potential psychiatric diagnoses to MDD, the likelihood of selection bias in recruitment, and considerable attrition. Due to these and other limitations, findings from this study are tentative and should ideally be replicated. Clinicians should have a high index of suspicion for identifying low mood in glioma patients, particularly those with functional impairment or previous depressive episodes. The HAD-D (suggested threshold 8+) can reasonably be used to screen for depression, if desired. Caution is required when prescribing antidepressants. Clinicians should be educated about the frequency and consequences of MDD in glioma. Researchers interested in psychological neuro-oncology could convene a meeting to guide future projects, particularly since multi-centre studies may be necessary to recruit sufficient sample sizes in future.
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Dedication

To mum and dad.
1 An Introduction to Glioma

This chapter is a short introduction aimed at readers unfamiliar with glioma. It focuses on topics relevant to the rest of the thesis. My study was, fundamentally, about people who had recently been given a diagnosis of brain cancer. It is therefore useful to understand the context in which they were recruited and followed up. To make this process easier for the reader, I structured the following background narrative around ‘milestones of discovery’ in the average patient’s clinical journey. These reflect our local practice. Basic medical knowledge is assumed.

1.1 Presentation and diagnosis

Within weeks, an adult can pass from living a full and healthy life to being disabled and facing a terminal illness. The very first symptom of glioma can be an epileptic seizure, striking without warning. The onset is usually sub-acute, however. By the time of presentation to hospital, patients often relate a short history of symptoms including: focal neurological deficit (e.g. unilateral weakness or sensory loss, dysphasia or hemianopia); raised intracranial pressure (e.g., headache, vomiting, blurred vision or cognitive dysfunction) or personality changes. (Snyder et al. 1993; Yuile et al. 2006) Glioma often strikes adults who were previously healthy. Many other cancers present with insidious, suspicious symptoms that patients may privately have acknowledged as potentially serious. Such symptoms could include unexplained weight loss, a persistent cough or hoarseness, or an obvious lump. With glioma, by contrast, symptoms often first appear only a few weeks before the diagnosis is made.

After clinical presentation, however occurring, the critical investigation is a contrast-enhanced CT (or MRI) scan of the head (Figure 1). (DeAngelis 2001) The patient will be told that the scan shows an abnormality but may not yet specifically be aware of the possibility of cancer. Anecdotal evidence suggests that some patients are informed in vague terms, of the presence of ‘a shadow’ or ‘a lesion’. Doctors often cannot truthfully be more precise. The differential diagnosis at this point may include stroke, multiple sclerosis, cerebral abscess, toxoplasmosis and tuberculosis. (Omuro et al. 2006)

In the UK, all patients newly presenting with radiologically suspected glioma should be discussed pre-operatively, at a neuro-oncology multidisciplinary team (MDT) meeting. Representatives should attend the MDT from neurosurgery, oncology, neuroradiology, neurology, neuropathology, neuropsychology and palliative care. The MDT process aims to ensure that diagnostic and management decisions are taken by specialists with access to the most complete information available. (NICE 2006) The MDT decides the most appropriate next step in patient management. For patients
with radiological suggestion of glioma, this includes deciding whether neurosurgical intervention is suitable.

Patients with a very poor prognosis may be deemed unsuitable for surgery and referred to palliative care at this stage. Other patients with slowly growing tumours may be treated under a ‘watch and wait’ protocol with surgery deferred until some point in the future. The decision on whether to operate is made primarily on the balance of benefit and risk. The benefits of surgery can include: obtaining a histopathological diagnosis; a variable degree of symptom relief; and cytoreduction (removal of tumour with the aim of prolonging life). (Rampling et al. 2004) The risks include intracranial haemorrhage, neurological deficit, intracranial infection and death. (Vives and Piepmeier 1999) Risk must be weighed especially carefully when the tumour is in an anatomically sensitive area (e.g., directly adjacent to the primary motor cortex), or when radiology suggests a diagnosis with a prognosis of many years even without surgery. (Whittle 2004)

![Figure 1. Coronal view, contrast-enhanced MRI scan of a probable glioma.](image)

Most patients with radiologically-suspected glioma do receive an operation. There is a broad choice of two kinds of neurosurgical procedure. The glioma can be biopsied, with only a small amount of tumour removed. The main aim of biopsy is usually to achieve a histopathological diagnosis by which to guide further management. Or, the tumour can be resected, with the surgeon removing as much tumour as they safely can. Evidence is accumulating that greater extent of glioma resection is independently associated with longer survival. (McGirt et al. 2009;Pichlmeier et al. 2008;Smith et al.
Biopsy tends to be reserved for patients with tumours in anatomically critical areas, or for those with radiologically diffuse tumours which would be impossible to fully resect.

Following the operation, it can take up to 14 days to reach a definitive histopathological diagnosis, discuss the patient again at the MDT meeting and decide on further management. At this point an oncologist will meet the patient to confirm their diagnosis for the first time, and explain its features.

1.2 Glioma classification and grading of malignancy

Gliomas are tumours of glial cells. Examples of glial cells include astrocytes and oligodendrocytes. The World Health Organisation (WHO) classifies gliomas according to their histological cell of origin. Thus an astrocytoma arises from astrocytes and an oligodendroglioma from oligodendrocytes. An oligoastrocytoma contains a significant amount of both cell lines. (Louis et al. 2007b)

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</tr>
<tr>
<td>Oligodendroglioma</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
</tr>
<tr>
<td>Glioblastoma (including gliosarcoma variant)</td>
</tr>
</tbody>
</table>

**Box 1. Examples of commonly diagnosed types of glioma.**

The WHO classification provides a useful framework for grading gliomas according to their relative level of malignancy. (Louis et al. 2007a) WHO grades 1 and 2 are less malignant, more slowly growing, ‘low-grade’ gliomas (LGG). Grades 3 and 4 are more malignant, quicker growing, ‘high-grade’ gliomas (HGG). By convention, a WHO grade 3 glioma may also be called ‘anaplastic’ whereas a WHO grade 4 tumour is also known as a ‘glioblastoma multiforme’ (GBM). Frequently diagnosed glioma types are listed in Box 1.

1.3 Glioma incidence and aetiology

Gliomas account for approximately one-third of all primary brain and CNS tumours (CBTRUS 2010) and represent fewer than 2% of all cancers. (NICE 2006) In Scotland, the crude incidence of glioma is
8.7 per 100,000. (IARC 2007) These figures may somewhat underestimate the true incidence in the UK. (Ogunbso et al. 2002) Gliomas occur slightly more frequently in men. (CBTRUS 2010)

Around 85% of newly diagnosed gliomas are HGG, and the remainder are LGG. (Rees 2002) GBM is the most frequent single glioma type at presentation and accounts for 53.8% of new glioma diagnoses in the USA. (CBTRUS 2010) In adults, most LGG are WHO Grade 2. Grade 1 tumours are more commonly a disease of childhood, often with rarer histological profiles. Peak age of glioma incidence rises with the level of malignancy and ranges from the fourth decade for Grade 2 glioma to the seventh decade for GBM. (Polednak and Flannery 1995; Warnke 2010)

Currently, the only proven causes of glioma are ionising radiation and inherited cancer syndromes (e.g., neurofibromatosis types 1 and 2, Von-Hippel-Lindau syndrome and Li-Fraumeni syndrome). (Wen and Kesari 2008) Many other aetiological agents have been hypothesised (e.g., mobile phones, cured meats, occupational exposure and head trauma) but none proven. (Wrensch et al. 2002) Unlike most cancers, smoking is not a clear risk factor for glioma. (Mandelzweig et al. 2009)

### 1.4 Primary treatment

Apart from surgery the mainstay of treatment for glioma is cranial radiation therapy (radiotherapy). (Laperriere et al. 2002; Rampling et al. 2004; van den Bent et al. 2005) Radiotherapy dose is measured in Grays (Gy). The choice of treatment schedule depends partly on glioma grade, and partly on the functional and cognitive status of the patient. Considering probable treatment side effects, radiotherapy is planned either as a radical six-week course (50-60Gy in 30 daily ‘fractions’, or visits) or a palliative two-week course (30Gy in 6 fractions). An alternative palliative dose schedule of 45Gy in 20 fractions is occasionally given. (Bleehen et al. 1991) Radiotherapy begins about four to six weeks after primary surgery. This delay is necessary to allow time for recovery from surgery and for the detailed planning of the radiotherapy treatment.

In adults with HGG, radiotherapy shortly after initial diagnosis significantly prolongs overall survival. (Laperriere et al. 2002) In patients with LGG, early radiotherapy delays time to progression but at the possible cost of higher long-term cognitive side-effects. (van den Bent et al. 2005) Therefore, while some patients with LGG receive radiotherapy immediately, in others it is deferred until the tumour progresses. The decision in LGG is made on a case-by-case basis.

Whether chemotherapy is given depends on the histological diagnosis and the patient’s functional status. The standard chemotherapeutic treatment in well-functioning adults with GBM is concomitant and adjuvant Temozolomide. (National Institute for Clinical Excellence 2007; Stupp et al. 2005)
Temozolomide is usually given alongside radiotherapy for six weeks (the ‘concomitant’ phase), followed by six, separate, week-long pulses at monthly intervals (the ‘adjuvant’ phase). Treatment with Temozolomide does not appear to adversely affect quality of life in randomised controlled trial participants. (Taphoorn et al. 2005) Alternatively, patients with GBM and > 90% surgical resection of tumour may receive Gliadel. (NICE 2007) This is a biodegradable wafer impregnated with carmustine which is placed in the resection cavity at the time of surgery. A randomised, placebo-controlled trial demonstrated a clinically and statistically significant survival benefit of Gliadel. (Westphal et al. 2006) For patients with LGG, decisions on chemotherapy are again made on a case-by-case basis.

Therefore HGG patients considered suitable for primary treatment will be offered either (1) radical radiotherapy combined with chemotherapy, (2) radical or palliative radiotherapy alone, (3) rarely chemotherapy alone, or (4) palliative care and best symptom control. For those with LGG, the exact nature and timing of treatment is decided individually in each case. Regardless of tumour grade, treatment decisions are informed by several factors including the precise diagnosis and tumour location, the patient’s functional status and wishes for treatment, and local preferences (Figure 2).

1.5 Factors influencing quality of life

Several other treatments may be offered to improve symptoms and increase quality of life. These include corticosteroids and antiepileptic drugs. Corticosteroids, for example dexamethasone, are prescribed to patients with symptoms suggestive of raised intracranial pressure (e.g. headache, vomiting or worsening focal neurological deficit). Recognised side effects include depression, insomnia, increased appetite, weight gain and possibly an increased risk of stomach ulcer. (BNF 2008)

Epileptic seizures can arise from the irritative effects of the tumour upon the cerebral cortex, or from gliosis secondary to surgery. (Villeure and de Tribolet 1996) Up to 80% of patients with LGG present with epilepsy (Cavaliere et al. 2005), roughly twice as frequently as HGG. (Moots et al. 1995; van Breemen et al. 2007) Antiepileptic drugs (AEDs) are therefore very commonly prescribed to patients with glioma. There is no good evidence as to which AED is most effective in patients with glioma. (Hildebrand et al. 2005; van Breemen et al. 2009) Throughout glioma treatment, adjustments are made to steroid and AED doses as clinically indicated.

All patients undergoing craniotomy, and all those with epilepsy, are automatically banned from driving. (DVLA 2010) The loss of independence can be particularly distressing and is often compounded by physical functional impairments including hemiparesis, hemianopia and dysphasia. (Bell et al. 1998) Fatigue is very common and some degree of cognitive dysfunction almost universal. Anxiety may arise from changes to role within the family and society. (Rosenblum et al. 2009)
Figure 2. The MDT is the focus of the main decision points in the initial primary treatment of glioma.
1.6 Prognosis

Favourable prognostic clinical factors upon diagnosis of HGG are: younger age; better physical function; better cognitive function; greater tumour resection; and histological tumour grade. (Gorlia et al. 2008) Those recognised in LGG are: younger age; smaller tumour size; tumour confined to one hemisphere; presentation with isolated epileptic seizures; and oligodendroglial histology. (Pignatti et al. 2002)

However, glioma is ultimately fatal. With best treatment the median survival time from diagnosis of GBM, in patients with good functional status, is 14.6 months. (Stupp et al. 2005) About one quarter of patients with GBM is alive at two years after diagnosis, with about 10% alive at five years. (Stupp et al. 2009) The natural history of lower-grade tumours is to progress slowly, transforming after a period of years into HGG or GBM. (Behin et al. 2003) Differences in patient populations, diagnostic methods and reporting make defining a single median survival time difficult in LGG. The median survival time from diagnosis of anaplastic glioma has been reported as between 2 and 7 years. (van den Bent et al. 2009; Wick et al. 2009) Patients diagnosed with a grade 2 glioma often survive 6 - 10 years, and sometimes more. (Chang et al. 2009)

1.7 Chapter summary

Glioma, or brain cancer, presents rapidly and has a profound impact on the patient’s life. Although a relatively rare form of cancer, glioma frequently affects adults of working age with young families. Treatments are toxic and provide limited benefit. Despite variations in the tempo of the disease, nearly everyone who develops a glioma will die from it.
2 An Introduction to Major Depressive Disorder

This chapter briefly summarises my understanding of major depression. It begins with a historical overview. As well as being hopefully an interesting story, it is important context. Our current definitions of major depression have their roots in events two centuries old. The chapter then describes current clinical concepts and knowledge of the modern syndrome of major depression, for comparison with data presented later in the thesis.

In creating the historical narrative I drew particularly on five reference sources: Horwitz and Wakefield’s The Loss of Sadness (Horwitz and Wakefield 2007); Burton’s The Anatomy of Melancholy (Burton 1971); Callahan and Berrios’ Reinventing Depression (Callahan and Berrios 2005); Blazer’s The Age of Melancholy (Blazer 2005) and the relevant chapter in The Oxford Textbook of Psychiatry (2nd Edition). (Pichot 2009) They are not otherwise referenced, except in recognition of specific intellectual points.

2.1 From Hippocrates to the HADS

2.1.1 Ancient history

It is difficult to track the history of depression continuously into the distant past. Before approximately 1800, when what is now known as depression was called “melancholia”, only islands of thought survive from famous texts or quotations. However, some ancient historical aspects of depression/melancholia are important. One of the earliest known references is attributed to Hippocrates (c. 5BC):

“If fear or sadness last for a long time it is melancholia...[with] aversion to food, despondency, sleeplessness, irritability, restlessness.” (Horwitz and Wakefield 2007)

For thousands of years, the defining characteristic of disordered low mood was a sense that melancholic symptoms were disproportionate to the patient’s circumstance. Disproportion could manifest in two ways. Symptoms could either last for too long, or be too severe in the context of the patient’s antecedent life circumstances. Conversely, any symptom lasting only for a short while or of appropriate severity in the circumstances tended to be regarded as part of normal healthy life (Box 2).
Aristotle (c. 350BC): “…If black bile be cold beyond due measure, it produces groundless despondency…”
Celsus (AD30): “…Prolonged despondency…”
Soranus (c. AD100): “…Weeping without reason…”
Aretaeus (c. AD200): “…Dejected…without any manifest cause…”
Imran (c. AD900): “…Irrational, constant sadness…”
Du Laurens (c. 1580): “…Sadness, without any apparent occasion…”
Bright (1568): “…When any conceite troublest you that hath no sufficient ground of reason…that is right melancholick…”

Box 2. For thousands of years, melancholia was considered a disorder if the symptoms were disproportionate to life circumstances (adapted from Horwitz and Wakefield, 2007).

In 1621, in the classic text “The Anatomy of Melancholy”, Robert Burton noted:

“Melancholy…is either in Disposition, or in Habite. In disposition, is that transitory melancholy, which comes and goes upon every small occasion of sorrow…from these, no man living is free. But oftentimes these Dispositions become Habits…and that which one, by his singular moderation and well-composed carriage can happily overcome, a second is no whit able to sustaine, but upon every small occasion of grief yeeldes so farre to passion, that his complexion is altered, his digestion hindred, his sleepe gone, his spirits obscured and his heart heavy…and he himself overcome with melancholy.”

Burton therefore used the word “melancholy” to describe both the transient, normal human response to sorrow and a more profound, abnormal state of prolonged sadness. In more recent times, authors have noted the same tendency for the word “depression” to do “double duty”. (Horwitz and Wakefield 2007)

Again like contemporary authors, Burton glossed over how to differentiate clearly between his two concepts of melancholy (normal sorrow versus disordered melancholia). His syndrome of abnormal low mood included, however, observable changes in somatic functions like sleep and digestion, alongside subjective psychological symptoms of “obscured spirits” and a “heavy heart”. This continued the historical trend evident in the writings of Hippocrates, and anticipated the modern syndrome of Major Depressive Disorder. Somatic symptoms, therefore, have always been a central part of humanity’s concept of clinical depression.

Burton observed that some people were more emotionally vulnerable than others to the vicissitudes of life. His statement that one person, “by his singular moderation” may cope better than another faced with the same loss, impressively foretells more recent research suggesting that genetic factors can mediate an individual’s sensitivity to the adverse emotional effects of stressful life events. (Caspi et al. 2003; Kendler et al. 1995)
Aetiological theories of melancholy abounded in the 17\textsuperscript{th} century. Mostly, they led to a ‘final common pathway’ derived from the dominant paradigm of the time: the four humours. Melancholia was thought to be caused by an excess of black bile. The mechanisms leading to an excess of black bile were legion. They included, as specifically listed by Burton: being constipated; being old; being bald; studying too much; not having enough sex and many other likely causes of low mood besides!

2.1.2 The development of psychiatry

The story of how the modern concept of depression developed from this point is closely related to that of psychiatry’s development as an independent medical specialty. During the 19\textsuperscript{th} century, the model of the four humours was discredited. Medicine embraced the anatomoclinical tradition, which taught that separate illnesses had separate causes. In 1801, Philippe Pinel founded psychiatry as a medical discipline. He believed that insanity was an illness which could be treated. He regarded its study as ‘a science which consists of carefully observed facts’. His pupil, Esquirol, placed equal emphasis on careful observation and analysis of the patient’s mental symptoms and behaviour. Later psychiatric thinkers including Griesinger and Kraepelin were influenced heavily by the descriptive clinical approach of these pioneering psychiatrists. Their methods emphasised and asserted the medical, scientific nature of the new discipline. Psychiatry developed alongside anatomoclinical advances in somatic medicine. Mental illnesses were similarly hypothesised to have specific causes.

The precise nature of these causes was disputed. Some regarded mental illness as diseases of the physical brain, as direct extension to diseases of the physical body. These ‘somatists’ were aided and probably biased in their thinking by the new asylum system, which tended to capture the more severe types of mental illness. Another professional faction (influenced by art, religion, romanticism and dualism) insisted that the causes of insanity resided in the soul. Some such ‘mentalists’ believed that the cause of mental illness was sin, committed by the patient. The influence of the latter group waned as the 19\textsuperscript{th} century progressed, asylums filled and psychiatry identified ever more strongly with the medical model.

I think that the ideological conflict between somatism and mentalism was of more than historical interest. It asserted and perpetuated a division of biological and psychological models of mental illness, respectively. The somatist cause was buttressed by the eventual discovery of physical treatments for mental illness. Such treatments included penicillin (for General Paresis of the Insane, caused by syphilis), insulin coma (for schizophrenia) and electroconvulsive therapy (for severe depression). Towards the end of the 19\textsuperscript{th} century, however, the psychological model was re-asserted. Some psychiatrists, inspired by public lectures given by the French neurologist Charcot, began to
study hysteria (which had been recognised for centuries) and the neuroses (a new and heterogeneous group of illnesses, including hysteria, which exploded in popularity in the late 19th century).

### 2.1.3 The rise of psychoanalysis

By the start of the 20th century, psychiatric opinion-leaders considered that the causes of mental illnesses could be both biological and/or psychological in nature. This recognition, combined with public interest in the neuroses, fostered the emergence of psychotherapy as a treatment for mental illness. Rather than being limited to asylum-based care of patients with severe mental illnesses, psychologically-orientated psychiatrists began to treat outpatients suffering from relatively minor symptoms. To some degree this extension of professional expertise must have reflected a similar change in public attitudes towards the concept of mental disorder. Society came to accept that relatively mild distress, when characterised as psychological in origin, could (and should) be treated by psychiatrists, using psychological therapies.

Many different psychological treatments were devised. Psychoanalysis, invented by Sigmund Freud around the turn of the 20th century, enjoyed particular popularity in Germany. When Hitler denounced psychoanalysis as Jewish, many German psychoanalysts immigrated to the United States. There they taught the tradition to a new generation of American trainees. Psychoanalysis grew to become the dominant ideology in American psychiatry. After the war the USA was the most powerful country in the world, and English the international language of psychiatry. The psychoanalytic tradition became the dominant paradigm for psychiatry globally.

Rather than biological models of mental illness, psychoanalysis favoured explicitly psychological aetiological theories. In the 1950s and 1960s, in the thrall of psychoanalysis, psychiatrists attributed many of the symptoms of mental illnesses directly to intra-psychic conflict. The sources of conflict lay in the person’s past. They were best identified by the psychoanalyst’s individual interpretation of the patient’s symptoms, and best treated with long courses of psychotherapy. Psychoanalysis was by nature subjective. It was a guiding principle of the psychoanalytic school that each new patient required a new, individually tailored approach to understanding their symptoms. The objective, descriptive clinical approach to psychiatric illness in populations of patients, championed by the likes of Pinel and Kraepelin, was derided as superficial.

Patients with severe depressive symptoms could still be diagnosed with “a primary [presumed biological] mood disorder…characterized by severely depressed mood, and mental and motor retardation.” However, most depression was explicitly classified as a reaction to stress. The symptoms of such “depressive neurosis” were officially regarded as “an excessive reaction of depression due to
an internal conflict or to an identifiable event such as the loss of a love object or cherished possession”. (APA 1968)

2.1.4 The return to descriptive psychiatry

The psychoanalytic tradition had strengths and weaknesses. It relied heavily on contextualising a patient’s symptoms, which was an advantage at an individual level. However at a population level, the same characteristic became a liability. Studies highlighted the embarrassing variability of psychiatric diagnoses. Psychodynamically-orientated psychiatrists were shown to be using different terms for the same concepts, or the same term for different concepts, sometimes without being aware of it. (Callahan and Berrios 2005) In Rosenhan’s notorious study, sane adults presented to A&E departments pretending to hear a voice. All were admitted to psychiatric wards, mostly having been diagnosed with schizophrenia. Despite immediately reverting to normal behaviour, these ‘pseudo-patients’ were kept in hospital and prescribed medication for up to 52 days. Although the study was flawed, Rosenhan pulled no punches, arguing forcefully in Nature magazine that psychiatric diagnoses were:

“…useless at best, and downright harmful, misleading, and pejorative at worst”. (Rosenhan 1973)

By the late 1960s, psychiatry was in crisis. Sections of an increasingly permissive American society regarded it as an agent of social control. Charges of intellectual charlatanry threatened research funding. The field’s dominant theory (psychoanalysis) and dominant treatment (psychotherapy) were under attack from within and out-with the medical profession. (Mayes and Horwitz 2005)

Yet some psychiatrists thirsted for recognition as medical scientists. Many believed, crucially, that legitimacy and scientific status demanded a clear diagnostic classification system. (Callahan and Berrios 2005) In 1972, Feighner and colleagues, psychiatrists at Washington University, reacted to these pressures by publishing the first set of explicit and practical criteria for diagnosing psychiatric disorders. (Feighner et al. 1972) In doing so they fundamentally changed the face of psychiatry.

2.1.5 The DSM era

The third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) can be viewed as a response to criticisms that psychiatry was non-scientific. The document returned to strictly descriptive clinical principles. (APA 1980) Instead of subjective judgements about aetiology, symptoms were recorded as “present” or “absent”, purely on the basis of clinical observation.
Sufficient symptoms were taken to constitute a “case” of a particular disorder. The main aim of this operationalised approach was to improve communication among clinicians and researchers. A secondary aim was to facilitate study of the suitability of the diagnostic categories themselves.

The diagnostic categories of DSM-III were created by committees, consisting mainly of white American male psychiatrists. It is important to recognise that the categorical syndromes were acknowledged at the time as hypotheses. Specifically, the authors of DSM-III hypothesised that, as in general medicine, co-varying symptoms would reflect a common underlying aetiology. (Kupfer et al. 2002) The choice of symptoms to include in each disorder category was based mainly on expert opinion. To the extent that DSM-III was intended for general use, illness categories may also have represented political compromises on what was thought likely to be acceptable by a wider population of clinical users.

The operationalised approach to diagnosing major depression continues in the most recent edition of the DSM series (DSM-IV, Text revision). (APA 2000) DSM-IV Major Depressive Disorder (MDD) is considered present when the patient experiences at least five symptoms, from a polythetic criteria set of nine possible symptoms. At least one endorsed symptom must be either depressed mood, or Anhedonia (pervasive loss of interest). Symptoms must be clinically significant (defined as causing “significant distress and/or social or functional impairment”). They must also be persistent (present most of the day, most days, for more than two weeks) and represent a change from normality (Box 3).

<table>
<thead>
<tr>
<th>Low mood and/or Anhedonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Plus:</td>
</tr>
<tr>
<td>Reduced appetite/weight or increased appetite/weight;</td>
</tr>
<tr>
<td>Insomnia or hypersomnia;</td>
</tr>
<tr>
<td>Fatigue;</td>
</tr>
<tr>
<td>Guilt;</td>
</tr>
<tr>
<td>Poor concentration;</td>
</tr>
<tr>
<td>Psychomotor retardation or agitation;</td>
</tr>
<tr>
<td>Suicidal ideation or recurrent thoughts of self-harm.</td>
</tr>
</tbody>
</table>

To be endorsed, a symptom must be significant, persistent and new. If five symptoms are present, including at least one of low mood or anhedonia, MDD can be diagnosed.

**Box 3. Symptoms of DSM-IV Major Depressive Disorder.**
It is important to remember that MDD is a hypothetical syndrome: a collection of symptoms judged to
be present or absent on clinical observation. The category of MDD is not a proven disease and the
authors of DSM explicitly caution against regarding it as such. (Kupfer et al. 2002) These caveats are
discussed further later in the thesis.

2.1.6 Other ways of measuring depressive impairment

Implementing standardised interviews in large research studies takes time, which costs money. Many
authors have therefore developed briefer rating scale instruments as a quicker and simpler method of
measuring the severity of depressive symptoms. These scales have often been validated against a
formal clinical interview using the DSM criteria for Major Depressive Disorder. This allowed
researchers to propose a numerical threshold on the scale, which represented an acceptable balance
between sensitivity and specificity for a concurrent clinical diagnosis of major depression. Examples
of such depression rating scales include the Hospital Anxiety and Depression Scale (HADS)
(Zigmond and Snaith 1983) and the Patient Health Questionnaire-9 (PHQ-9). (Kroenke et al. 2001)
Rating scale scores are a proxy measure for the likelihood of the presence of major depression. Their
introduction expanded the horizon of disorder in the psychiatric literature. It also made clear
communication essential, since “depression” could now mean one of several different things (Box 4).

In clinical research studies of the last 30 years, the word “depression” can refer to any of i) a clinical
diagnosis based on a formal structured clinical interview using operationalised criteria such as those
listed above, ii) a supra-threshold score (yes/no) on any one of a variety of depression rating scales, or
iii) a continuous score along a rating scale, representing the severity of a potentially wide variety of
symptoms.

In the rest of this thesis, I will use the term ‘MDD’ to refer specifically to DSM-IV Major Depressive
Disorder.

I will use the term ‘major depression’ to imply a categorical diagnosis based on clinical interview.

“Depressive symptoms” will refer to the output of depression rating scales.

I will also use “depression” as a general short-hand term without implying any particular definition.

Box 4. A short note on terminology used in this thesis.
2.2 **Current clinical knowledge of depression**

2.2.1 **Prevalence**

The UK National Psychiatric Morbidity Survey interviewed 10,108 adults randomly selected from the entire UK population in 1993/4. The study reported a point prevalence of major depression of 2.1% (95% CI 1.9% - 2.3%). (Jenkins et al. 2003) In another study, the mean prevalence of major depression among 8,764 adults in five European countries was 6.6% (95% CI 5.4% - 8.4%) (Ayuso-Mateos et al. 2001) Among 9,090 community-dwelling adults in the USA, the 12-month prevalence of MDD was 6.6% (95% CI 5.9% - 7.3%). (Kessler et al. 2003) Authors using ICD-10 and DSM-IV approaches in the same study report a similar prevalence of major depression in the study population regardless of which method is used. The point prevalence of major depression in Western communities is therefore probably in the region of 5%.

2.2.2 **Risk factors**

Accepted risk factors for major depression in the general population include: female patient sex; childhood adversity; low socioeconomic status; poor social support; being unmarried; and having a physical illness, neurotic personality or family history of major depression. (Joyce 2009) Adverse life events are also associated with major depression. (Goodwin 2009)

2.2.3 **Pathophysiology**

No biological changes have ever been found to consistently distinguish between depressed and non-depressed patients. (Goodwin 2009) As described above, major depression is a hypothetical construct and may not have a distinct pathophysiology at all. Alternatively, several different aetiologies could contribute to the same operationalised diagnosis. (Drevets 2001) The lack of consistent evidence may itself be due partly to aetiological heterogeneity within and between research samples. However, there are two major biomedical theories of the pathophysiology of major depression. These are: the monoamine hypothesis; and the hypothalamic-pituitary-adrenal (HPA) axis hypothesis.

The monoamine hypothesis states that major depression results from reduced synaptic availability of monoamine neurotransmitters (principally serotonin, noradrenaline and/or dopamine). In support of this hypothesis is the observation that drugs designed to increase the availability of these neurotransmitters tend to improve mood, while interventions designed to deplete them tend to worsen...
Some researchers have observed a modulating effect of a serotonin transporter gene polymorphism on how life stresses impact on the individual’s mood. (Caspi et al. 2003) However, the monoamine hypothesis, derived from the mechanism of currently available antidepressants, has been described as “at its best, a theory about drug action”. (Goodwin 2009) Despite a huge amount of research, no consistent deficiency has been identified in concentrations of the neurotransmitters themselves. (Belmaker and Agam 2008)

The HPA axis hypothesis states that chronic stress causes endogenous hypercortisolaemia, mediating depressive symptoms. In support of this hypothesis, plasma cortisol levels have been found to be raised in some depressed patients compared with healthy controls. (Vreeburg et al. 2009) MRI scans have revealed pituitary and adrenal hypertrophy in some patients with major depression. (Goodwin 2009; Rubin et al. 1995) Oral dexamethasone suppresses endogenous cortisol secretion in normal controls but not patients with major depression, suggesting that depressed patients have a hyperactive HPA axis. (Carroll et al. 1981) However, this effect is less specific when depressed patients are compared with other medically ill populations, weakening the diagnostic value of this test. (Goodwin 2009) Somewhat confusingly, oral dexamethasone may also improve mood in patients with major depression. (Arana et al. 1995; Dinan et al. 1997) Other criticisms of the HPA axis hypothesis include uncertainty over whether the critical agent is cortisol or corticotrophin releasing hormone (Belmaker and Agam 2008), and that biochemical changes could represent the body’s homeostatic response to a state of depressed mood rather than a primary pathophysiological mechanism. (Goodwin 2009)

Major depression has also been hypothesised to be due to: altered neurotransmission of glutamate and/or GABA; disruption to circadian rhythms; impaired endogenous opioid function; cytokine-mediated neuronal dysfunction; thyroxine abnormalities and impaired cerebral neurogenesis. (Belmaker and Agam 2008; Goodwin 2009)

Functional neuroimaging studies (e.g. functional Magnetic Resonance Imaging, fMRI) of the brains of patients with major depression often attempt to localise its anatomical and metabolic substrates. Comparing the results of these studies is difficult. Data can be affected by many factors including patient age, extent of family history, precise depressive symptom pattern and choice of treatment or experimental intervention. (Drevets 2001) However, fMRI studies often implicate frontal brain structures in the state of major depression. (Goodwin 2009) Similarly, many studies utilising Positron Emission Tomography (PET) report reduced cerebral blood flow or glucose metabolism in the prefrontal cortex. Whether this is the dorsolateral, ventrolateral, orbitofrontal or mediofrontal prefrontal cortex varies according to the study. (Grasby 2009) Despite a lack of anatomical precision, most research suggests that connectivity between limbic and frontal brain regions is somehow implicated in emotional regulation. (Goodwin 2009)
Treatments for major depression split broadly into two categories: physical treatments (including antidepressant medicines) and psychotherapies. (Paykel and Scott 2009) UK national clinical guidelines currently recommend a combination of antidepressant medication and psychotherapy for the treatment of adults with major depression. (NICE 2009b)

There are three main antidepressant drug classes. These are the selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). A fourth class is chemically diverse (Box 5). Antidepressants are associated with statistically significant reductions in depressive symptoms, compared to placebo in: patients with a primary diagnosis of depression (Furukawa et al. 2003; Guaiana et al. 2007); primary care (Arroll et al. 2009); the physically ill (Rayner et al. 2010); psychotic depression (Wijkstra et al. 2005); the depressed elderly (Mottram et al. 2006) and in patients who have had a stroke. (Hackett et al. 2008) Whether these reductions are clinically meaningful is less clear.

<table>
<thead>
<tr>
<th>Tricyclic antidepressants</th>
<th>Minimum effective daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>75mg</td>
</tr>
</tbody>
</table>

**Box 5.** Classes of antidepressant drugs relevant to this thesis, and their minimum effective daily dose.

SNRI = Serotonin and Noradrenaline Reuptake Inhibitor. SSRI = Selective Serotonin Reuptake Inhibitor. Minimum effective daily dose as stated in the Maudsley Handbook (Taylor et al. 2007).

The two best-evaluated psychotherapies for depressive symptoms are Cognitive Behaviour Therapy (CBT) and Inter-Personal Therapy (IPT). (Paykel and Scott 2009) They appear to be equally effective, and superior to ‘treatment as usual’. (Churchill et al. 2001; Whitfield and Williams 2003)
2.2.5 Natural history

Major depression often begins with sub-threshold (mild) depressive symptoms, which develop over time into more severe mood disturbance. Rates of onset peak in the fourth and sixth decades of life. Later-onset depression appears to be associated more with adverse life events and less with heritability. (Angst 2009)

In community observational studies, the median duration of a treated major depressive episode is thought to be about 3 months. (Angst 2009; Spiker et al. 2002) With treatment, approximately half of patients with major depression will become symptom-free (i.e., attain remission) and half will have a varying degree of residual symptoms.

Major depression has been shown to recur in up to 85% of cases. (Goodwin 2009) Risk factors for recurrence include previous recurrence, longer duration of episodes, and older age. (Angst 2009) Incomplete remission and initial severity of depression are also strong risk factors for future recurrence. (Paykel et al. 1995) Severe residual symptoms correlate with poor social functioning and impairments in interpersonal relationships. Patients with major depression have twice the mortality risk of the general population. (Angst 2009)

2.3 Chapter summary

Opinion on whether major depression is a biological disease or a psychological reaction has varied over time. Recurring historical themes include tension between those who believe that psychiatrists should treat only severe mental illnesses and those who would treat mild symptoms of distress. Some psychiatrists support diagnosing mental illness on the basis of observable symptoms and behaviours. Others place greater emphasis on subjective, theoretical aetiological models.

In this context, the advent of DSM-III and DSM-IV changed the dominant global paradigm of psychiatry. Practitioners moved from an individual, psychologically-orientated model to a more rigid, research-friendly, ‘medical’ model. In this thesis I define major depression according to DSM-IV. Applying the DSM-IV criteria in a clinical interview is currently the internationally accepted criterion standard method of diagnosing major depression.

The prevalence of major depression among adults in the community appears to be about 5%. The syndrome consists of at least five symptoms, one of which must be low mood or anhedonia. Depression causes significant socioeconomic and psychological morbidity. Treated episodes can persist for at least three months, and often recur.
3 A brief overview of depression in cancer

Glioma is distinguished among cancers by its association with profound neurological and cognitive morbidity, social impairment and lethality in a relatively young population. These characteristics warrant specific studies of the psychological consequences of a diagnosis of glioma. However it is useful to first consider the wider context of depression in cancer, generally. There is a large literature of research into depression in cancer. Some of the issues raised in this field are relevant to a study of depression in glioma.

In this short chapter, I will outline the known prevalence, associations and impact of major depression in patients with cancers arising from outwith the central nervous system (“systemic cancer”). I will then briefly discuss some particular difficulties acknowledged by other researchers in this field.

3.1 Prevalence/associated features

Existing reviews of major depression in patients with systemic cancer suggest that prevalence ranges from 15% - 25% (median 19%) in hospitalised patients with cancer (Massie 2004), and from 6% - 32% (median 15%) in cancer-predominant palliative care populations. (Hotopf et al. 2002) Caution is needed when estimating the ‘typical prevalence’ of depression in cancer. Studies can differ significantly in methodology and in population, limiting their comparability. (Chochinov 2001) Failure to control for variables that could affect mood also limits study generalisability. (Massie 2004) The weight of evidence indicates, however, that major depression is approximately three or four times more common in studies of patients with cancer than it is in studies of the general population.

Factors which have been associated with depressive symptoms in cancer populations include: functional impairment; concern at being a burden to others; reduced social support; and pain. (Akechi et al. 2004;Spiegel et al. 1994) There appears to be a relative lack of association between depressive symptoms and female sex, among cancer patients. (DeFlorio and Massie 2008) However, methodological differences make it difficult to directly compare studies.

3.2 Impact on clinical outcomes

In patients with chronic physical illnesses, depression has been associated with increased medical costs, amplification of physical symptoms, increased functional disability, poor self-care, and reduced treatment adherence. (DiMatteo et al. 2000;Katon and Ciechanowski 2002)
Depression is also associated with mortality in cancer. Satin et al. conducted a meta-analysis of 25 studies that had used a variety of methods to measure depressive symptoms in many different cancer populations. The authors reported that depressive symptoms independently predicted risk of death (RR = 1.25; 95%CI 1.12 - 1.40; p < 0.001). Depression did not appear to predict cancer progression. Only three of these studies had diagnosed depression using clinical interview, however. (Satin et al. 2009a) In another review of 76 prospective studies, over 90% of included studies reported a relative risk for death, in depressed cancer patients, of > 1.0. This suggested that depression is usually associated with higher mortality in studies of cancer patients. (Pinquart and Duberstein 2010) Individual studies conducted in the palliative care setting suggest that, here too, self-reported depressive symptoms may be an independent predictor of mortality. (Lloyd-Williams et al. 2009) These findings reflect the general literature associating depression with increased mortality. (Wulsin et al. 1999)

Scottish cancer patients appear to have an increased risk of completed suicide compared to the general population (overall RR = 1.5; 95%CI 1.29 - 1.76). (Camidge et al. 2007) In Edinburgh, an estimated 7.8% of cancer outpatients endorsed thoughts of suicide, especially those who were also in greater distress. (Walker et al. 2008) This frequency is roughly three times the reported prevalence of suicidal ideation in a population sampled using the same outcome measure. (Goldney et al. 2001) Major depression independently predicts the desire for hastened death in terminally ill cancer patients. (Breitbart et al. 2000)

3.3 Specific difficulties regarding depression in cancer

Major depression can be difficult to diagnose in patients with cancer (Chochinov 2001) or terminal illness (Stiefel et al. 2001), for several possible reasons. First, there is a tension between the probable continuous nature of symptom severity (Massie 2004) and the more categorical approach of DSM-IV. Rather than allowing symptoms to be described on a continuum, the DSM approach promotes a sharp demarcation between normality and disorder; symptoms are either present or absent. Symptoms which are of moderate severity necessitate a judgement about whether the criterion is more or less likely to be fulfilled. (Block 2000;Stiefel et al. 2001) In extreme cases, a supposedly categorical diagnosis of MDD could therefore be a product of nine rather fine judgements. The rigidity of the DSM model could be regarded as artificial when compared with clinical reality.

Second, in patients with cancer, normal and disordered emotional responses can be difficult to separate. Cancer may bring profound changes in a person’s social, occupational and family roles, pain, fear, loss of health, control and/or hopes for the future, toxic treatments, repeated threats to life and existential angst. In this context the distinction between normality and disorder (in terms of depressive
(Massie 2004) This problem may be especially relevant for the “psychological” set of depressive symptoms: low mood; anhedonia; poor concentration; guilt and suicidal ideation. (Chochinov 2001) In practice, the distinction between normal and abnormal response is often a matter of clinical judgement.

Another potential judgement concerns the likely aetiology of certain symptoms. Somatic symptoms (appetite change; sleep change; fatigue and psychomotor retardation) occur in depression, but are also a frequent consequence of cancer and its treatment. Such “criterion confounding” is a possible threat to the validity of a diagnosis of MDD in cancer patients. (Pirl 2004;Trask 2004) Several solutions to this problem have been proposed for use when diagnosing depression in patients with comorbid medical illness. The “exclusive” approach to depression diagnosis advocates excluding somatic symptoms, regardless of their suspected cause. (Bukkberg et al. 1984) The “substitutive” approach suggests removing somatic symptoms and replacing them with additional psychological ones. (Endicott 1984) The “aetiologic” approach calls for a case-by-case judgement on whether to count a symptom or not, based on the most likely aetiology. (von Ammon Cavanaugh et al. 2001) Supporters of the “inclusive” approach count all symptoms regardless of assumed aetiology. (Rifkin et al. 1985)

None of these methods have been shown to be clearly superior to the others. (Koenig et al. 1997) Many researchers use the “inclusive” approach, because it avoids underestimating the frequency of depression. (Chochinov et al. 1994;Ganzini et al. 2008;Hoffman and Weiner 2007;Strong et al. 2007) The inclusive method also avoids making unfounded aetiological assumptions about the nature of symptoms (Ring et al. 1998) and is regarded by some as the most reliable of the diagnostic approaches on offer. (Koenig et al. 1997)

There is some evidence to support including all somatic symptoms, regardless of their suspected cause, when diagnosing depression in cancer patients. Yates and colleagues studied 1500 psychiatric outpatients with Major Depressive Disorder. Fatigue, insomnia, appetite change and psychomotor dysfunction were each equally prevalent in patients with and without a co-morbid chronic medical illness. (Yates et al. 2004) If these symptoms had been due simply to medical illness, it is reasonable to expect that they would have been much more common in the medically ill group. The fact that they were not provides some evidence that somatic symptoms are a prominent and important feature of ‘primary’ depression. This study therefore provides some justification for continuing to count fatigue, insomnia, appetite change and psychomotor dysfunction as indicative of depression in the medically ill. The proportion of participants with cancer was not stated, however, so it is unclear how easily the results of this study can be generalised to patients with cancer.

Simon et al. studied 439 primary care outpatients filing new antidepressant prescriptions. They analysed the prevalence of individual depressive symptoms in patients with and without comorbid medical conditions. Symptoms of fatigue, insomnia, appetite change, and psychomotor function were
largely independent of the presence or absence of medical co-morbidity. Minor differences were however observed for some individual symptoms. For example, medically ill patients endorsed ‘fatigue’ at a statistically significantly milder severity of depression than patients who were medically well. These differences were not consistent for all somatic depressive symptoms. For example, psychomotor retardation only tended to be endorsed at a higher severity of depression in the medically ill, compared to the medically well. (Simon and von Korff 2006) This study therefore suggested that subtle differences may exist in response thresholds to individual symptoms, between patients with and without medical co-morbidity. The magnitude of this effect was small and inconsistent. The authors concluded that they had found only modest evidence that somatic depressive symptoms are any less diagnostically valid in the medically ill.

Akechi et al. examined associations between depressive symptoms in 220 mixed-site cancer patients with a diagnosis of MDD. Appetite change and poor concentration were independently associated with anhedonia, after controlling for physical functioning and pain. Fatigue and insomnia, by contrast, were not associated with anhedonia. The authors concluded that fatigue and insomnia contribute nothing to the diagnosis of MDD in cancer patients. (Akechi et al. 2003) However, this study lacked a control group of cancer patients without MDD. I think that this study provides some evidence to suggest that the relative diagnostic value of the different somatic symptoms of depression may vary in patients with cancer. It is conceivable that different symptoms may carry different weight in different cancer populations. Including or excluding all somatic symptoms, in a blanket fashion, may therefore be less sensitive than cancer-specific diagnostic criteria.

In an attempt to mitigate the extent of criterion confounding, DSM-IV requires the clinician to judge whether symptoms “are not better accounted for” either by a general medical condition (such as cancer) or concurrent medication (such as a corticosteroid). In practice, it is often impossible to make this judgement confidently. (Hoffman and Weiner 2007)

3.4 Chapter summary

Most researchers assert that it is possible to diagnose major depression in patients with cancer. Several consensus documents on the management of depression in patients with cancer acknowledge the challenging nature of making an accurate diagnosis, but promote screening for depressive symptoms regardless. (Dy et al. 2008;Stiefel et al. 2001) Even eloquent critics of the medicalisation of normal sadness concede that MDD can be diagnosed after the loss of health. (Wakefield et al. 2007) However, beyond an understanding that a structured interview is preferable, there is no agreement on the correct method of evaluating symptoms. Many researchers choose to count all relevant symptoms regardless of their possible cause. There is some evidence to support this practice.
4 Using the NCCN Distress Thermometer to screen for emotional distress in cancer

4.1 Introduction

I will return to depression, but first would like to consider aspects of general emotional distress in systemic cancer patients. In the USA, the National Comprehensive Cancer Network (NCCN) defines emotional distress as:

“A multifactorial unpleasant emotional experience of a psychological…social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.” (NCCN 2010)

Emotional distress therefore encompasses, but is a broader concept than depression. Distress occurs frequently in cancer (Carlson et al. 2004; Strong et al. 2007; Zabora et al. 2001) and may pass unrecognised in clinical practice (Fallowfield et al. 2001). As with depression, it is becoming increasingly common to routinely screen cancer patients for distress. In the USA, the National Comprehensive Cancer Network (NCCN) recommends that every new cancer patient is screened for distress using their Distress Thermometer (DT). (NCCN 2010)

The DT is a single-item, self-report screening tool on an 11-point Likert scale constructed to look like a thermometer. Scores range from 0 - 10, anchored at point 0 with “no distress” and at point 10 with “extreme distress”. A threshold ≥ 4 (“4+”) is currently recommended by the NCCN to represent ‘high’ (clinically significant) distress requiring further investigation. The DT is accompanied by a ‘Problem Checklist’ of potential causes of distress, which the patient may endorse (see Appendix 9). The tool was originally piloted in prostate cancer patients. (Roth et al. 1998) The subsequent adoption of the DT by the NCCN, alongside the reframing of distress as the ‘sixth vital sign’ in cancer (Bultz and Carlson 2005), has greatly popularised its use in the USA and the UK.

As a single-item screen, the DT is regarded as an ‘ultra-short’ screening method. A recent systematic review of the utility of ultra-short screening methods in cancer concluded that they identify depression and anxiety with sensitivity, but not specificity. (Mitchell 2007) However, this review focused on the diagnostic validity of distress screening instruments. It did not report the body of basic observational data pertaining specifically to DT-defined distress in cancer. Although distress is a frequent and important complication of cancer, and its measurement by the DT beginning to encroach on routine clinical practice, descriptive studies using the DT have not yet been systematically reviewed.
In this chapter I aimed to systematically search for and review studies of the frequency, clinical associations and common causes of emotional distress, as measured by the NCCN DT in adult cancer patients; asking:

1. In what kind of cancer populations has the use of the DT been studied?
2. What DT thresholds have authors chosen to represent ‘high distress’, and why?
3. What is the reported range of frequency of high distress in cancer, and does it vary with the choice of threshold?
4. What clinical or demographic variables are consistently and independently associated with high distress?
5. What is the reported longitudinal course of distress in cancer generally, and glioma specifically?
6. What distressing problems are most commonly endorsed on the problem checklist?

4.2 Methods

I identified all English-language, peer-reviewed studies of the DT in adults with cancer. Studies administering other distress screening tools to cancer patients (for example, the Hospital Anxiety and Depression Scale) were excluded unless participants completed the DT at the same time. Reviews of distress screening methods and studies of the DT’s use in non-cancer populations were excluded. I also excluded conference abstracts, studies solely recruiting adult survivors of childhood cancer, and studies published in languages other than English.

On 24th Feb 2010, I systematically searched MEDLINE, MEDLINE In-process, EMBASE, PsycINFO and the British Nursing Index using the following search strategy, adapted from Mitchell et al. (Mitchell 2007): (distress* or anxi* or depress* or mood) and (screen* or detect* or recogni* or diagnos* or case-finding) and (cancer or oncology or malignant or tumo* or metastatic) and (NCCN or thermometer). The same databases were also searched using “distress thermometer” as a keyword. Searches were limited to 1996 or later, because use of the DT was first reported in 1998.

I screened reference lists of eligible studies for potentially relevant titles, reviewing their abstracts and/or full text for eligibility. I searched ‘online first’ collections of the journals Cancer, Psycho-Oncology, and Supportive Care in Cancer. Data were extracted from all eligible studies and entered into a Microsoft Excel spreadsheet.
4.3 Results

4.3.1 Search results

The initial search strategy identified 59 individual peer-reviewed titles. Twenty-one were ineligible on abstract screening. The full text of 38 manuscripts was obtained. I then excluded another six manuscripts that either duplicated data presented in another publication, or were superceded by a larger dataset incorporating the same patients. I found another four eligible studies from the separate search for ‘distress thermometer’, three from journal Online First collections and none from reference searching. Therefore, 39 studies were eligible for this review (Figure 3). (Akizuki et al. 2003; Akizuki et al. 2005; Bauwens et al. 2009; Bulli F et al. 2009; Campbell et al. 2009; Clover et al. 2009; Dabrowski et al. 2007; Dolbeault et al. 2008; Gessler et al. 2008; Gil F et al. 2005; Grassi et al. 2009; Graves et al. 2007; Hegel et al. 2008; Hoffman et al. 2004; Hurria et al. 2009; Jacobsen et al. 2005; Johnson et al. 2009; Keir et al. 2008b; Khatib et al. 2003; Kvale 2009; Lynch et al. 2010; Mehnert et al. 2007; Mitchell et al. 2010; Nelson et al. 2010; Nelson et al. 2009; Ozalp et al. 2007; Podnos et al. 2007; Ransom et al. 2006; Roth et al. 1998; Roth et al. 2003; Shim et al. 2008; Shimizu et al. 2005; Steinberg et al. 2009; Thékumputrath, V 2009; Thewes et al. 2009; Trask 2002; Tuinman et al. 2008; Yamagishi et al. 2009; Zainal 2007)

4.3.2 Characteristics of included studies

The growth in popularity of the DT as a research tool through the first decade of the 21st century is reflected in the literature: 30 studies were published worldwide 2005 - 2009 compared to just eight in the earlier half of the decade. Almost all studies were cross-sectional and/or based in oncology outpatient departments. Median sample size was 182 (IQR 99 - 328; range 33 - 716) with a total of 9218 individual participants enrolled. The number of patients that actually completed the DT was slightly lower (n = 9009). Women and men were roughly equally represented (n = 4828 and n = 4390, respectively). The mean age of participants was 58 years (SD 6.8; range 48 - 71 yrs) (Table 1).

Most studies enrolled patients with differing cancers (“mixed-site cancer patients”). Others enrolled solely patients with prostate, lung, brain, breast or gynaecological cancer. The most frequently specified pathology was breast cancer (n = 2384 reported participants) (Table 2).
Figure 3. Flowchart of identification of studies for a systematic review of the use of the Distress Thermometer in adults with cancer.

BNI = British Nursing Index.
<table>
<thead>
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<th>Study</th>
<th>Location</th>
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<th>Sample (n)</th>
<th>Getting DT (n)</th>
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<th>Female (n)</th>
<th>Mean age (yrs)</th>
<th>Gender</th>
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**Table 1.** Characteristics of included studies of the DT in adults with cancer (part 1). Study design, patient eligibility, recruitment, patient sex and age.

C = Cross-sectional; L = Longitudinal. † Including a repeat analysis of the 385 patients in Roth (1998)
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**Table 2.** Characteristics of included studies of the DT in adults with cancer (part 2). Cancer sites represented in each study.

Haem = haematological (leukaemia, myeloma, lymphoma); GI = gastrointestinal (stomach, pancreas, bile duct, colorectal); GU = genitourinary (including prostate); Gyn = gynaecological; H&N = head and neck; Oth = other (usually not specified); Unk = unknown (diagnosis not known in original study); Miss = missing (either known to be missing in original study, or data gathered but not presented in publication).
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<th>Frequency of high distress (%)</th>
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**Table 3.** Choice of DT threshold, mean score and the frequency of high distress.

ROC = Receiver Operating Characteristic analysis of own data. Lit RV = Literature Review (at least one referenced article justifying choice of cut-off). NS = Not Stated. SD = Standard Deviation.
4.3.3 **Choice of DT threshold**

The cut-off, or threshold, demarcating ‘high’ distress ranged from 3+ to 7+ (out of 10). The most frequent threshold was 4+ with a significant minority favouring 5+. Generally, choice of threshold was either informed by a brief literature review or else based on Receiver Operating Characteristic (ROC) curve analysis of original data gathered in that particular study. ROC curve analyses mostly compared the DT against a variety of distress rating scales, rather than against clinical interview. Literature review appeared to result in a narrower range of thresholds (ranging from 4+ to 6+) than ROC curve analysis (ranging from 3+ to 7+).

4.3.4 **Frequency of high distress**

‘High’ distress, however defined by the study authors, was identified in a median of 44% of participants (IQR 37.8% - 51%; range 28.6% - 70%). The mean of all mean DT scores was 3.7 (SD 0.7, range 2.1 - 4.9). Unsurprisingly, a higher threshold resulted in a lower reported frequency of distress (median = 47.3% among studies using a threshold of 4+, 44.2% with 5+ and 37.1% with 6+). *(Table 3).*

4.3.5 **Independent associations with DT score**

Only five studies reported multivariable analyses. The factors consistently and independently associated with high distress were pain, functional impairment, depression and anxiety. Single studies reported independent associations between distress and younger age, female patient sex, psychosocial adversity, poorer social support and being the recipient of current psychological treatment *(Table 4).*

4.3.6 **Longitudinal course of distress**

Few studies reported the longitudinal course of DT-defined distress in cancer. One group reported that the instrument may be sensitive to change (mirroring changes, in either direction, of the HADS over an eight-week period). (Gessler et al. 2008) Another studied the course of 165 mixed-site cancer patients found to have high distress (threshold 6+), of whom 115 reported a reduction of distress levels to less than 6 within a median of 17 days. (Yamagishi et al. 2009) By contrast, one group observed no significant reduction in mean DT score in the three months after surgery, in a sample consisting solely of patients with advanced gastrointestinal cancer. (Podnos et al. 2007)
4.3.7 The Problem Checklist

Fifteen studies reported data from the DT ‘Problem Checklist’. Because the composition of the Checklist varied from study to study, direct comparisons were difficult. However it was possible to draw general conclusions. The most consistently reported problems in cancer were fatigue, sleep, worry, pain and nervousness. Fatigue was a ‘top 5’ problem in every study reporting this data, and the others were ‘top 5’ problems in more than three studies. Other particularly common problems are listed in Table 5. Distress level and overall problem count were consistently correlated. (Graves et al. 2007; Keir ST et al. 2008; Ozalp et al. 2007; Tuinman et al. 2008)

High distress was always significantly associated with physical and with emotional problems, and usually also with family and practical problems. High distress was usually not associated with spiritual problems.

4.4 Discussion

4.4.1 Main findings

Few studies have examined the use of the DT in patients with glioma. Most studies using the NCCN Distress Thermometer recruited mixed-site cancer patients, and were cross-sectional in design and/or based in outpatient departments. The instrument usually detected clinically significant emotional distress in around 40% of patients. The choice of threshold influenced the frequency of ‘high’ distress to some extent. Although the NCCN advises a threshold of 4+, many studies validating the thermometer against original data chose a threshold of 5+.

Distress was consistently and independently associated with pain, functional impairment, depression and anxiety. Independent associations were also reported between distress and younger age, female patient sex and psychosocial adversity. Evidence associating distress with any other clinical or demographic variables was weak, absent or contradictory.

The individual problems reported most often by cancer patients were fatigue, sleep, worry, pain and nervousness. High distress was consistently associated with both physical and emotional difficulties.
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<td></td>
<td></td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Graves 2007</td>
<td>4+</td>
<td>Depression</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety/nervousness</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
<tr>
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<td>Younger age</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Hurria 2009</td>
<td>4+</td>
<td>Functional impairment</td>
<td>Medical Outcomes Survey, Physical Function subscale</td>
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<tr>
<td>Tuinman 2008</td>
<td>5+</td>
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</tr>
<tr>
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<td>‘Emotional control’ difficulty</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
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<td>Pain</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical fitness</td>
<td>Self-report (Y/N; DT problem checklist)</td>
</tr>
<tr>
<td>Akizuki 2003</td>
<td>5+</td>
<td>Pain</td>
<td>Bespoke four-tiered scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression</td>
<td>(None at all; A little; Tolerable; Intolerable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unstructured psychiatric clinical interview</td>
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Table 4. Reported independent associations with high distress as measured by the NCCN distress thermometer.
<table>
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<tr>
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<td>Sleep</td>
<td>57</td>
<td>32</td>
<td>40</td>
<td>33</td>
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<td>-</td>
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<td>Worry</td>
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<td>51</td>
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<td>-</td>
<td>-</td>
<td>72</td>
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<td>49</td>
<td>30</td>
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<td>41</td>
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<td>-</td>
<td>-</td>
<td>31</td>
<td>39</td>
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<tr>
<td>Breathing</td>
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<td>43</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Getting around</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>41</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Insurance</td>
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<td>-</td>
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<td>28</td>
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<td>-</td>
<td>32</td>
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<tr>
<td>Anxiety</td>
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<td>-</td>
<td>-</td>
<td>90</td>
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<td>-</td>
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<td>87</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>74</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5. The ‘Top 5’ individual distressing problems reported in each study using the DT Problem Checklist, and their frequencies (%).
4.4.2 Limitations of this study

Studies of mixed-site cancer patients recruit a heterogeneous population that may not be relevant to patients with glioma. The results of this review may be less representative of patients in non-English speaking countries, since we excluded non-English language papers and did not search non-English-language databases. In the narrative review no adjustments were made for study quality, nor weighting for power.

4.4.3 Results in context

How does the 44% median frequency of DT-defined ‘high’ emotional distress compare with the frequency of distress identified by other methods in cancer patients? I identified several recent large studies (sample n > 2000) that screened mixed cancer outpatients for distress. The 53-item Brief Symptom Inventory (BSI) identified ‘high’ distress in 35.1% (n = 4496) (Zabora et al. 2001); the shortened, 18-item version of the BSI in 37.8% (n = 2776) (Carlson et al. 2004); the 12-item General Health Questionnaire (GHQ-12) in 36.4% (n = 2297) (Fallowfield et al. 2001) and the HADS in 22% (n = 3071). (Strong et al. 2007) It can be seen that the DT labelled a greater proportion of patients as ‘distressed’ compared to longer screening methods. A DT threshold of 4+ may therefore have relatively high sensitivity, but a low specificity, for identifying emotional distress. Clinicians must weigh this against the DT’s relative speed and simplicity. (Mitchell 2007)

Specificity could be improved by raising the threshold. The current internationally accepted convention is for the threshold to be 4+. However, it is perhaps notable that the three studies setting a threshold of 6+ reported a mean distress frequency of 37.1%, closer in operating characteristics to the more detailed screening methods outlined above.

Differences in threshold could potentially affect the comparison of variables associated with high distress in different studies. For this reason I sought corroborated, independent associations. Pain, functional impairment, depression and anxiety were the only factors repeatedly and independently associated with high distress on the DT. Researchers using longer screening tools report independent associations between higher distress and younger age (Carlson et al. 2004; Strong et al. 2007; Zabora et al. 2001); female patient sex (Carlson et al. 2004; Strong et al. 2007); minority ethnicity (Carlson et al. 2004); lower income (Carlson et al. 2004); longer duration of illness (Carlson et al. 2004) and the presence of active disease. (Strong et al. 2007) None of these factors were repeatedly and independently associated with high distress in the studies eligible for this review. However, few eligible studies conducted multivariable analyses.
As with the measurement of distress severity, there are different ways to record a patient’s current problems. Reviews of studies of mixed-site cancer patients, in which different methods were used to measure problems, identify the same recurring difficulties including fatigue, insomnia, appetite loss, concentration problems and sadness. (Kim et al. 2009; Teunissen et al. 2007) However, the DT Problem Checklist is a general screen which may not be ideally suited to individual cancers, particularly those (like brain, or head and neck cancer) with troublesome site-specific symptoms. Some authors have therefore added extra items to it. (Tuinman et al. 2008) Although this may improve clinical relevance, it potentially limits comparability between studies.

Cancer patients scoring highly on the DT tend to endorse physical and emotional problems simultaneously. Services should therefore be available locally to routinely and appropriately manage psychological difficulties. Yet time in clinic is often limited and clinicians may choose to prioritise the assessment and management of physical symptoms. This risks missing, or minimising, the emotional component to high distress that is emphasised in this review.

4.5 Chapter summary

In this chapter, I systematically reviewed published studies of the NCCN DT in adults with cancer. There is generally a “supra-threshold” distress frequency of around 40%, in a surprisingly wide range of clinical populations. Few researchers have investigated the use of the DT in glioma patients, however. The two studies that did were small, and cross-sectional in design.

Younger cancer patients, women, those in psychosocial adversity and the functionally impaired may benefit from more detailed evaluation for broadly defined emotional distress. Clinicians should anticipate providing increased support services for these higher-risk groups. Conversely, any cancer patient screening sufficiently highly for distress should be assessed specifically for the presence of pain, depression and anxiety.

Emotional distress is a broad concept. In the next chapter I re-focus more tightly on one specific cause or aspect of distress, found to be independently associated: depression.
5 Systematic review of observational research into depression in glioma

5.1 Introduction

Depression is a well-recognised complication of cerebral glioma (Litofsky and Resnick 2009; Pangilinan et al. 2007; Weitzner 1999) but it can be challenging to study. (Anderson et al. 1999; Mainio et al. 2005a) Primary symptoms of depression are difficult to distinguish from the consequences of tumour or treatment. (Cummings and Bogousslavsky 2000) However, true clinical depression can and does develop following a decline in health (Pace and Pompili 2005; Wakefield et al. 2007), and is of great practical relevance to patients. Among all cancer patients, those diagnosed with glioma have the highest risk of clinically significant psychiatric complications in the period surrounding their diagnosis. (Benros et al. 2009; Dalton et al. 2009) Poor mental health has potentially important consequences. Depression may adversely quality of life (Catt et al. 2008; Litofsky and Resnick 2009; Pangilinan et al. 2007; Weitzner 1999) and is an independent predictor of mortality in systemic cancer arising beyond the nervous system. (Satin et al. 2009b)

Many things remain unknown about depression in glioma. Depression in these patients has been conceptualised as a biological disease (Gathinji et al. 2009; Irle et al. 1994; Mainio et al. 2005a; Taphoorn et al. 1999; Weitzner 1999; Wellisch et al. 2002), a psychological reaction to the losses associated with brain cancer (Diaz et al. 2009; Grant et al. 1994; Junck 2004; Pace and Pompili 2005; Pelletier et al. 2002), or both. (Anderson et al. 1999; Fox et al. 2007; Giovagnoli 1999; Litofsky and Resnick 2009; Pangilinan et al. 2007) Estimates of the frequency of depression in patients with glioma range from 0% (Anderson et al. 1999) to 93%. (Litofsky et al. 2004) There are conflicting observational data regarding associations between depression in glioma and: patient sex (Gathinji et al. 2009; Irle et al. 1994); functional status (Gathinji et al. 2009; Litofsky et al. 2004); past psychiatric history (Mainio et al. 2005a; Wellisch et al. 2002); tumour size (Hahn et al. 2003; Irle et al. 1994); tumour laterality (D'Angelo et al. 2008; Hahn et al. 2003); tumour grade (Anderson et al. 1999; Arnold et al. 2008); affected lobe (Litofsky et al. 2004; Wellisch et al. 2002); steroids (D'Angelo et al. 2008; Litofsky and Resnick 2009); radiotherapy (Litofsky and Resnick 2009; Price et al. 2008); chemotherapy (Giovagnoli et al. 1996; Pelletier et al. 2002); medical complication rates (Gathinji et al. 2009; McGovern et al. 2003) and survival. (Brown et al. 2006; Gathinji et al. 2009) Potential sources of these discrepancies include differences in study methods (Diaz et al. 2009; Litofsky and Resnick 2009; Weitzner 1999), study populations (Grafman and Warden 2000; Pringle et al. 1999), sampling time-points (Grafman and Warden 2000; Irle et al. 1994; Pringle et al. 1999), and the quality of study reporting. (von Elm et al. 2007)
These uncertainties reinforce the need to study depression in patients with glioma. A better understanding of its diagnosis, frequency, and associated clinical characteristics may help focus future research priorities and support evidence-based patient care. Previous reviews on this topic were not conducted systematically; in addition, they included data on conditions that are fundamentally different from glioma, such as meningiomas and pituitary tumours. I therefore conducted a systematic literature search and review of observational studies of depression in adults diagnosed with glioma. I specifically examined: (1) the extent of heterogeneity in diagnostic methods, (2) the reported frequency of depression, (3) clinical factors associated with depression in glioma patients, and (4) the quality of study reporting.

5.2 Methods

I conducted a search of the published English-language literature in the MEDLINE, EMBASE and PsycINFO databases from January 1, 1980, to September 16, 2009, using the search terms shown in Box 6. I included all cohort, case-control and cross-sectional studies that presented original data on any aspect of depression in patients with a supratentorial glioma who were older than 18 years of age at diagnosis. I allowed any method of diagnosing glioma, and all methods of diagnosing depression, except depression subscales of general quality-of-life (QOL) assessment instruments. I excluded QOL subscale data because QOL scales measure a wider construct than depression-specific rating scales and are not designed to identify clinical depression.

Search strategies (conducted 16/9/2009)

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>PsycINFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(depressive disorder major.sh. OR depressive disorder.sh. OR depression.sh,ti,ab. OR dysthymic disorder.sh. OR adjustment disorders.sh.) AND (brain neoplasms.sh. OR glioma.sh,ti,ab. OR astrocytoma.sh,ti,ab. OR oligodendroglioma.sh,ti,ab. OR glioblastoma.sh,ti,ab. OR glioma subependymal.sh.)</td>
<td>(major depression.sh. OR depression.sh,ti,ab. OR depressive.ti,ab. OR dysthymia.sh. OR adjustment disorder.sh. OR mood.sh OR mood disorder.sh.) AND (brain tumour.sh. OR glioma.sh,ti,ab. OR astrocytoma.sh,ti,ab. OR oligodendroglioma.sh,ti,ab. OR glioblastoma.sh,ti,ab.)</td>
<td>(major depression.sh. OR depression.ti,ab. OR depressive.ti,ab. OR dysthymia.ti,ab. OR affectiv*.ti,ab. OR affective disorders.sh. OR dysthymia.ti,ab.) AND (brain neoplasms.sh. OR astrocytoma.ti,ab. OR oligodendroglioma.ti,ab. OR glioblastoma.ti,ab. OR glioma.ti,ab.)</td>
</tr>
</tbody>
</table>

Box 6. Search strategy used in systematic review of observational studies of depression in glioma.
I also excluded case reports, clinical trials of medication and studies with fewer than 10 glioma patients (because with so few patients it was difficult to differentiate between a case series and a very small cohort). To keep this review as specific as possible, I excluded any study that included intracranial tumours with cell origins different from glioma (e.g., studies enrolling patients with glioma, meningioma and pituitary tumours) unless more than 50% of the sample had glioma, the glioma data were presented separately, or histological tumour type was specifically shown to have no association with depression in that study. I excluded all studies published before January 1, 1980, based on the assumption that the lack of widespread computerized tomography scanning before that date would weaken their reliability (the older literature has also been reviewed elsewhere). (Price et al. 2008)

I performed the systematic search, screened all titles and abstracts, obtained all potentially eligible papers in full text, and checked their eligibility. All titles identified via references were obtained in full text and checked for eligibility.

A data extraction form was designed by consensus with supervisors. I extracted the data from all eligible studies, entered them into a Microsoft Excel database, and synthesised the results in a narrative review in consultation with supervisors. Data were recorded for high-grade glioma (HGG) and low-grade glioma (LGG) separately if they were clearly presented in the original study. Where possible, the World Health Organisation (WHO) grading system (Louis 2007) was used to categorise gliomas, based on their histological features of malignancy, into HGG or LGG. Clinical associations were grouped into four broad categories of variables related to the patient, the tumour, the treatment, and the outcome. I used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al. 2007) as a guide for evaluating the quality of reporting of the primary studies.

5.3 Results

5.3.1 Search results

The initial search strategy identified 1076 titles: 402 from MEDLINE; 553 from EMBASE; and 121 from PsycINFO. Title screening and elimination of duplicate publications left 155 publications: 89 from MEDLINE; 49 from EMBASE; and 17 from PsycINFO. I then excluded 75 publications after reviewing the abstract and obtained the remaining 80 studies in full text, of which 35 were eligible for inclusion in this review. Additional studies were identified by reference scanning (n = 3) and my own knowledge (n = 4) for a total of 42 eligible studies (Figure 4). (Anderson et al. 1999; Armstrong et al. 2002a; Armstrong et al. 2002b; Arnold et al. 2008; Brown et al. 2006; Chang et al. 2003; D'Angelo et al. 2008; Price et al. 2008).

5.3.2 Overview of study design and aims

The design and aims of all included studies are listed in Table 6. Most studies were cross-sectional and focussed on outcomes other than depression. Depression was an outcome in 10 prospective cohort studies, three of which were drawn from a single dataset. All cohort studies had a baseline measurement of depression at or around the time of the primary surgery. The most common research questions among the 19 studies that focussed primarily on depression were about its frequency and clinical associations. Few studies examined depression with respect to aetiology, methods of diagnosis, phenomenology, clinical course, and naturalistic treatment. Ten studies included a control group.

5.3.3 Participants

Demographic data from eligible studies are presented in Table 7. The 42 eligible studies reported data on a total of 4683 patients (median sample size = 51 patients, range = 10 - 1052 patients). After adjusting for overlap between studies published from the same dataset, there were 4089 unique glioma patients. Among studies that specified glioma grade, 3308 unique patients had HGG and 355 had LGG (see Table 7 for full details of how these numbers were derived). These proportions of patients with HGG (90.3%) and LGG (9.7%) are reasonably reflective of the proportions of HGG (85%) and LGG (15%) previously reported in clinical populations. (Rees 2002) There was, however, a slight bias towards the inclusion of HGG patients. Among included studies, slightly more of the participants were men (median = 56%, range = 40% - 71%). This slight male bias is consistent with the demographics of glioma. (Wrensch 2002) The median age of subjects at study entry was 46 years (range = 26 - 61 years). The incidence of glioma increases with increasing age (Wrensch 2002); therefore, eligible studies may have been biased towards including younger patients. Most studies did not report data on ethnicity, marital status, and employment status. In those that did, most participants
were white Caucasian (median = 93%, range = 63% - 100%), and married (median = 73%, range 67% - 78%), whereas their employment status varied considerably (median = 45%, range = < 25% - 100%).

5.3.4 Heterogeneity in diagnostic methods

Twenty-five distinct methods were used to diagnose depression in the 42 eligible studies (Table 8). General diagnostic approaches included clinical interview, a variety of continuous and dichotomised patient and clinician-rated scales, review of hospital discharge records, physician report, caregiver report, and patient interview or report. Only one study diagnosed depression in the basis of a structured clinical interview (Wellisch 2002).

Most methods of diagnosing depression relied upon patient self-report. The single most commonly-used instrument for measuring depressive symptomatology was the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith 1983), which was used in 10 studies. Eight distinct clinician-based methods of diagnosing depression were applied in a further nine studies. By contrast, there was far less variability in the methods used to diagnose glioma; in most studies, a glioma diagnosis was based on histopathology, and less often on radiology or (very occasionally) patient self-report.

5.3.5 Frequency of depression

Depression was reported as a categorical variable (e.g., as “present” or “absent” according to either a rating scale score or clinical judgement), a continuous variable (e.g., a scale score presented without reference to a diagnostic threshold), or a combination of both. Patient-rated measures usually returned a higher prevalence of depression (median 27%, range 0% - 93%) than clinician-rated measures (median 15%, range 5% - 28%). Studies that used the same diagnostic method generally reported similar mean scores for the severity of depression. For example, in the 10 studies that used the HADS depression subscale (HAD-D, which ranges from 0 [no symptoms of depression] to 21 [the highest possible depression score]), the mean score (SD) ranged from 3.2 (2.3) to 6.2 (not given) (see Table 8 for further details). Because a HAD-D threshold score of 11 or higher is often used to represent clinically significant depression (Zigmond & Snaith 1983), the average severity of depressive symptoms across the whole sample was low in all the studies that provided mean HAD-D score data.
Figure 4. Flowchart of identification of studies eligible for a systematic review of observational research on depression in adults with glioma.
<table>
<thead>
<tr>
<th>Focus *</th>
<th>Reference</th>
<th>Country</th>
<th>Recruitment</th>
<th>Sampling †</th>
<th>Questions with regard to depression</th>
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</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Anderson 1999</td>
<td>UK</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Frequency and associations with clinical variables</td>
</tr>
<tr>
<td></td>
<td>Armstrong 2002</td>
<td>USA</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Etiology (psychological reaction or direct neurological effect)</td>
</tr>
<tr>
<td></td>
<td>Arnold 2008</td>
<td>USA</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Frequency and associations</td>
</tr>
<tr>
<td></td>
<td>Dalton 2009</td>
<td>Denmark</td>
<td>Retrospective</td>
<td>NA</td>
<td>Risk of hospitalisation with depression after diagnosis of glioma</td>
</tr>
<tr>
<td></td>
<td>D'Angelo 2008</td>
<td>Italy</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Frequency, associated clinical characteristics and course over time</td>
</tr>
<tr>
<td></td>
<td>Diaz 2009</td>
<td>Spain</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Association with perioperative information-giving</td>
</tr>
<tr>
<td></td>
<td>Gathinji 2009</td>
<td>USA</td>
<td>Retrospective</td>
<td>NA</td>
<td>Association with overall survival</td>
</tr>
<tr>
<td></td>
<td>Irle 1994</td>
<td>Germany</td>
<td>Retrospective</td>
<td>NA</td>
<td>Association with tumor location</td>
</tr>
<tr>
<td></td>
<td>Kaplan 2000</td>
<td>USA</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Association with relationship characteristics</td>
</tr>
<tr>
<td></td>
<td>Kilbride 2007</td>
<td>UK</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Frequency and causes</td>
</tr>
<tr>
<td></td>
<td>Litofsky 2004</td>
<td>USA</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Frequency, associated clinical characteristics and course over time</td>
</tr>
<tr>
<td></td>
<td>Mainio 2005a‡</td>
<td>Finland</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Associations, course over time</td>
</tr>
<tr>
<td></td>
<td>Mainio 2005b‡</td>
<td>Finland</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Association with 5-year overall survival</td>
</tr>
<tr>
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<td>Mainio 2006a‡</td>
<td>Finland</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Association with QOL</td>
</tr>
<tr>
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<td>Mainio 2006b‡</td>
<td>Finland</td>
<td>Prospective</td>
<td>Longitudinal</td>
<td>Association with 10-year overall survival</td>
</tr>
<tr>
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<td>Pelletier 2002</td>
<td>Canada</td>
<td>Prospective</td>
<td>Cross-sectional</td>
<td>Correlation with fatigue, distress and QOL</td>
</tr>
<tr>
<td></td>
<td>Pringle 1999</td>
<td>UK</td>
<td>Prospective</td>
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<td>Frequency and associations</td>
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<td>Frequency</td>
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**Table 6.** Design and aims of included studies in a systematic review of observational research into depression in adults with glioma.

QOL = quality of life. RT = radiotherapy. LGG = low-grade glioma.

*Primary: the main hypothesis of the study regards depression, either as a dependent or independent variable. Secondary: depression was measured as part of a wider battery of tests, or was explicitly stated to be a secondary outcome.

† NA = not applicable: retrospective analysis of depression occurring at any time-point in the sampled data.

‡ Four papers presented from the same dataset.
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<th>Approached (n)</th>
<th>Sample (n)</th>
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<th>HGG (n)*</th>
<th>LGG (n)*</th>
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Table 7. Demographic characteristics of subjects in included studies.

NA = not applicable. HGG = high-grade glioma. LGG = low-grade glioma.
Where figures are absent, they either were not stated or were difficult to extrapolate from reported data.
* Only subjects clearly stated to have glioma/HGG/LGG are counted.
† Median.
‡ Four papers from same dataset. Only data from Mainio 2006b was counted towards the total of unique glioma patients given in the text.
§ Two papers from the same dataset. Only data from Litofsky et al. was counted towards the total of unique glioma patients given in the text.

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<th>Other M (%)</th>
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### Table 8. Dichotomous and continuous methods of measuring depression in glioma, and its frequency upon first measurement in each study.

Studies which did not state any measure of depression frequency are excluded from this table. NS = not stated. * “Post-op” means any time between primary surgery and the start of radiotherapy. In longitudinal studies with several measurements, only the first is reported.
† Rounded to the nearest 1%. ‡ This study represents four publications from the same dataset.
§ These studies may have a degree of overlap from the same dataset.
Raw scores from depression rating scales including the HADS, the Beck Depression Inventory (BDI), the Patient Health Questionnaire-9 (PHQ-9) and the Zung Self-Rating Depression Scale (ZSDS) can be dichotomised to indicate either the likely presence or the likely absence of depression. However, because they each measure slightly different symptoms, different scales may differ in the frequency with which they identify similar patients as depressed. This appeared to be the case in patients with glioma. The BDI identified depression in 38% - 42% of patients screened (median = 39%), a frequency similar to that returned by the PHQ-9, which found a depression prevalence of 41% in the single study to use this instrument. By contrast, the HADS (Depression Subscale) returned much lower frequency estimates (median prevalence = 16%, range 0% - 21%), as did the ZSDS (8% and 10% in two studies).

Data from clinical interviews, which are methodologically more robust than rating scales, recorded a depression prevalence ranging from 6% to 28% (median = 15%). The BDI and PHQ-9 scales therefore appeared to overestimate the frequency of depression in glioma compared with studies that used clinical interview methodology. Further information about the diagnostic methods, sampling time-points and depression frequency is presented in Table 8.

5.3.6 Clinical associations of depression

Associations between most clinical variables and depression, when studied, were inconsistent across studies. Statistical analyses were usually univariate. Associations that were examined in studies in which depression was a primary outcome are presented in Table 9. A summary of the current evidence for these variables is presented in Table 10.

5.3.6.1 Patient-related factors

5.3.6.1.1 Patient sex

Although some studies found an association between female sex and depressive symptoms in glioma, most did not. The two studies basing the diagnosis of depression on clinician report found no relationship. (Litofsky et al. 2004; Rooney et al. 2009b) Studies of patients with HGG consistently found no association, whether peri-operatively (Diaz et al. 2009; Gathinji et al. 2009; Litofsky et al. 2004), before chemotherapy (Brown et al. 2006) or after recurrence. (Giovagnoli et al. 2005) Two small studies of patients with LGG reported significant univariate associations (Armstrong et al. 2002; Taphoorn et al. 1994). Therefore, it remains possible that sex may play a larger role mediating symptoms of depression in patients with LGG than in those with HGG. Overall, female patient sex
was not a clear risk factor for depression. Considering that depression in the general population is generally accepted to be more common in women, the apparent absence of a sex bias suggests a relatively increased risk for depression in male glioma patients. (Rooney et al. 2009b)

5.3.6.1.2 Age

Age was studied often. It appeared to have no relationship with depression either in glioma generally (Anderson et al. 1999; Arnold et al. 2008; Irle et al. 1994; Mainio et al. 2005a; Pelletier et al. 2002; Wellisch et al. 2002) or in HGG specifically. (Brown et al. 2006; Diaz et al. 2009; Gathinji et al. 2009; Giovagnoli 1999; Litofsky et al. 2004) Equally, there was no relationship whether depression was measured using a scale or diagnosed with clinical judgement in these studies. There was no evidence specific to LGG.

5.3.6.1.3 Marital status

Married patients with mixed types of glioma were as likely to experience depression as unmarried patients, whether assessed pre-operatively (Mainio et al. 2005a), post-operatively (Kaplan and Miner 2000), during follow-up (Arnold et al. 2008; Pelletier et al. 2002; Wellisch et al. 2002) and after recurrence. (Giovagnoli et al. 2005) We found no studies specific to HGG or LGG. The evidence therefore suggests that marital status is not a risk factor for depression in glioma.

5.3.6.1.4 Past psychiatric history (PPH)

Two studies reported an association between past psychiatric history (PPH) and depression (Arnold et al. 2008; Mainio et al. 2005a) and two did not. (Anderson et al. 1999; Wellisch et al. 2002) Direct comparison of positive and negative studies was difficult because they used different definitions of PPH (e.g., any psychiatric illness, treatment for depression specifically, or previous suicide attempt). The relationship between PPH and depression was unstudied in HGG/LGG specifically. Overall, PPH was not established as a clear risk factor for depression in glioma.

5.3.6.1.5 Function

Reduced physical function was associated with an increased likelihood of depression in most studies (Anderson et al. 1999; Fox et al. 2007; Grant et al. 1994; Litofsky et al. 2004; Mainio et al. 2005a), although not all (Gathinji et al. 2009; Hahn et al. 2003; Pelletier et al. 2002) Function was most commonly measured with the Karnofsky Performance Scale (KPS) (Karnovsky and Burchenal 1949) or the Barthel Index, which is a measure of disability. (Mahoney and Barthen 1965) The most
consistent relationship was between greater disability (Barthel Index) and a higher HADS depression score in glioma patients during follow-up. (Anderson et al. 1999; Grant et al. 1994) There was no evidence specific to LGG patients, who more commonly have epilepsy than physical impairments. The balance of evidence suggests that functional impairment is associated with depression in glioma.

5.3.6.1.6 Cognitive impairment

Studies consistently showed an association between cognitive impairment and depression. However, a specific pattern of impairment across cognitive domains was not apparent, perhaps because different tests were applied at different times and in different populations. Depression was associated with cognitive impairment in LGG pre-chemotherapy (Armstrong et al. 2002a), HGG during follow-up (Fox et al. 2007) and in any glioma patients both postoperatively (Irle et al. 1994) and during follow-up. (Anderson et al. 1999; Grant et al. 1994) All studies that examined this relationship used continuous scale scores to measure depression, and all positive studies used formal neuropsychological screening batteries. The only study using the Mini Mental-State Examination (MMSE) found no association (Brown et al. 2006), perhaps because this test is relatively insensitive. When detailed neuropsychological testing is used, depression is associated with cognitive impairment in glioma.

5.3.6.1.7 Race or ethnicity

Few eligible studies enrolled black, Asian, Hispanic or Native American patients with glioma. In one study, black patients with HGG were at significantly higher risk ($p = 0.001$) of depression in one study (Litofsky et al. 2004), compared with patients of other ethnicities. However, the number of black patients in that study was small (18 out of 598 patients were black), increasing the risk of a type I error. Two other studies, one in HGG patients pre-operatively (in which 337 of 1003 patients were non-white) (Gathinji et al. 2009) and one sampling any glioma patients in follow-up (in which 18 of 363 patients were non-white) (Arnold et al. 2008) reported that race or ethnicity was not related to risk of depression. We found no evidence specific to LGG. Overall, there was no consistent evidence that race or ethnicity is a risk factor for depression in glioma.

5.3.6.1.8 Education level

Education level was measured in three studies (Arnold et al. 2008; Giovagnoli 1999; Pelletier et al. 2002) which provided conflicting results. Each used a different depression outcome measure and a different definition of ‘education level’. The effect of education level on depression in patients with LGG specifically was not studied. Overall education level was not a clear risk factor for depression.
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDI 10+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>Yes</td>
<td>Litofsky 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physician (form)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Gathinji 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physician (notes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>Yes</td>
<td>Pelletier 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDI-II cont.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Reported associations between clinical variables and depression in adults with glioma.

Only studies with a primary focus on depression are shown (see text for studies where depression was a secondary outcome). Cont = continuous outcome (scale score). Cut-offs for dichotomous outcomes are as indicated. RT = radiotherapy. AED = Antiepileptic drug. * Multivariable analysis (defined as controlling or adjusting the outcome for at least one other variable). Multivariable preferred to univariate analyses where both are reported.
This table summarises the balance of the available evidence. Further research is needed into whether these conclusions are accurate. * Direction of change over time is not clear.

**Table 10. Currently hypothesised relationships between clinical variables and depression in glioma.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Association with depression in studies enrolling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All glioma</td>
</tr>
<tr>
<td><strong>Patient-related</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sex</td>
<td>Unclear</td>
</tr>
<tr>
<td>Age</td>
<td>No</td>
</tr>
<tr>
<td>Marital status</td>
<td>No</td>
</tr>
<tr>
<td>Prior depression</td>
<td>Unclear</td>
</tr>
<tr>
<td>Function</td>
<td>Yes</td>
</tr>
<tr>
<td>Cognition</td>
<td>Yes</td>
</tr>
<tr>
<td>Education</td>
<td>Unclear</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Tumour-related</strong></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>No</td>
</tr>
<tr>
<td>Grade</td>
<td>Unclear</td>
</tr>
<tr>
<td>Location</td>
<td>Unclear</td>
</tr>
<tr>
<td>Laterality</td>
<td>No</td>
</tr>
<tr>
<td>Size</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treatment-related</strong></td>
<td></td>
</tr>
<tr>
<td>Extent of resection</td>
<td>No</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>No</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Unclear</td>
</tr>
<tr>
<td>Steroid use</td>
<td>No</td>
</tr>
<tr>
<td>Antiepileptic drug use</td>
<td>No</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>Yes*</td>
</tr>
<tr>
<td>Survival</td>
<td>Unclear</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Not studied</td>
</tr>
<tr>
<td>Employment</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
5.3.6.2 Tumour-related variables

5.3.6.2.1 Histology

Among studies that enrolled small numbers of patients with brain tumours of different histological kinds (e.g. metastasis, pituitary tumour or meningioma), patients with glioma appeared to have a similar risk of depression as patients with other kinds of brain tumour. This was the case whether depression was measured as a continuous (D'Angelo et al. 2008; Hahn et al. 2003; Mainio et al. 2006a; Pelletier et al. 2002) or a dichotomous outcome. (Mainio et al. 2005a; Siegel et al. 2008) In studies eligible for this review, different brain tumour histologies therefore showed no particular association with depression.

5.3.6.2.2 WHO grade

In most studies (Anderson et al. 1999; Brown et al. 2006; Gathinji et al. 2009; Hahn et al. 2003; Irle et al. 1994; Litofsky et al. 2004; Mainio et al. 2005b; Pelletier et al. 2002), WHO tumour grade and depression were not associated. Patients with grade I tumours were found to have a statistically significantly lower frequency of depression in one study compared with patients with higher-grade tumours. (Arnold et al. 2008) However, in that study, the threshold for diagnosing depression was notably low (a PHQ-9 score of 6 or greater, compared to a usual PHQ-9 threshold of 10). Whether this association would have persisted using a higher threshold, with a greater severity of symptoms, is unclear. The lack of an association between tumour grade and depression in most studies should be interpreted cautiously because of the general lack of statistical power in comparisons of tumour grade subgroups. In addition, the largest studies examined the relationship between tumour grade and depression in HGG (WHO grades 3 and 4) only. (Brown et al. 2006; Gathinji et al. 2009; Litofsky et al. 2004) In most studies, the assessment of depression was either conducted around the time of neurosurgery or at a much later stage in the outpatient clinic. It is perhaps in the intervening period (c.1 - 3 months post-operatively) that tumour grade might particularly be expected to mediate differences in mood, as patients adjust to their different prognoses and treatment courses. Most studies that examined the relationship between depression and tumour grade did not assess patients at this potentially important time. Currently however there is no clear evidence that WHO glioma grade is associated with depression.

5.3.6.2.3 Lobe

Five studies found no association between tumours in the frontal lobe and depression. (Brown et al. 2006; Gathinji et al. 2009; Hahn et al. 2003; Litofsky et al. 2004; Mainio et al. 2005a) However, frontal
tumour location was independently associated with clinical depression in one study. (Wellisch et al. 2002) Studies that examine this relationship can be hard to compare directly because of differences in the method of classifying tumour location. It was variously recorded according to lobe, more specifically according to intra-lobe region, and less specifically according to anterior or posterior location in the brain. The most anatomically detailed study (which divided the frontal lobe into three areas) reported an association between postoperatively lowered mood and tumours in the “ventral frontal” lobe. Notably, the mood of patients classified as having “lateral frontal” and “all frontal” lobe involvement actually improved relative to preoperative measurements. (Irle et al. 1994) To date, no study has further examined the hypothesis that tumours in different regions of the frontal lobe may exhibit differential associations with depression. It remains possible that negative studies may have been insufficiently anatomically detailed to identify such an association. Currently, there is no consistent evidence that anatomical glioma location and depression are associated.

5.3.6.2.4 Laterality

In seven studies, hemispheric laterality of glioma was not associated with depression. (Armstrong et al. 2002; Arnold et al. 2008; Brown et al. 2006; D’Angelo et al. 2008; Hahn et al. 2003; Irle et al. 1994; Wellisch et al. 2002) One study reported an association between left-sided tumour and lower mood in female patients. (Pringle et al. 1999) Studies that analyse the association between depression and hemispheric tumour laterality need particularly careful interpretation. They are potentially biased if they exclude patients with severe language difficulties, as some did. (Armstrong et al. 2002a; Hahn et al. 2003; Irle et al. 1994; Pringle et al. 1999) Patients with profound language impairment may often have dominant/left- hemisphere tumours and may be more distressed at their wider range of disabilities. Other authors examining this relationship did not specify whether severely dysphasic patients were excluded or not. (Arnold et al. 2008; Brown et al. 2006; D’Angelo et al. 2008; Wellisch et al. 2002) Among the studies in this review however, depression was not more likely to occur in patients with left-sided glioma.

5.3.6.2.5 Size

Large tumours were associated with depression in two studies (Irle et al. 1994; Litořínský et al. 2004) but not in another study. (Hahn et al. 2003) Neither study that reported a positive association clearly stated its criteria for considering a tumour ‘large’. All three of these studies used differing methods of diagnosing depression in selected groups of generally well-functioning patients. The authors of one study hypothesised that tumour size and depression may show a stronger association for tumours in certain anatomically critical locations. (Irle et al. 1994) We found no studies exploring this hypothesis in more detail, however. There were also no data for LGG specifically. Tumour size is a possible risk factor for depression in glioma, but the current evidence is inconsistent.
5.3.6.3 Treatment-related variables

5.3.6.3.1 Extent of resection (EOR)

No study found an association between EOR and depression, whether depression was measured pre-operatively (Gathinji et al. 2009; Kilbride et al. 2007) or post-operatively. (Brown et al. 2006; Litofsky et al. 2004; Mainio et al. 2006a; Pringle et al. 1999) EOR was classified differently among the studies, with some comparing biopsy with any resection and others additionally distinguishing between partial and total resection. However it was recorded, there was no evidence associating EOR with depression in glioma among studies eligible for this review.

5.3.6.3.2 Radiotherapy

Treatment with cranial radiotherapy was not associated with depression, whether assessed pre-operatively (Mainio et al. 2005c) or post-operatively. (Brown et al. 2006; Gregor et al. 1996; Litofsky et al. 2004; Pelletier et al. 2002) No studies examined this relationship in patients with LGG, however. Associations between depression and separate radiotherapy schedules (e.g., radical/palliative) also remain to be studied in glioma. Additionally, the longer-term impact of any form of radiotherapy on depression in glioma is largely unknown. Only one small study recruited patients more than 1 year after the original glioma diagnosis (Gregor et al. 1996), and it found no association. The evidence currently suggests that cranial radiotherapy is not associated with depression in glioma patients; however, potentially important long-term consequences of radiotherapy with respect to depression are not well understood.

5.3.6.3.3 Chemotherapy

Treatment with chemotherapy was not associated with depression, whether depressive symptoms were measured before (Gathinji et al. 2009) or after surgery. (Hahn et al. 2003; Litofsky et al. 2004; Pelletier et al. 2002) Most studies examining this relationship were conducted before temozolomide became the standard chemotherapy for GBM. No studies examined the relationship between chemotherapy and depression in LGG. There is currently no evidence that chemotherapy per se is associated with depression in glioma, but studies specific for patients treated with temozolomide are lacking.
5.3.6.3.4 Corticosteroids

Although corticosteroids have been specifically implicated in reviews as a potential cause of depression in glioma (Litofsky and Resnick 2009; Pangilinan et al. 2007), there was little evidence for such an association either in patients with glioma in general (Pringle et al. 1999) or with HGG in particular. (Brown et al. 2006; Hahn et al. 2003; Litofsky et al. 2004) One large longitudinal study of patients with HGG reported a statistically significant univariate association between steroid prescription and depression at six months postoperatively. (Litofsky et al. 2004) In this study, the frequency of depression was 71.4% among patients taking steroids vs 44.3% among those who were not (p = 0.002). However, this analysis did not control for relevant confounding variables, including functional impairment. There were no data specific for patients with LGG. There is currently no consistent evidence that steroids are associated with depression in patients with glioma.

5.3.6.3.5 Antiepileptic drug use

Few studies have examined associations between antiepileptic drug (AED) use and depression in glioma. In those that have, prescription of AEDs was not associated with depression in the postoperative period, in patients with HGG (Brown et al. 2006; Hahn et al. 2003) or any grade of glioma. (Irle et al. 1994) Associations between AED use and depression were not studied specifically in patients with LGG, despite the much higher prevalence of epilepsy in this subgroup. (Rees 2002) This area deserves further study because AEDs have been associated with the onset of depression in other patient groups. (Reijs et al. 2004) Currently however, there is no evidence that AEDs are associated with depression in patients with glioma.

5.3.6.4 Outcome-related variables

5.3.6.4.1 Change over time

Two longitudinal studies found that depression levels in glioma patients generally declined during the first three months postoperatively. (Mainio et al. 2005a; Pringle et al. 1999) In one of them (Mainio et al. 2005a), depression continued to reduce statistically significantly throughout the entire year following tumour diagnosis in men (p = 0.047), but not in women. By contrast, other studies with a longer duration of follow-up studies (ranging between one and six years) observed increasing levels of depression over time. (Armstrong et al. 2002; D'Angelo et al. 2008) The single study with long-term follow-up data in LGG (albeit for just 6 out of 57 patients) reported that mean depression scores increased statistically significantly 4 - 6 years after baseline measurement (p < 0.02). (Armstrong et al. 2002a) The longitudinal course of depression cannot be determined from cross-sectional studies.
However, in cross-sectional studies, the duration since glioma diagnosis consistently was not associated with depression, regardless of whether sampling was perioperative (Irle et al. 1994) or during long-term follow-up. (Arnold et al. 2008; Hahn et al. 2003; Pelletier et al. 2002) Overall, longitudinal data suggest that patients’ depression levels do change over time, but the direction of change is inconsistent. It is possible that after a diagnosis of glioma, depression levels initially reduce in frequency and severity over several months, but increase thereafter. Longitudinal studies are needed to examine this hypothesis.

5.3.6.4.2 Survival

In a univariate analysis, physician-defined depression was associated with reduced survival in one large prospective study of patients with HGG. (Litofsky et al. 2004) Another large, retrospective study found depression to be an independent predictor of reduced survival in HGG. (Gathinji et al. 2009) Although the authors of the latter study controlled for several important survival-related confounders, they did not appear to control for radiotherapy dose. Higher levels of depression were associated with reduced 5- and 10-year survival in analyses of 16 patients with LGG. (Mainio et al. 2005b; Mainio et al. 2006b) These analyses controlled for some, but not all, relevant variables. Depression may be associated with reduced survival in glioma but existing research does not exclude a potential confounding effect of unmeasured variables. This important outcome remains to be studied further.

5.3.6.4.3 Quality of life (QOL)

Seven studies reported that depression was associated with reduced QOL in glioma (Fox et al. 2007; Giovagnoli et al. 1996; Giovagnoli 1999; Giovagnoli et al. 2005; Mainio et al. 2006a; Pelletier et al. 2002; Weitzner et al. 1995), and two found that it was not. (Brown et al. 2006; Janda et al. 2007) Another study observed that the relationship between depression and QOL may be mediated by functional status, cognitive function or patient sex. (Mainio et al. 2005a) There was not enough corroborative evidence to draw firm conclusions for patients with LGG or HGG specifically. However, in general, the balance of evidence suggests that depressed glioma patients have a reduced quality of life.

5.3.6.4.4 Complications

Few studies examined the association between depression and the frequency of medical complications in glioma patients. One group (Litofsky et al. 2004) found that depression was statistically significantly associated with deep vein thrombosis (DVT), and another group (Gathinji et al. 2009) reported that it was not. Depression was also associated with epileptic seizures, systemic infections
and adverse drug reactions in the only study to measure these outcomes. (Litofsky et al. 2004) The same study found no association with post-operative wound infections, contradicting a retrospective review which concluded that depression was independently associated with wound infection in HGG patients who had received Gliadel. (McGovern et al. 2003) The potential impact of depression on medical complication rates in LGG, and glioma patients as a whole has not been studied. Ultimately, associations between depression and any single medical complication were not independently corroborated by another study.

5.3.6.4.5 Employment

There was no data for patients with LGG regarding the association between depression and employment status, even although these patients may often return to work after surgery. Two studies that used similar scales to assess depression in patients with any grade of glioma reached different conclusions. Patients in the positive study were younger and in follow-up after primary treatment at the point of assessment for depression. (Pelletier et al. 2002) By contrast, the negative study analysed pre-operative, rather than postoperative depression and employment status. (Mainio et al. 2005a) The patients in these two studies therefore represent separate clinical groups that cannot easily be compared. Another study found that depression was independently associated with reduced work productivity among survivors of HGG. (Feuerstein et al. 2007) The bulk of the available evidence suggests that post-operative depression may be associated with reduced likelihood of returning to work.

5.3.6.5 Associations examined once in published literature

Factors that were found to be independently associated with depression in glioma in a single study include anxious personality traits (D'Angelo et al. 2008) and a family history of psychiatric illness. (Wellisch et al. 2002) Univariate associations were examined and found, in a single study, between depression and: somatising personality traits (Armstrong et al. 2002a), lower intelligence (Irle et al. 1994), multi-focal tumours (Litofsky et al. 2004) and having tumour recurrence. (Giovagnoli et al. 1996) A greater frequency of depression in the glioma patient was also associated with greater caregiver distress. (Sherwood et al. 2006) Variables that were not associated with depression in the single study to examine them included awareness of prognosis (Anderson et al. 1999), previous medical illness (Arnold et al. 2008), and rate of drop-out from a longitudinal study. (Walker et al. 2003)
5.3.7  **Depression treatment**

Few observational studies examined the treatment of depression in glioma patients. Where reported, antidepressants were prescribed in 6.0% – 16.8% of patients. (Armstrong et al. 2002a; Feuerstein et al. 2007; Hahn et al. 2003; Litofsky et al. 2004) Where depression prevalence and antidepressant prescription frequency were reported in the same study, antidepressants appeared to be under-prescribed. For example, in one study, 33% of patients were considered ‘depressed’ and 12% were prescribed antidepressants. (Armstrong et al. 2002a) In another study, 15% of patients were diagnosed with depression by their doctors, and 7% were taking antidepressants. (Litofsky et al. 2004) In one study, 41% of patients had symptoms of depression (Arnold et al. 2008), but only 26% were taking “psychiatric medication”. Concurrent antidepressant treatment was not associated with a reduced frequency of depression or improved QOL in one uncontrolled longitudinal study of a selected sample of patients. (Litofsky et al. 2004) No observational study reported outcomes of psychological treatments for depression in glioma.

5.3.8  **The ‘Super Seven’**

So far in this chapter, I have reviewed the evidence base broadly, without going into great detail about any individual study. For my thesis, some studies captured by this literature search are more important than others. The following section briefly reviews (in no specific order) the studies which I think stand out from the crowd: the ‘super seven’.

5.3.8.1  **Davies et al.**

Davies et al. conducted a descriptive cohort study of adults with histologically-diagnosed malignant cerebral glioma. They explored patients’ experiences following diagnosis using an unvalidated, semistructured qualitative interview. Participants were interviewed at three points: within three months following glioma diagnosis, after radiotherapy had finished, and following deterioration/recurrence. Relatives were also surveyed at these times.

Out of 105 eligible patients, 75 participated. Attrition was high and only 27 received the third interview. The main finding was that at the start of radiotherapy, only a quarter of patients were fully aware of prognosis, and that those with greater awareness were more distressed. Relatives were generally fully aware of the prognosis and were distressed more often still. The authors did not study depression specifically. At the first interview, six patients “seemed” severely depressed, but what happened to them over time was not reported.
Despite the lack of focus on depression, this study had several important strengths. It was a relatively large prospective cohort study. The addition of a qualitative component (e.g., extent of awareness) provided context for quantitative results (e.g., level of distress). Arguably this increased the clinical relevance of the manuscript: readers could apply qualitative data to individuals, and quantitative data to populations. The authors also laid equal emphasis on the experience of relatives. Most research on depression in glioma has focussed only on the patient. Davies et al. also attempted to couple interviews to clinical landmarks in the patient’s illness journey. This is increasingly common practice in palliative care research (Murray et al. 2007), but most longitudinal studies on depression in glioma interviewed patients at arbitrary time-points after diagnosis (e.g., 0, 3 and 6 months). (Armstrong et al. 2002a; D’Angelo et al. 2008; Litofsky et al. 2004; Mainio et al. 2005a)

However, the method of diagnosing depression appears to have been based on an un-validated interview. The study was not focussed on depression and therefore any conclusions that can be drawn with respect to depression in glioma are limited.

5.3.8.2 Armstrong et al.

Only one group has attempted to systematically examine the aetiology of depression in glioma. Armstrong et al. studied 57 adults with a histological or radiological diagnosis of supratentorial low-grade primary brain tumour, approximately six weeks after primary surgery.

The authors wanted to find out whether depression was neurological or psychological in origin. Neurological variables were: tumour type; tumour location; tumour size; extent of surgical resection, and cognitive function. Psychological variables were measures of the extent of: denial; the use of psychological defences; hypochondriasis; hysteria, and fatigue. Depressive symptoms were measured with the Minnesota Multiphasic Personality Inventory (MMPI). Linear regression was used to identify variables associated with greater depressive symptoms. Increasing fatigue, posterior tumour location and a greater extent of surgery were the only variables to show a statistically significant independent association with depression.

This study was, however, too small to stand a reasonable chance of reliably answering its question. In For example, unmeasured but potentially relevant factors included serotonin gene polymorphisms, prior depression, family history of depression, presence of epilepsy, awareness of prognosis, neuroticism, coping strategies other than denial, and drug or alcohol use. A huge sample would have been required to control properly for so many variables. In addition, the MMPI was not necessarily the best measure of depression, being designed principally to measure personality characteristics.
I think the importance of this study lies primarily in its novelty. The basic model (to group variables into different conceptual categories and see which category best predicts depression) lends itself to an iterative process of repeated study and experimentation. It is also one of the few studies of depression in low-grade glioma specifically.

5.3.8.3 Litofsky et al.

Litofsky et al. analysed data from 598 American patients with histologically-proven high-grade glioma who were enrolled into the multicentre Glioma Outcomes Project (GOP) between 1997 and 2000. The primary aim of the GOP was to study factors associated with survival in glioma. During data collection however, the presence or absence of depression had been recorded prospectively on the study form. Analysing the main study, the authors noted depression to be a common complicating factor and subsequently conducted a series of post-hoc analyses.

Patients were assessed immediately postoperatively, and again at three and six months after surgery. Depression was diagnosed by any of three methods: patient report (Short Form-36 Mental Health score of < 62); another method of patient report (answering “yes” to any of three verbal screening questions); and the report of the patient’s treating physician (who recorded the presence of depression on the study form, having been “instructed to use DSM-IV criteria” to assess mood).

Patient-reported and physician-reported depression differed wildly (> 90% of patients meeting self-report criteria compared to < 23% of physicians diagnosing depression at all time points). Physician-reported depression was associated with statistically significantly shorter median survival time (34.0 weeks in depressed patients vs. 41.1 weeks in patients without clinical depression, p < 0.01), and with reduced quality of life. Antidepressants often were not prescribed. In patients who received them, treatment with antidepressants was not observed to alter quality of life or survival.

There were a number of significant methodological limitations to this study. Depression was not the primary outcome. The paper was based on a retrospective analysis of data, collected on forms which were not designed specifically to address questions regarding depression. Diagnostic interviews were probably not standardised. Patients were diagnosed by their own (i.e. many different) physicians. These things would tend to limit internal validity of the study.

In my opinion, the biggest problem was that patients were not consecutively enrolled. It was a huge 57-centre study and although enrolment rates varied between centres, most patients were not recruited. To illustrate, the 4th most prolific enrolling centre enrolled only 15% of their total eligible patients.
Selection bias affects external validity, limiting the generalisability of study results to routine clinical practice.

However this study remains the largest prospective cohort study yet conducted of depression in glioma. It is a wide-ranging and ground-breaking study of depression prevalence, associations, and impact on other outcomes in glioma. Its value lies particularly in demonstrating clearly that depression is a frequent and important complication of glioma.

5.3.8.4 Wellisch et al.

The authors of this cross-sectional American study analysed data from 89 adults with a primary brain tumour. Their multidisciplinary neuro-oncology clinic model appears to have referred all patients to the team psychiatrist routinely. Consecutive patients were therefore sampled once, at varying stages in their disease journey. Major depression was diagnosed using a structured clinical interview. Logistic regression was used to identify variables associated significantly with MDD.

The prevalence of MDD was 28%. Independent associations were observed with: co-occurring sadness and anhedonia; a positive family psychiatric history; and tumour located solely within the frontal lobe.

The population studied was heterogenous in respect to timing of sampling and tumour type. Although the authors state that the sample was unselected, they did not specify that every single consecutive patient was referred to the team psychiatrist. I would have preferred a clear statement that every consecutive patient was approached, agreed to participate, and to see a psychiatrist. The diagnosing psychiatrist was also part of the research team that hypothesised the increased incidence of depression, introducing the possibility of observer bias. Although alternative diagnoses were “carefully differentiated” between, the authors did not specify how such a difficult decision was made. Estimates of precision (e.g. confidence intervals) were not presented.

This is an important study, being the only one to diagnose depression in glioma using a structured interview and DSM-IV criteria. The involvement of a psychiatrist benefited the research, leading to relatively detailed analyses of depressive symptoms.
5.3.8.5 The Mainio series

In the early 1990s, a Finnish PhD student conducted a prospective cohort study in 77 adults with a histological diagnosis of primary brain tumour. The results of this study were subsequently presented in a number of separate papers, four of which reported depression-related outcomes. Others report data on brain tumour-related anxiety (Mainio et al. 2003) and obsessionality. (Mainio et al. 2005b)

Depressive symptoms were measured using the Beck Depression Inventory (BDI) and were presented either as categorical outcomes (“depression” being present with a BDI score 10+) or as continuous scale score data. Patients were sampled pre-operatively, then again three months and one year after surgery. Follow-up was good and 62/77 patients completed the study protocol. This partially reflected the histological diagnoses, which were mainly of meningioma and LGG.

The authors examined whether depressive symptoms were associated with reduced survival in glioma. In the main paper to address this issue, depression was found to be associated with a statistically significantly reduction in median survival among the subgroup of 16 patients with LGG. Of six patients with pre-operative depression, only two survived to 60 months, compared to nine of 10 patients without baseline depression. (Mainio et al. 2005c) They had appropriately adjusted Kaplan-Meier survival curves for patient age (a prognostic variable for survival in LGG). (Pignatti et al. 2002) However they also adjusted for patient sex and employment status, which are not known to be associated with survival in patients with LGG. Correcting for them was unnecessary. The authors did not control for location of tumour and extent of resection, despite both variables being associated with survival time in their own cohort.

In the second of their papers to examine survival, this time after 10 years of follow-up, the authors controlled appropriately for age and tumour laterality. (Mainio 2006b) However they again controlled for patient sex, and for no other prognostic variable.

These two studies therefore identified a possible association between depression and shortened survival in LGG – but with residual confounding, and further research is needed.

The other papers in this series showed that supra-threshold depressive symptoms were associated, in univariate analyses, with reduced functional status and a prior history of depression (Mainio et al. 2005a) and reduced quality of life, particularly in women. (Mainio et al. 2006a)

The strengths of the Mainio series include: its longitudinal study design; incorporating pre-operative assessment (relatively rare in this literature); good 12-month follow-up; and considerable output in terms of the number of papers produced from the data. The main weaknesses are: the reliance on a
self-report depression scale to diagnose depressive symptoms; confounding of analyses; and small subgroup sizes. To an extent, I experienced a sense that some of the publications could have been combined in a single paper.

5.3.8.6 Gathinji et al

Gathinji et al. also studied the impact of depression on survival. They retrospectively reviewed the clinical records of 1052 patients with HGG. They compared the survival of patients with a pre-operative clinical diagnosis of depression against those with no depression pre-operatively. Depression was recorded as present if the patient had been “medicated and diagnosed… by their primary care or psychiatric physicians prior to surgery”.

The authors controlled for several relevant variables including: age; functional status; WHO grade; and chemotherapy. Pre-operative depression was associated with increased mortality (RR = 1.4, 95%CI 1.1 - 1.9). This effect only became statistically significant after 12 months post-operatively, however.

Unfortunately Gathinji et al. didn’t control for radiotherapy, which is the treatment associated with the biggest survival effect in glioma. (Rampling et al. 2004) The multivariable analysis could therefore have been confounded by different treatment schedules. Retrospective case-note reviews are also prone to selection bias. If clinical note-keeping was at all imperfect, some depressed patients could have been counted as non-depressed.

This paper was the first to suggest that any adverse effect of depression upon survival in HGG may only become apparent after a year. This possibility highlights the importance of ensuring long follow-up in future studies examining an association between depression and survival in glioma.

5.3.8.7 Irle et al

Irle et al. conducted a prospective study to examine the relationship between tumour location and emotional state in 141 primary brain tumour patients, before and shortly after surgery. Patients’ scores were compared with two control groups. Depressive symptoms were measured using a German questionnaire (a list of 123 adjectives constituting the following factors: vigour; fatigue; extraversion; anger; and 'anxiety/depression').
This is a notable study in part because of how the authors constructed the ‘tumour location’ variable. Most researchers, before and since, have simply recorded the individually affected lobes (e.g., frontal, temporal, parietal, occipital and other). Irle et al. recorded detailed inter- and intra-lobe categories (e.g., ventral frontal and lateral frontal / fronto-parietal and fronto-temporal, etc).

The authors found that depression scores increased post-operatively, in patients with a tumour in the ‘ventral frontal’ lobe or the ‘temporo-parietal’ area. In all the other glioma patient groups, mean depression scores reduced post-operatively in most patients. The increases in the ‘ventral frontal’ and ‘temporoparietal’ groups were statistically no different to the changes observed in two separate control groups. This pattern of results suggested that brain tumour surgery to the ventral frontal or temporo-parietal areas could inhibit the rate of resolution of depressive symptoms, relative to lesions in other brain areas.

The major limitation to these results was the small size of subgroup samples, and the study can be regarded only as a pilot.

The strength of this study lies in its innovative approach. Emotional neuronal networks are thought not to be restricted to individual lobes. (Cummings and Bogousslavsky 2000) Irle et al. demonstrate one way of studying the association between tumour location and depressive symptoms with greater sensitivity.

5.3.9 Quality of study reporting

Returning to the general literature, I found that the quality of study reporting varied considerably compared with the STROBE guidelines. The extent of selection bias was often unclear because many authors did not state the total number of patients who had been approached to participate in their study. (Armstrong et al. 2002a; Armstrong et al. 2002b; Arnold et al. 2008; Brown et al. 2006; Chang et al. 2003; Diaz et al. 2009; Feuerstein et al. 2007; Grant et al. 1994; Hahn et al. 2003; Kaplan and Miner 2000; Litofsky et al. 2004; Mainio et al. 2005a; Mainio et al. 2005c; Mainio et al. 2006a; Mainio et al. 2006b; Pringle et al. 1999; Sherwood et al. 2006; Walker et al. 2003; Zbinden et al. 2006) It is likely that some patients who were asked to participate refused, given that only three of the 16 studies reporting this information achieved 100% recruitment. (Steinbach et al. 2006; Taphoorn et al. 1992; Wellisch et al. 2002) Many studies did not formally state the exclusion criteria. (Anderson et al. 1999; Brown et al. 2006; Chang et al. 2003; Feuerstein et al. 2007; Grant et al. 1994; Gregor et al. 1996; Janda et al. 2007; Kaplan and Miner 2000; Litofsky et al. 2004; Steinbach et al. 2006; Wellisch et al. 2002; Zbinden et al. 2006) Although some studies may have included all patients by default, many others excluded patients with severe cognitive impairment and/or dysphasia. (Armstrong et al. 2002a; Armstrong et al.
Among the eligible studies, elements of the statistical analyses were often unsatisfactory. Most of the larger studies did not provide power calculations, or correct for multiple statistical tests. (Arnold et al. 2008; Gathinji et al. 2009; Irlé et al. 1994; Litofsky et al. 2004; Mainio et al. 2006a) In some studies, multiple regression analysis was used to provide confounder-adjusted estimates. Ordinarily this approach would be beneficial, but in an underpowered study it could increase the risk of a false-positive result. It has been estimated that each variable included in a multivariable model requires a minimum of 10 case patients (i.e., 10 patients with depression). (Peduzzi et al. 1996), Based on this rough ‘rule of thumb’, some studies appear to have conducted multiple regression analysis using a larger number of variables than was appropriate. (McGovern et al. 2003; Wellisch et al. 2002) Other authors limited their use of multiple regression analysis for precisely this reason. (Giovagnoli et al. 1996)

Occasionally, studies also highlighted results which had a high likelihood of occurring by chance. Although not strictly inaccurate, a casual reader could mistakenly infer significance from these statements. For example (our italics), one states: “…married patients reported a higher incidence of depressive symptoms (44% versus 25% of single individuals).” (Kaplan and Miner 2000) Another states: “Among patients with an anteriorly located tumour the mean depression score before surgery was greater compared with those harbouring a posterior tumour”. (Mainio et al. 2005a) A review notes: “In the Glioma Outcomes Project, patients were more likely to be depressed if the patient had a stereotactic biopsy instead of a gross total resection”, and discussed possible mechanisms for this. (Litofsky and Resnick 2009) Closer inspection of the data showed that none of these findings were statistically significant.
The STROBE guidelines were published in 2007, after many of the studies eligible for this review. My main aim in highlighting shortfalls in the quality of study reporting is to identify areas that were commonly overlooked in previous studies, and to guide the design and reporting of future research in this area. It would be particularly useful for authors to state clearly the total number of patients who were eligible and approached, to record exclusion criteria, and to present estimates of precision (e.g., 95% confidence intervals) where appropriate. Authors of future studies should consider performing sensitivity analyses to examine the stability of their results. Large sample sizes may be needed to control for the multiple confounding variables present in this population of patients.

5.4 Discussion

5.4.1 Main findings

Most observational studies of depression in adults with glioma were small, cross-sectional and/or retrospective. Among the instruments used to screen for depression, the BDI appeared to inflate depression frequency compared with clinical interview. The HADS may be a better choice as an initial screening instrument. Clinically diagnosable depression occurred in roughly 15% of glioma patients, among whom clinicians should anticipate this frequency of psychological morbidity. Depression was consistently associated with functional impairment, cognitive dysfunction and reduced quality of life. Depression was also associated with reduced survival, but the studies of this important association had methodological flaws. Evidence for other associations was contradictory or absent. Few studies conducted multivariable analyses. The quality of study reporting was variable, which limited comparability and generalisability of the findings.

5.4.2 Limitations of the review

These conclusions should be considered in light of potential limitations of this review. There was a risk of selection bias in included studies because I excluded non-English language papers, and studies of depression in children with glioma. The search strategy was relatively insensitive for palliative care populations because I deliberately excluded studies in which glioma patients constituted only a small proportion of the total sample. Therefore, the results are probably less representative of the terminal phase of the illness. I also excluded studies that recruited patients with a primary brain tumour, if the number of patients with glioma was not stated. Although I took these steps to improve the specificity of our results to glioma, some glioma-specific data may have been excluded as a result. Included studies were generally biased towards young patients with reasonable cognitive and physical function.
The results of this review therefore apply more to these clinical groups. Despite considerable efforts, it was often difficult to directly compare results from different studies. The findings represent my interpretation of the balance of the current evidence.

5.4.3 Results in context

Many different methods of diagnosing depression in glioma were identified in this review. To my knowledge, no depression rating scale has yet been validated for use in glioma patients. Studies that used the BDI and PHQ-9 reported a clinically significantly higher prevalence of depression than those that used the HADS. The HADS is designed to minimise confounding from somatic symptoms of depression, such as changes in appetite and sleep. I recognise that some caution is needed in comparing results drawn from different patient samples. The PHQ-9 was also only used in one study, at a low and possibly non-specific threshold. Nevertheless existing data suggest that the HADS may be the more accurate initial depression screening instrument in glioma, perhaps partly because it largely excludes somatic items. When initially screening glioma patients for depression, I suggest using the HADS (Depression Subscale). This scale has been criticised for having poor receiver operating characteristics in palliative care populations. (Lloyd-Williams 2001) It can also be difficult to use in patients with hemiparesis, hemianopia, neglect or dysphasia. However it was the most widely-used individual depression rating scale among studies included in this review, increasing the chance of comparability of data with previous studies, and identified suprathreshold levels of depressive symptoms with roughly the same frequency as clinical interview.

This review also illustrates the potential impact of depression on the lives of glioma patients. Positive associations between depression and reduced quality of life, functional and cognitive impairment, carer distress and reduced likelihood of returning to work reinforce the importance of identifying and treating depression in adults with glioma. Although depression is associated with reduced survival in patients with systemic cancers (Satin 2009), an association between depression and survival in glioma is less clear. Partly this is because studies of this relationship are scarce, and partly because of inadequate controlling for important prognostic variables. However, such an association cannot be excluded and may exist based on the available evidence. Detecting differences in survival in such a naturally aggressive disease as glioma may require large sample sizes. Both studies reporting increased mortality with depression in HGG to date recruited over 500 patients. (Gathinji et al. 2009; Litofsky et al. 2004)

The absence of strong associations between depression and other variables (including tumour location, histology and EOR) implies that depression in glioma is primarily a psychological mediated response to losses, including the loss of health. However, this review does not exclude the possibility that
tumour-related factors play an indirect role in the aetiology of glioma-associated depression, for several reasons. First, many associations have been studied too infrequently to draw firm conclusions. Second, existing studies are difficult to compare reliably. Third, lobe-based analysis of tumour location, in particular, is a crude measure. Neural circuits thought to be involved in mood regulation cross multiple anatomical boundaries. (Grafman and Warden 2000) A shift in emphasis toward the examination of the impact of brain tumours on functional neuroanatomical networks has been proposed and deserves to be studied. (Irle et al. 1994) It is important to recognise that the impact of tumour biology on the pathogenesis of depressive and other emotional responses to glioma diagnosis remains largely unknown.

This review may help to educate clinicians about various aspects of depression in glioma. Awareness that men, older patients and those with low-grade glioma appear to have an equal risk of experiencing depression may improve screening and recognition rates. Wherever possible, authors of future observational studies of depression in glioma should follow the STROBE guidelines when reporting their findings. Coupled with the peer review process, these measures may improve the quality of reporting and facilitate comparisons among studies. To this end, variables that may benefit from clear definition include marital status, past psychiatric history, physical function, cognitive function, race and ethnicity, tumour lobe, tumour histology, tumour size, EOR, radiotherapy, chemotherapy, steroids, epilepsy, QOL and medical complications.

5.5 Chapter summary

In this chapter I described a thorough systematic review of observational research studies of depression in adults with glioma. Key findings were that the current literature is of low quality and an introduction of the possibility of using the HADS as a preferred screening instrument. These provide some context for the original research study presented from Chapter 7 onwards.

Before describing that study, I would like to turn to the issue of depression treatment. Presenting some of my work at patient and brain tumour charity conferences has reinforced that patients and carers often ask: “How should depression in glioma be treated?”
6 Pharmacological treatment of depression in patients with a primary brain tumour

In this chapter I set out to discover whether any drugs are proven to be effective, or cause significant side-effects, when prescribed to treat depression in patients with brain tumours. Non-pharmacological treatments for depression (e.g. psychotherapy) are not covered in this review. The chapter focuses on brain tumours in general, but the conclusions are applicable to glioma. Its content contributed to a Cochrane review. (Rooney and Grant 2010)

6.1 Introduction

In Chapter 5, I showed that depressive symptoms are common among glioma patients. Depression can have important consequences for the affected person. If depression in brain tumour patients could be effectively treated, personal or family suffering could potentially be reduced.

In Chapter 2, I noted that antidepressants are an effective treatment for depression in a number of clinical populations. However it is possible that the side-effects of antidepressants outweigh any benefit for the specific population of brain tumour patients. Antidepressants may lower seizure threshold (Gross et al. 2000), impair memory (Peretti et al. 2000) or cause fatigue. (Cassano and Fava 2004) Patients with primary brain tumours are already at high risk of these complications. The question as to whether the benefit of antidepressants outweighs the risk, in these patients, is clinically relevant. (Rooney and Grant 2010)

Yet despite uncertainty, the effectiveness and risks of pharmacotherapy for depression in primary brain tumours has not previously been systematically reviewed. The aim of this chapter is therefore to determine the evidence for the benefit and harm of pharmacological treatment of depression in patients with a primary brain tumour.

6.2 Methods

6.2.1 Inclusion / exclusion criteria

For evidence of benefit (efficacy), only randomised controlled trials (RCTs) were eligible. Evidence of harm (adverse effects) was sought from RCTs, non-randomised controlled studies, cohort studies and case-control studies.
Eligible studies were those recruiting adults (aged 18 and over), with a histological diagnosis of any primary brain tumour, being treated for a co-morbid baseline diagnosis of depression. Depression could be diagnosed by any validated method satisfying the original trial authors that pharmacological treatment of depression was reasonable and necessary. Studies recruiting only patients with metastatic (i.e., non-primary) brain tumour, or those administering only unlicensed herbal remedies (e.g. St. John's Wort) were excluded.

I tried to find all published and unpublished studies in any language. Any category of prescription drug was eligible, if prescribed to treat depression.

### 6.2.2 Outcome variables

The primary outcome was change in depression at final follow-up. This could be measured in several different ways. The outcome variable could be: the mean change in depression scale score; the proportion of patients meeting pre-defined criteria for improvement in scale score; or changes in the proportion of patients with a categorical diagnosis of depression (i.e., depression 'present' or 'absent').

Secondary outcomes were quality of life, general emotional distress and the length of time from diagnosis of brain tumour to death.

Antidepressants have many potential adverse effects (BNF 2008). I aimed to study those which might be most likely in brain tumour patients. These were: epileptic seizures (seizure frequency measured by patient or carer report); cognitive dysfunction (e.g. poor memory, if measured by validated neuropsychological testing), and; fatigue (if measured by a validated rating scale).

### 6.2.3 Search methods for identification of studies

I searched The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2009, MEDLINE (1950 to July 2009), EMBASE (1980 to July 2009), PsycINFO, the British Nursing Index, LILACS, Psyndex, the NHS National Research Register, the NHS Centre for Reviews and Disseminations’ Database of Abstracts of Reviews of Effectiveness (DARE) and Web of Knowledge (covering Science Scisearch, Social Sciences Citation Index and Biological Abstracts) up to July 2009. Indexing terms varied so I constructed individual search strategies for each database (Appendix 1).
I completed the online Cochrane Collaboration handsearching course, then handsearched the following journals published in the last 10 years: the Journal of Neurology, Neurosurgery and Psychiatry; the Journal of Neuro-Oncology; the Journal of Clinical Oncology, and Neuro-Oncology. I also searched Proquest Dissertations & Theses, the System for Information on Grey Literature (SIGLE) and conference abstracts in the handsearched journals.

With the help of a senior medical student (Mr. Aidan McIvor) I contacted pharmaceutical companies manufacturing all antidepressants listed in the British National Formulary (BNF); the International Network of Agencies for HTA (INAHTA) and the British Library Document Supply Centre (BLDSC).

A supervisor (RG) and I initially, independently, filtered studies based on scrutiny of the title and abstract. Full copies of potentially relevant studies were obtained and we independently assessed these for eligibility. We conferred with a statistician in the Cochrane Gynaecological Cancers Group for a third opinion on the final list.

6.2.4 Data extraction and management

I planned to extract data independently from eligible studies using a form. For the categorical outcome of depression I aimed to abstract the number of depressed patients in each arm at final follow-up in order to estimate relative risk (RR). For continuous outcomes I aimed to abstract the mean and standard deviation of the outcome of interest in each arm at final follow-up.

I aimed to estimate from the means and standard deviations whether the data were skewed: if they were I planned to write to authors requesting the mean and standard deviations of log transformed data.

For time-to-death data I aimed to abstract the hazard ratio (HR) and its variance from trial reports. If these were not presented I would attempt either to estimate them, or abstract relevant data from Kaplan-Meier survival curves, and failing this to estimate RR as outlined above.

Where possible participants were to be analysed in the groups to which they were randomised, regardless of the treatment they actually received. I planned to enter eligible data into RevMan using the duplicate entry facility.
6.2.5 **Assessment of risk of bias in included studies**

I aimed to code the randomisation of participants to intervention groups as either: adequate (e.g. a computer-generated random sequence or a table of random numbers); quasi-randomised (e.g. date of birth, clinic id-number or surname), or; unclear (e.g. not reported).

I would code allocation concealment from treatment providers and participants as: adequate (e.g. where the allocation sequence could not be foretold); unclear (e.g. not reported); inadequate (e.g. the computer-generated random sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope), or; not used.

I aimed to code the blinding of participants, treatment providers and outcome assessors (Yes, No or Unclear). I aimed to record the number of participants in each intervention arm whose outcomes were not reported at the end of the study, noting whether loss to follow-up was reported. Controlled non-randomised studies were to be similarly assessed, with analysis of baseline comparability of treatment and comparison groups, and whether analysis was adjusted for potential confounding factors. If as a result of these assessments a study was considered likely to be biased it would be exclude it from the meta-analysis.

6.2.6 **Statistical plan**

When summarising the categorical depression outcome I aimed to calculate relative risk (RR). When comparing continuous outcome data from studies using different rating scales I aimed to use the standardised mean difference (SMD); for studies using the same scale I aimed to calculate the weighted mean difference (WMD).

I aimed to use random effects models for all meta-analyses. If treatment effects were thought not to be sampled from a symmetric distribution (an assumption of the random effects model), I would use a fixed effects model to conduct further meta-analyses. Missing measures of uncertainty (for example confidence intervals and standard deviations) were to be calculated where possible, or the study authors contacted to request their data. I did not plan to impute missing data.

I aimed to calculate statistical heterogeneity using the $I^2$ statistic, taking an $I^2$ value of $> 50\%$ as evidence of substantial heterogeneity (and a meta-analysis not in this case being performed). I aimed to examine funnel plots corresponding to the primary outcome. I aimed to conduct sub-group analysis
by antidepressant class, tumour histology and WHO grade of tumour, and sensitivity analyses by
excluding studies which did not report adequate (i) concealment of allocation or (ii) blinding of the
outcome assessor.

6.3 Results

No studies were eligible for the Cochrane Review. Nonetheless others have previously described, to
some extent, the effects of pharmacotherapy for depression in adults with a brain tumour. These
studies were excluded from the full Review because of methodological weaknesses. I will briefly
summarise them for this thesis.

Meyers et al. conducted a prospective cohort study of 30 adults with malignant glioma who had
clinically significant neuro-behavioural slowing. The mean duration since glioma diagnosis among
participants in this study was 46 months. The authors prescribed the psychostimulant Methylphenidate
in an initial dose of 10mg daily, increasing as required and tolerated. The primary outcome was
cognitive functioning. Depressive symptoms were also measured using the BDI, at baseline and at
least one follow-up point. Concurrent major depression was an exclusion criterion. At baseline, the
mean BDI score among participants was 12.8/63. Mean BDI scores remained statistically similar post-
Methylphenidate. There was a tendency (t test p < 0.1) for reduced depressive symptoms in those
patients taking 20mg Methylphenidate daily. (Meyers et al. 1998)

This study was the first systematic evaluation of the effect of any psychotropic medication on
depressive symptoms in glioma. However there were considerable limitations including the potential
for selection bias, small sample size, lack of a control group and lack of clarity over the timing of
follow-up. I also think that the use of matched sample t-tests to compare differences between baseline
and follow-up depression was inappropriate. With a small sample and ordinal data, a non-parametric
test would have been a better choice. The assumptions of the parametric test may not have been met,
invalidating the statistical analysis. The change in BDI score, in this sample, was of doubtful clinical
significance. Because patients with clinical depression were excluded, the results cannot really be
generalised to the wider population of depressed glioma patients in any case.

Another American group studied the effect of a different psychostimulant (Modafinil). Details about
study methodology and results are limited because the research has so far been presented only as a
conference abstract. All participants (n = 30) were adults with glioma, and moderate to severe
cognitive impairment and/or fatigue. The authors randomised them to receive either 200mg or 400mg
Modafinil per day, in a double blind method. Depressive symptoms were measured using the
Hamilton Depression Rating Scale (HDRS, an observer-rated scale) at baseline, then eight and twelve
weeks later. The authors reported that HDRS score reduced significantly at follow-up. (Wellisch et al. 2006) The authors did not present data on the magnitude of any changes, nor which dose of Modafinil (if either) was more effective. The abstract does not detail whether patients were depressed at baseline, or the mean HDRS score of the sample. I attempted but was unable to contact the authors for clarification. It is therefore not yet possible to fully evaluate their findings.

One team reported results of a prospective open-label study of Donepezil in 24 adults with a primary brain tumour, in a period of stable disease following previous cranial radiotherapy. Donepezil, an acetylcholinesterase inhibitor, was given in a dose of 5mg per day, increasing if tolerated to 10mg per day after 18 weeks. The primary outcome was change in cognitive impairment at 24 weeks. Depressive symptoms were measured using the Profile of Mood States Questionnaire (POMS, a patient-rated adjective checklist). At 24 weeks, the mean depression score of the cohort was statistically similar to the mean score at baseline. (Shaw et al. 2006) As with other studies, the authors chose not to restrict eligibility to depressed brain tumour patients. This means that these results do not necessarily apply to depressed glioma patients in clinical practice.

Litovsky et al. conducted a longitudinal cohort study of adults with high-grade glioma and reported depression prevalence and the frequency of antidepressant prescription (see Chapter 5). These authors observed that antidepressant prescription was not associated with a difference in frequency of depression being diagnosed. However, they did not systematically prescribe treatment for depression and did not limit participation to patients with depression. (Litofsky et al. 2004)

One study was only published in Russian. I had the abstract translated by the Cochrane Collaboration. The authors studied a cohort of 225 patients following operation for brain tumour. They assessed the influence of different antidepressants on the post-operative normalization of mood. The authors concluded that there was some evidence to support prescribing trazodone, tianeptin, or sertraline for depression. However again, participation in this study was not limited to depressed patients. It is also difficult to fully evaluate the authors’ conclusions because the methods section was not translated. Relevant information may well have been missed by relying on an abstract translation. (Koval'chuk 2007)

With regard to adverse effects, Rabey reported the cases of three patients with a developing, but initially occult, cerebellar brain tumour. Each had first presented with a main complaint of low mood or apathy, combined with mild symptoms of nausea, dizziness, instability or headache. Each was initially diagnosed as suffering from depression and commenced on Amitriptyline (dose range 75 - 100mg/day). In each case, the patient re-presented four or five days later with ataxia, nystagmus and/or intention tremor at which point their cerebellar tumour was diagnosed. Each patient died shortly after surgery. The authors did not state whether Amitriptyline had been discontinued pre-operatively. The authors concluded that in patients with a posterior fossa brain tumour, Amitriptyline
may cause cerebellar symptoms and signs to worsen. (Rabey and Avrahami 1985) In this collection of case studies causality was not proven, however. A case-control study would be a useful next step to examine this interesting hypothesis.

Other RCTs of antidepressants in mixed-site cancer patients have enrolled a small number of brain tumour patients. One was an open-label phase II trial of an antidepressant (Bupropion) on fatigue in mixed cancer patients including brain tumour, which also measured levels of depression. Participation was restricted to patients with severe fatigue rather than severe depression. (Moss et al. 2006) Another RCT compared Paroxetine with placebo in a population of mixed cancer patients, including patients with a brain tumour. Although depression was measured as an outcome, the intervention was given primarily to treat fatigue and once again participation was not restricted to depressed patients. In addition, data for the small number of patients with brain tumours were not reported separately. (Morrow et al. 2003)

In summary, existing studies of the efficacy of medication on depression in adults with glioma are few in number, have used different medicines and different outcome scales, and have generally regarded depression as a secondary outcome. Most importantly, none have restricted study entry to include only patients who are clinically depressed. This failure limits the generalisability of the results of these studies to depressed glioma patients.

Risk of bias and the beneficial and adverse effects of any intervention could not be assessed, because no eligible studies were found.

6.4 Discussion

In this systematic review, I found no eligible randomised controlled trials, controlled trials, cohort studies or case-control studies of the pharmacological treatment of depression in patients with primary brain tumours. Two RCTs, three Phase II trials and two cohort studies examined aspects of drug treatment of symptoms (including depressive symptoms) in brain tumour patients, but participation in all cases was open to depressed and non-depressed patients alike. The results of these studies therefore cannot be applied directly to the population of depressed brain tumour patients that is the focus of this review. The lack of evidence is an important finding because as I argued in Chapter 5, depression is a common complication of brain tumour, with serious consequences for quality of life and possibly survival. Doctors need to know how to treat it.

The search strategy was not designed to identify 'qualitative' research studies describing the individual's experience of having a brain tumour. Results from RCTs and other 'quantitative' study
designs provide information about the "average" response to treatment, but may not easily be applied to individual patients. Although the search strategy was thorough for antidepressants, it may have missed studies of other pharmacological agents, such as psychostimulants or acetylcholinesterase inhibitors. Searches on the foreign language databases (LILACS and Psynex) were limited mainly to English language terms. English translations of abstracts are often included in these databases so it is possible but unlikely that we missed important relevant studies. I assumed that the lack of reply from any drug companies is indeed because they have not studied this issue.

Other non-systematic reviews of depression in brain tumours also note a lack of high-quality evidence for its treatment. (Litofsky and Resnick 2009; Pangilinan et al. 2007; Price et al. 2008; Weitzner 1999)

National guidelines for the treatment of depression cannot have been based on high-quality evidence specific to brain tumours. Antidepressants appear to be effective in patients with other medical illnesses but their effectiveness in patients with a brain tumour should not be assumed. Brain tumours are unlike many other illnesses: rapidly progressive, biologically active and with significant structural and functional effects upon the very organ primarily implicated in depression. Brain tumours (and their surgical treatment) have been hypothesised to disrupt neuronal circuits crucial to the experience of emotion (Grafman and Warden 2000; Irle et al. 1994; Litofsky and Resnick 2009) or else alter local levels of biochemical mediators. (Mainio et al. 2005a) Anti-epileptic drugs can affect the bioavailability of antidepressants (Salzberg and Vajda 2001), and corticosteroids are well-known to have potential psychiatric side effects. (BNF 2008; Warrington and Bostwick 2006) There are good reasons to be cautious about assuming that antidepressants are effective in brain tumour patients.

Brain cancer is also associated with epilepsy, cognitive dysfunction and fatigue, which are in turn recognised side-effects of antidepressants. (BNF 2008) It is important to highlight the lack of evidence about the possible adverse effects of antidepressants in these high-risk patients. Alternatively, antidepressants could improve these outcomes since depression has been associated itself with epilepsy (Hesdorffer et al. 2000; Hesdorffer et al. 2006), impaired cognition (Stefanova et al. 2006) and fatigue. (Cassano and Fava 2004; Moss et al. 2006)

Three low-quality studies used a pharmacological agent other than an antidepressant. These drugs could help treat a wider range of symptoms than antidepressants. To date however, no studies have primarily evaluated the benefit, or harm, of pharmacological treatment of depression in patients with a primary brain tumour. Direct study of this question requires that eligibility is restricted to patients with high levels of depression at baseline.
6.5 Chapter summary

In this chapter I reported the results of an exhaustive literature search, discovering that there is no good evidence base to guide the treatment of depression in adults with glioma. Best practice would suggest that doctors treating depressed brain tumour patients discuss the lack of evidence with the patient, document their views and use their clinical judgement. If drug treatment is started, close follow-up may help detect any adverse effects. Future prospective studies addressing the risks and benefits of antidepressants, and randomised controlled trials are vital.

The three systematic reviews presented in Chapters 4, 5 and 6 have summarised our current knowledge of DT-defined emotional distress in adults with cancer, and observational and interventional studies of depression in adults with glioma. In the remainder of the thesis I will report the design, conduct and results of a prospective study of depression and emotional distress in adults with glioma.
7 Main study methodology and recruitment results

7.1 Introduction

In preceding chapters I introduced the topics of glioma and depression, and examined the existing literature on distress and depression in adults with glioma. Methodologically:

- Most previous studies are small and cross-sectional;
- Few have approached consecutively presenting patients;
- Few have used a structured clinical interview to diagnose depression;
- Few have conducted multivariable analyses on their data;
- None have provided precision estimates (e.g. 95% confidence intervals).

Existing knowledge, gathered specifically in and about glioma patients, is scant:

- The frequency and associations of emotional distress have rarely been studied, and the longitudinal course of distress has not been studied at all;
- No depression or distress screening instruments have been validated for use;
- The frequency of major depression and the variables with which it may be independently associated are poorly understood, and the course of major depression is unknown;
- Whether antidepressants influence seizure frequency is unclear;
- Patient, GP and specialist attitudes to the diagnosis and treatment of depression in glioma have never been studied.

The rest of the thesis describes a prospective cohort study designed to improve knowledge in each of these areas. In this chapter I will outline the study methodology. The final protocol used in the study is included as Appendix 2.

In order to focus following chapters more closely on the topics outlined above, I have included the more basic results of study recruitment and demographic data at the end of this chapter.

7.2 Methods

A flowchart outlining the main methods of the study is presented in Figure 5.
Figure 5. Flowchart of patient pathway through the study.
7.2.1 Design

I conducted an initial literature search and used this to inform the early development of the study protocol. I was supervised in this by Dr. Robin Grant and, in the early stages of study design, Prof. Michael Sharpe. The initial literature review revealed a lack of good quality, descriptive cohort studies of depression in glioma. I therefore chose to design a twin-centre, prospective, observational cohort study with 6-month follow-up.

7.2.2 Setting

7.2.2.1 Recruitment centres

Participants were recruited from two tertiary neuro-oncology referral centres covering a total population of approximately 4.3 million people, or roughly 80% of the Scottish population: the Edinburgh Centre for Neuro-Oncology, Western General Hospital, Edinburgh (hereafter “Edinburgh”) and the Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, Glasgow (“Glasgow”). I recruited all patients at both sites, and was assisted in identifying and approaching patients by the local neuro-oncology Clinical Nurse Specialists (CNS). Most patients were recruited from the outpatient clinic, others while receiving radiotherapy as inpatients and some directly from home.

7.2.2.2 Recruitment phase

Recruitment lasted 24 months. Subjects were recruited from 1st November 2007 until 31st October 2009 in Edinburgh. Recruitment in Glasgow ran from 1st June 2008 until 31st October 2009.

7.2.3 Subjects

Patients were eligible if they were aged 18 or over, with a new histological diagnosis of primary supra-tentorial glioma, were getting some form of active management (including watchful waiting) and were able to provide informed consent. All exclusion criteria are shown in Table 11. Some were added as the study progressed and as the need to consider these issues arose.
<table>
<thead>
<tr>
<th>Exclusion criterion</th>
<th>Definition</th>
<th>Reason(s)</th>
</tr>
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<tbody>
<tr>
<td>Palliation</td>
<td>Active treatment is considered inappropriate. Patient is referred for best supportive care due to poor functional status, cognition or prognosis.</td>
<td>Patient unlikely to survive to end of study period, increasing the dropout rate. Palliated patients are a distinct clinical group from actively treated patients. Impracticality of following these patients up with home visits.</td>
</tr>
<tr>
<td>Geographical isolation *</td>
<td>Patient is not resident on the Scottish mainland or within the boundaries of the treating Health Board.</td>
<td>Hospital transport pressures made clinic interviews hard to schedule.</td>
</tr>
<tr>
<td>Non-English speaking</td>
<td>English is not the patient’s primary language and they are unable to speak it fluently.</td>
<td>Informed consent impractical. Patient and researcher unable to communicate clearly.</td>
</tr>
<tr>
<td>Severe dysphasia</td>
<td>Receptive dysphasia: patient is unable to understand the study information leaflet and follow a verbal three-stage command.</td>
<td>Informed consent impractical. Questionnaires impractical or impossible to administer.</td>
</tr>
<tr>
<td></td>
<td>Expressive dysphasia: researcher is unable to reasonably understand the patient’s speech.</td>
<td>Responses to clinical interview not clear.</td>
</tr>
<tr>
<td>Severe cognitive impairment</td>
<td>Patient is generally unable to remember recent autobiographical events, or is disorientated in time and place.</td>
<td>Informed consent impossible. Patient responses unreliable.</td>
</tr>
<tr>
<td>Severe learning disability *</td>
<td>Patient is under the care of community learning disability services.</td>
<td>Questionnaires and interviews were not designed for use in a learning-disabled population.</td>
</tr>
<tr>
<td>Severe visual impairment *</td>
<td>Patient is unable to read the PIL due to severe visual impairment.</td>
<td>Most of the questionnaires impossible for the patient to complete without assistance.</td>
</tr>
<tr>
<td>On advice of treating team</td>
<td>Patient’s consultant decides that any approach by the researcher could be harmful to the patient.</td>
<td>Ethical obligation to ‘first do no harm’.</td>
</tr>
</tbody>
</table>

Table 11. Study exclusion criteria, their definitions and rationale.

* Added after study began in response to previously unforeseen circumstances.
In both centres, eligible patients were identified at the weekly multidisciplinary team (MDT) meeting. I attended the MDT in Edinburgh and a neuro-oncology nurse (MM / MF) recorded details of eligible patients in Glasgow. I kept complete records of all eligible and ineligible patients presenting to both centres during the recruitment phase.

7.2.4 **Procedure**

7.2.4.1 Initial approach

The initial approach consisted of a usual team member giving the Patient Information Leaflet (the PIL, Appendix 3a and 3b) to an eligible patient. Changes were made to the process in both centres as the study progressed, as described below.

In Edinburgh, the protocol proposed giving the PIL to patients immediately after they had received histological confirmation of their diagnosis, in the first post-operative clinic appointment. This was chosen as the first opportunity to introduce the study after determining eligibility. However it gradually became clear that some patients were too upset, in the opinion of the treating doctor, to receive the PIL at this time. We tried to quantify the extent of this problem, but our audit sheet was not always completed and returned by busy clinicians.

On approaching patients for formal consent, we also found that not all those receiving the PIL had actually read it. ‘Information overload’ at the time of glioma diagnosis was a frequent explanation. We concluded that in practice, the first post-operative clinic was an unreliable time to initially approach patients. The difficulties it caused included delay in recruitment, increased work for the researcher and potential embarrassment for patients. We therefore looked for an alternative time.

For patients presenting to Glasgow, the protocol proposed that the CNS ask their permission to post the PIL out, during a routine telephone follow-up call one week after they had been given their diagnosis (a service not offered in Edinburgh). After some months we noticed that eligible patients were being missed, and that more patients were refusing even to receive the PIL than in Edinburgh. We felt that recruitment could be improved and again looked for an alternative time to approach patients.

The timing of the initial approach was therefore changed in both centres from occurring before, to occurring after the start of radiotherapy. After approximately one year of recruitment, three separate strategies had evolved and were being used in both centres:
1. HGG patients receiving chemoradiotherapy were approached by clinical staff during routine review in a weekly clinic that is run in both centres.

2. Alternatively, HGG and LGG patients receiving radiotherapy were given an envelope containing the PIL by radiographers on their usual treating machine.

3. Because LGG on a ‘watch and wait’ management strategy only receive infrequent neurosurgical follow-up, the PIL was posted to them with a covering note explaining the voluntary nature of the study. They were later telephoned to discuss taking part.

7.2.4.2 Consent

The study consent form is presented in Appendix 4. Written informed consent to participate was obtained after the start of radiotherapy. Patients not receiving radiotherapy (e.g. LGG) were eligible to give consent at an equivalent time-point after primary surgery. Patients were given at least 24 hours to read the PIL, and encouraged to discuss the study with their family before consenting. If they were unable to sign their name – e.g., patients with a dominant hemiparesis – a staff or family member acted as a witness.

I answered any questions the patient or relative had about the study before obtaining consent. Generally this was done in a private clinic room, a hospital ward, or the patient’s home. The first interview was then conducted. GPs were sent a letter informing them that their patient was taking part in the study (Appendix 5a).

7.2.4.3 Timing of study interviews

7.2.4.3.1 Patients receiving radiotherapy

Participating patients were scheduled to receive three study interviews. The first interview (T1) occurred as soon as possible after the start of radiotherapy, usually immediately after the patient consented to participate. Follow-up interviews were anchored to the date of starting radiotherapy. Thus the second interview (T2) was scheduled to occur three months after, and the third interview (T3) six months after the first day of radiotherapy.
7.2.4.3.2 Patients not receiving radiotherapy

To determine when to approach patients who were not receiving radiotherapy, I calculated the mean number of days between the surgical operation and the start of radiotherapy in HGG patients. I used this data to identify a comparable study ‘start’ date for patients not receiving radiotherapy, after which they could be approached and consented. Follow-up interviews were anchored upon this date.

7.2.4.4 Conduct of interviews

Because most patients were attending for radiotherapy, most first interviews could be held in clinic. However, all patients receiving a craniotomy are banned from driving, and transport is consequently problematic. For convenience, follow-up interviews were therefore usually conducted in the patient’s home. Where specifically requested by the patient, interviews were arranged to coincide with scheduled clinic appointments.

Patients were given the choice of whether or not to have their relatives present during the interview. If present, relatives were encouraged not to help the patient complete the questionnaires, but were encouraged to contribute to the SCID interview.

Some patients with hemiparesis were cognitively intact, but physically unable to write to complete the questionnaires. In such cases, I read the questionnaires to them and marked their response on the questionnaire.

If DSM-IV Major Depressive Disorder was present the patient was informed. The GP was sent a brief letter advising them of the diagnosis and requesting that they “treat the patient as you usually would”. If the patient endorsed suicidal ideation in the SCID, a standard risk assessment was conducted separately and acted on appropriately in keeping with Good Clinical Practice.

7.2.4.5 Follow-up interviews

An electronic diary system was used to keep track of T2 and T3 interview due dates. When the second and third interviews fell due, I telephoned the patient’s GP to check that the patient was still alive. I then telephoned or emailed the patient to arrange a suitable interview time.
7.2.5 Variables

7.2.5.1 Dependent variables

The primary outcome variable was MDD. Secondary outcome variables, depending on the question under study, were: DT score; HAD-D score; PHQ-9 score; antidepressant prescription; patient attitudes to depression treatment; and GP/specialist doctor attitudes to depression diagnosis and treatment.

7.2.5.2 Independent variables

Independent variables were: age; patient sex; marital status; past medical history (PMH) of depression; presence of epilepsy; WHO glioma grade; histological type; affected lobe; hemispheric laterality; extent of surgical resection (EOR); current use of antiepileptic drugs (AEDs); radiotherapy schedule; and chemotherapy schedule.

7.2.5.3 Confounding variables

I measured the following potential confounding variables: current steroid prescription; cognitive dysfunction; and functional impairment. Variables were constructed as outlined in Table 12.

7.2.6 Materials

7.2.6.1 Data collected at baseline only

I obtained the date of primary surgery and EOR data from the Consultant neurosurgeon’s handwritten operation note. If this was not available, I scrutinised the inpatient discharge letter or histopathology records. When a patient had two operations as primary treatment (e.g., a biopsy followed shortly afterwards by a debulking) only the date of the second operation was recorded.

Information on glioma histology and WHO grade was obtained from the Consultant histopathologist’s post-operative report; radiotherapy schedule and start dates from the local computerised planning
systems and chemotherapy schedule from outpatient clinical records. I did not record the dates of adjuvant chemotherapy pulses.

I recorded the anatomical tumour location (lobe/laterality) from Consultant radiologist reports of pre-operative contrast-enhanced MRI scans (where possible) or CT scans (all other times). I recorded all lobes mentioned as containing tumour in the report. Bilateral tumours were those noted to be extending across the midline in this summary.

To identify a past history of depression, I wrote to the GPs of all consenting patients requesting full details of their patient’s Past Medical History and Drug History. Where patients had already died, we obtained their full historical GP record through NHS Practitioner Services in both Edinburgh and Glasgow. PMH depression was determined either by a clear record of a diagnosis of depression, or of antidepressant prescription, or of referral to a mental health specialist. Simple allusions to low mood (without diagnosis, treatment or referral) were ignored. I also examined the in-patient clerking of each participant for evidence of prior depression, and asked each whether they had ever taken an antidepressant in the past.

To survey glioma patient attitudes to antidepressants, we administered a simple questionnaire asking the patient to imagine how they would respond if a doctor suggested taking an antidepressant or attending counselling in the future. This questionnaire was developed by discussion and was not piloted in patients before use.

7.2.6.2 Data collected at each interview

7.2.6.2.1 Medicines

I asked the patient and/or relative about the current dose of Dexamethasone, and about any changes to the dose in the preceding four weeks. I asked whether they were taking an antidepressant and, if they were, recorded the name and dose directly from the drug packaging. If an antidepressant was prescribed in low dose as night sedation, or to treat pain I recorded this but did not count it as treatment for depression. I asked each participant, and their relative when present, whether they were taking medicines for ‘epilepsy’. I also asked specifically about medicine for ‘seizures’ in case some patients did not regard a seizure disorder as epilepsy. Whenever possible I corroborated the participant’s medication with the relative, or reviewed prescription sheets, outpatient records, inpatient records or pharmacy dosette boxes as appropriate. As a final general screen for drug prescription I asked “are you taking any other medicines?”
<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>• Continuous variable: age (yrs) at entry to study</td>
<td>Clinical notes</td>
</tr>
<tr>
<td>Patient sex</td>
<td>• Male</td>
<td>Clinical notes</td>
</tr>
<tr>
<td></td>
<td>• Female</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>• Married</td>
<td>Asked patient at study entry</td>
</tr>
<tr>
<td></td>
<td>• Cohabiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Single</td>
<td></td>
</tr>
<tr>
<td>Glioma histology</td>
<td>• Glioblastoma Multiforme</td>
<td>Consultant histopathologist report</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
<td></td>
</tr>
<tr>
<td>WHO glioma grade</td>
<td>• High grade glioma (HGG – WHO grades 3 or 4)</td>
<td>Consultant histopathologist report</td>
</tr>
<tr>
<td></td>
<td>• Low grade glioma (LGG – WHO grades 1 or 2)</td>
<td></td>
</tr>
<tr>
<td>Hemispheric laterality</td>
<td>• Right</td>
<td>Consultant radiologist report</td>
</tr>
<tr>
<td></td>
<td>• Left</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bilateral</td>
<td></td>
</tr>
<tr>
<td>Tumour location</td>
<td>• Frontal only</td>
<td>Consultant radiologist report</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
<td></td>
</tr>
<tr>
<td>Extent of surgical resection</td>
<td>• Biopsy</td>
<td>Surgical discharge letter; clinical notes</td>
</tr>
<tr>
<td></td>
<td>• Resection</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy schedule</td>
<td>• Radical</td>
<td>Radiotherapy planning sheet; clinical notes</td>
</tr>
<tr>
<td></td>
<td>• Palliative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• None</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy schedule</td>
<td>• Temozolomide</td>
<td>Clinical notes</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• None</td>
<td></td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>• Yes</td>
<td>Asked patient/relative and/or checked current prescription; clinical notes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
<td></td>
</tr>
<tr>
<td>Current use of antiepileptic drugs (AEDs)</td>
<td>• Yes</td>
<td>Asked patient/relative and/or checked current prescription; clinical notes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
<td></td>
</tr>
<tr>
<td>Recent epileptic seizures</td>
<td>• Yes</td>
<td>Asked patient/relative and took clinical history</td>
</tr>
<tr>
<td></td>
<td>• No</td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>• Karnovsky Performance Status (KPS, score ranges used 100, 90, 80, 70, &lt; 70)</td>
<td>Clinical observation and questioning with KPS determined according to operationalised criteria</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>• Continuous variable: Addenbrooke’s Cognitive Examination score (ACE, potential score 0 - 100)</td>
<td>Structured assessment at each time-point</td>
</tr>
<tr>
<td>Presence of DSM-IV Major Depressive Disorder.</td>
<td>• Yes</td>
<td>Structured clinical interview for DSM-IV (SCID) at each time point</td>
</tr>
<tr>
<td></td>
<td>• No</td>
<td></td>
</tr>
</tbody>
</table>

**Table 12.** Independent variables measured in the study.
7.2.6.2.2 Epilepsy

To determine whether the participant had suffered epilepsy pre-operatively, I reviewed the post-operative neurosurgical discharge letter and oncology clinic letters. I reasoned that clinical records would be more reliable than patient recall at this point, due to the likelihood of sudden presentation, a lack of patient involvement with rapid treatment decisions, the relatively short time-frame and greater cognitive impairment pre-operatively. Seizures were only recorded as present if they were obvious, or stated as being clinically suspected by the consultant writing the letter. Seizures were recorded as either Generalised Tonic-Clonic (GTC) or partial seizures.

However, for post-operative epilepsy data we relied on patient and relative report. I reasoned that by this point they would be more involved with treatment, and that outpatient clinical records could be patchy for the time period covered by follow-up interviews. I asked patients/relatives whether the patient had suffered any seizures or epilepsy in the past month, and to describe what had happened. I decided whether the description represented a GTC seizure, or a partial seizure. The presence or absence of each kind of seizure was recorded. I did not attempt to distinguish between epileptic and non-epileptic attacks.

7.2.6.2.3 Emotional distress

I measured general emotional distress using the NCCN Distress Thermometer (DT, Appendix 9). As reviewed in Chapter 4, the DT is an 11-point ordinal scale on which patients rate their level of distress over the past week, from 0 (none) to 10 (extreme), and a 38-item problem checklist. In line with international NCCN guidance I used a threshold of 4+ to represent high distress.

7.2.6.2.4 Depression

Major Depressive Disorder was diagnosed using the depression module of the Structured Clinical Interview for DSM-IV (SCID) (Appendix 6a and 6b). (First et al. 1996) This is an interview structured around the nine symptoms of major depression. To be counted as present, a symptom must be significant, persistent and new. MDD is diagnosed if five symptoms are present, including either sadness or anhedonia.

I gave all the SCID interviews. I watched the training videos before starting the study. I also had 18 months experience as a psychiatric SHO and had obtained the first part of the MRCPsych before commencing the study. I received ongoing supervision in giving SCID interviews to patients, with a consultant neuropsychiatrist (AC). Where patients gave consent, interviews were audio-recorded. Once data collection was complete, AC listened to a random sample of 10% of SCID interviews to
provide a measure of inter-rater reliability of diagnoses. The process by which interviews were randomly selected is outlined in Box 7.

10% of interviews were listened to by an external rater (a Consultant neuropsychiatrist). In order to give enough time for this process, interviews were selected on 1st February 2010, when roughly 30 follow-up interviews were still to be held. I therefore used attrition data from the first 100 subjects to project an estimate for the final total number of interviews, and selected 10% of this likely final number from those interviews which had already been recorded.

T1: n = 155
T2 (attrition data suggests 66%): projected n = 102
T3 (attrition data suggests 57%): projected n = 84

= estimated total 341 interviews
= 36 recordings selected on 1st February (rounded up to allow 2:1 ratio)

I randomly selected 12 MDD interviews and 24 non-MDD interviews from all recorded interviews. To do this, all MDD interviews were grouped together and numbered sequentially. A random number was selected from this list 12 times using the website mathgoodies.com/calculators/random_no_custom.html. The process was repeated to select 24 non-MDD interviews. I chose a ratio of 1:2 MDD to non-MDD to reflect the fact that MDD was the less common outcome, while still including enough interviews to test discrimination between the diagnoses reasonably often. The selected interviews were then combined and numbered sequentially (1-36). The same website was used to randomly re-order this list of numbers. The interviews were then sent to the external rater, who was blind to my diagnoses.

Box 7. The random selection of interviews for assessment of inter-rater reliability.

Once the first 20 patients were shown to tolerate the interviews, I added the Hospital Anxiety and Depression Scale (HADS, Appendix 7). I chose this self-report questionnaire because it was designed for use in patients with medical illness. The depression subscale (HAD-D) consists of seven questions, mostly about anhedonic symptoms, scored on a four-point Likert scale (total range 0-21). Results from the original HADS validation sample (100 general medical outpatient clinic attendees) suggested two possible cut-offs for the depression subscale: 8+ and 11+. These scores represented the lower and upper limits of the “borderline” depressed range, respectively. The authors suggested that choice of cut-off would depend on the aims of future researchers. (Zigmond and Snaith 1983) Because the
HADS has not been validated in glioma patients, I chose neither cut-off a priori, planning instead to identify an appropriate cut-off from our sample for use in subsequent analyses.

At the time of adding the HADS I also added the 9-item depression module from the Patient Health Questionnaire (PHQ-9, Appendix 8). I chose this self-report questionnaire because it consists of the same nine criteria upon which a diagnosis of DSM-IV Major Depressive Disorder is based. MDD can be diagnosed if five or more symptoms are present, subject to the clinician checking the patient’s positive responses and excluding medical conditions and grief due to bereavement. The PHQ-9 also rates severity of symptoms (from 0-27) with each symptom scored on a four-point Likert scale. In the original PHQ-9 validation sample (580 primary care and obstetric/gynaecology outpatient clinic attendees) a cut-off of 12+ was 83% sensitive and 92% specific for MDD as diagnosed by structured telephone interview. (Kroenke et al. 2001) The PHQ-9 has been validated in patients with traumatic brain injury (Fann et al. 2005), and stroke (Williams et al. 2005), but not glioma.

I asked patients to complete the HADS and PHQ-9 themselves. If they did not comprehend fundamentally how to complete the questionnaire I gave them brief guidance. If they could not hold a pen, they gave an answer verbally and I completed it for them. If they asked which response they should give, I asked them to complete it as they saw fit, and said I could not tell them how to answer. I quickly checked responses for completeness, but did not score the questionnaires until after the entire interview.

7.2.6.2.5 Cognitive status

At each interview, I assessed the patient’s cognitive function using the Addenbrooke’s Cognitive Examination (Revised) (ACE-R, Appendix 10). (Mioshi et al. 2006) Rather than an in-depth neuropsychological test battery, the ACE-R is an extended screening tool. It incorporates the Mini Mental State Examination (MMSE). Patients completed the same version (v1) at each visit.

The ACE-R is scored on five domains. The possible score ranges from 0 - 100. Patients unable to complete specific tasks due to physical impairment were simply asked to complete as much of the ACE as possible. Reasons for missing data were recorded. In analyses, the raw score was standardised to lie on a range 0 - 100.

7.2.6.2.6 Functional status

Functional status was measured using the Karnofsky Performance Scale (KPS). (Karnovsky and Burchenal 1949) The KPS is a clinician-rated 11-point ordinal scale constructed in steps of 10, anchored at 0 (patient is dead) and ranging up to 100 (no symptoms of disease are present). I
‘operationalised’ scoring to maximise consistency. In a small number of patients (estimated at < 10%), KPS was recorded directly from, or estimated from information contained in the clinical records (see Section 7.2.9.2).

7.2.6.3 Order of collection of data

Data were generally gathered in the same order throughout the study, as detailed in Box 8. The HADS, PHQ-9 and NCCN thermometer, however, were originally given before the SCID. The aim of this had been to give participants time to feel comfortable with the line of questioning. These three questionnaires were moved to the end following two observations. Firstly, an interim analysis suggested that high NCCN ‘distress’ was associated with MDD (Rooney et al. 2009a) and I was worried that this knowledge may bias the SCID. Secondly, because participants occasionally required help with questionnaire completion, I was not always blind to the self-rated PHQ-9 or HADS results before conducting the SCID interview. Moving them to the end minimised the possibility of introducing expectation bias to the SCID interview.

<table>
<thead>
<tr>
<th>Basic demographic information (at T1 only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current steroid information</td>
</tr>
<tr>
<td>Current seizures information</td>
</tr>
<tr>
<td>Current AED prescriptions</td>
</tr>
<tr>
<td>Current antidepressant prescriptions</td>
</tr>
<tr>
<td>SCID interview</td>
</tr>
<tr>
<td>Questionnaire: attitudes to depression treatment</td>
</tr>
<tr>
<td>Questionnaire: HADS</td>
</tr>
<tr>
<td>Questionnaire: PHQ-9</td>
</tr>
<tr>
<td>Questionnaire: DT</td>
</tr>
<tr>
<td>Functional status (KPS)</td>
</tr>
<tr>
<td>Cognitive status (ACE)</td>
</tr>
</tbody>
</table>

**Box 8.** Final order of interview items in the main study.
7.2.7 Statistical analyses

7.2.7.1 General plan

With statistical advice, I planned the following analyses in the study protocol. For descriptive data, count rates were presented and confidence intervals calculated. Sensitivity and specificity of the DT/HAD-D/PHQ-9 were analysed using a ROC curve. Chi Square and Fisher’s Exact Tests were used to examine univariate associations between independent and dependent variables. Independent predictors were analysed by logistic regression.

7.2.7.2 Sample size calculation

I conducted an a priori sample size calculation (see Appendix 2) which suggested that a minimum of 141 subjects would be needed to estimate depression prevalence to within acceptable limits (+/- six percentage points).

7.2.7.3 Logistic regression considerations

A formal sample size calculation was not conducted for logistic regression. Instead I estimated that 10 cases of depression would be required for every variable included in the model. (Peduzzi et al. 1996) For example, if prevalence was 30% and sample n = 150 (giving 45 depressed patients) I could include four variables in the final model, including the outcome variable of depression.

I recognised that the number of independent (predictor) variables that could be analysed would depend on the number of cases of depression accruing in the study. I stated, a priori, that predictor variables would be tested in the following order until no longer appropriate: age; sex; past history of depression; tumour grade; radiation therapy; tumour location; tumour laterality; and adjuvant chemotherapy.

7.2.7.4 Other statistical considerations

Inter-rater diagnostic agreement for MDD was analysed using Cohen’s Kappa (see Chapter 10 for the result of this analysis).
I was aware of the possibility of diagnostic inflation, for example from the side-effects of corticosteroids. I therefore performed a sensitivity analysis on MDD frequency data and clinical associations. I automatically discounted any symptom of i) appetite increase/weight gain and ii) insomnia, when it occurred in a patient taking any dose of corticosteroid concurrently. The proportion of patients meeting criteria for MDD at each time-point according to this ‘exclusive’ approach was recalculated. Clinical associations were re-analysed. The purpose of this sensitivity analysis was to seek evidence on whether results were markedly confounded by the most frequently-encountered side-effects of corticosteroids. This analysis is presented in Chapter 10.

I conducted some post-hoc statistical analyses which are reported in the relevant chapters.

Reasons for loss to follow-up were recorded. I did not attempt to impute missing data.

7.2.8 Ethical and regulatory approval

As a twin-centre NHS study, ethical and regulatory approval ultimately was required from four bodies. These were: the Scotland A Multi-centre Research Ethics Committee (MREC), NHS Lothian Research & Development (R&D), NHS Greater Glasgow & Clyde R&D and the Clinical Trials Executive Committee of the Beatson West of Scotland Cancer Centre (CTEC). The study was planned to start first in Edinburgh and then in Glasgow.

I attended MREC along with a supervisor (RG) on 28/06/2007. MREC requested changes to the study design before giving the protocol final approval on 29/08/2007 (REC Reference 07/MRE00/55). An application was submitted to NHS Lothian R&D and approved on 26/06/2007. Recruitment began in Edinburgh on 1st September 2007.

A few months later we began the process of obtaining regulatory approval in Glasgow, which ultimately was obtained on 30/04/2008.

7.2.9 Differences between study protocol and thesis

Alterations to how and when patients were approached, to the order in which data were collected, and the addition of the HADS and PHQ-9 questionnaires have been discussed. Where appropriate I wrote to MREC to inform them of these changes (Appendix 11a and Appendix 11b).
7.2.9.1 Patient recruitment

Occasionally I missed the opportunity to recruit eligible patients during radiotherapy. Later in recruitment we decided to make efforts to include them anyway, to take advantage of the unique opportunity to study them. However, the first day of radiotherapy was no longer an appropriate anchor point for their second and third interviews, because in some cases the ‘per protocol’ dates for these latter interviews had passed.

I decided that patients recruited up to two months after the start of radiotherapy would be eligible for the study ‘per protocol’. I chose two months as the cut-off because the SCID interview covers symptoms occurring in the previous month, reasoning that the three-month interview would still be comparable among all patients. For the small number of patients first consenting after the two month cut-off point, I used the date of the first interview as the anchor point, with follow-up interviews occurring three and six months after that date.

In practice, I therefore recruited two longitudinal cohorts: a large group consenting to participate within two months of the start of radiotherapy (or appropriate date for LGG) and a much smaller cohort of glioma patients recruited at various stages later in their course of treatment. These two groups were combined in the final analyses.

7.2.9.2 Recording functional status

Functional status was originally measured using a timed 10m walk. However this relied on having a measured 10m distance. Once the decision was taken to follow patients up at home the method became impractical. I changed to recording Karnofsky Performance Status. For patients whose function had already been recorded using the timed 10m walk (approx. 20), I recorded KPS from a review of their clinical records where possible. If this information was not available I took a 10m walk time of > 8.0 seconds to represent a KPS of 70, and a faster time to represent a KPS of 90. (Clyde et al. 1998)

7.2.9.3 Recording steroid prescription

Throughout the study I asked patients to state their prescribed steroid doses over the previous 28 days. Ultimately, I reasoned that this recollection (although useful) was potentially less reliable than simply asking whether steroids were currently prescribed. In this thesis I present the latter variable only.
7.2.9.4 Recording seizures

In a similar vein, I recorded the patient’s perceived number of seizures in the preceding month. However in the thesis I have reduced this simply to whether seizures were present or not, reasoning that this is a more reliable outcome measure than the exact number of seizures recalled.

7.2.9.5 Removal of other diagnostic information

In the protocol, and in the actual study, I also asked patients about symptoms of anxiety and adjustment disorder. These have been omitted from the current analysis, along with data from the HADS Anxiety subscale, to improve the clarity of the report.

7.3 Basic results

7.3.1 Recruitment of subjects

Recruitment started in Edinburgh on 1st September 2007, and in Glasgow on 14th May 2008. It ran in both centres until 30th September 2009. During this time, 305 new glioma patients presented (100%; Edinburgh [E] = 157 and Glasgow [G] = 148). Eighty-two (26.9%) were excluded. Reasons were: immediate palliation (n = 54: E27, G27); geographical isolation (n = 12: E3, G9); severe dysphasia (n = 6: E4, G2); cognitive impairment (n = 4: E3, G1); being unable to speak English (n = 4: E1, G3); severe learning disability (n = 1: E1, G0); and being blind (n = 1: E1; G0). Therefore 223 patients were eligible (73.1%; E117, G106).

Eighteen eligible patients were not approached. In two cases, I was advised by the Edinburgh clinical team not to approach the patient due to their high distress. The other 16 patients were missed due to procedural errors (E5, G11: 5.2% of total or 7.2% of eligible). Procedural errors included: patient non-response to telephone calls; researcher holiday; miscommunication within the team and short radiotherapy duration limiting opportunities to recruit patients. Therefore 205 patients were approached (67.2% of total or 91.9% of eligible; E110, G95).

Of these patients, 157 consented (E92, G65). However, two did not complete any study interview (one Edinburgh patient moved house and could not thereafter be contacted, and one Glasgow patient deteriorated clinically before the first interview took place).
The final sample available for analysis was 155 (50.8% of all new glioma patients; 69.5% of all eligible; E91, G64).

In summary, across both centres during the recruitment phase, 305 adults received a histological diagnosis of primary cerebral glioma, 223 met eligibility criteria and 155 provided data for analysis (Figure 6)

7.3.2 Recruitment biases

I found no differences in patient sex or tumour grade between participants and eligible non-participants, either within or between centres (Table 13).

Eligible patients from Edinburgh were, however, significantly more likely to participate than those from Glasgow (92/117 vs 65/106; p = 0.005, Pearson’s Chi square). I explored reasons for this. One possibility is that eligible patients could have been missed more frequently in Glasgow. In Glasgow, I missed 11/106 eligible patients compared to 5/117 in Edinburgh (p = 0.078, Pearson’s Chi Square). These figures suggest a tendency for patients to be missed more frequently in Glasgow, and recruitment procedures in this centre were improved half-way through the study. However the trend is not strong enough to account for the difference in overall participation between the centres.

Among patients who were actually approached, those in Glasgow were significantly less likely to consent to participate than those in Edinburgh (65/95 vs. 92/110 respectively; p = 0.01, Pearson’s Chi Square). Recruitment appears to have been better in Edinburgh mostly because eligible patients in this centre were more likely to give consent when approached.

7.3.3 Completeness of follow-up and reasons for attrition

Follow-up was 108/155 (69.8%) at T2 and 88/155 (56.8%) at T3. Drop-out was most frequently due to death or clinical deterioration (n = 49). ‘Clinical deterioration’ included cognitive impairment, neurological impairments (e.g. dysphasia) and excessive fatigue. A smaller number of patients (n = 11) chose to leave the study for personal reasons.
Figure 6. Flowchart of patient eligibility, recruitment and drop-out across both centres.
Table 13. Age, patient sex and tumour grade of consenting and non-consenting patients in each centre.

Consenting: Total n = 157; Edinburgh n = 92; Glasgow n = 65.
Non-consenting: Total n = 66; Edinburgh n = 25; Glasgow n = 41.
a. Student’s t-test.
b. Pearson Chi Square.

7.3.4 Baseline characteristics of participating patients

Mean age of participants was 54.2 years (SD 12.3). Reflecting the epidemiological distribution of glioma, 57.4% of the sample was male. Most patients were married (71.0%) and had undergone surgical debulking of the tumour (74.8%). Reflecting the wider population, 85.8% of patients had high-grade glioma. The most frequent single histological diagnosis was GBM (72.9%). Most patients had radical radiotherapy (78.1%) and were taking dexamethasone (69.7%). About half had chemotherapy of some kind (55.5%). The sample was relatively well-functioning (81.9% had a KPS score > 70). Median standardised ACE-R score was 88 (IQR 81 - 93), meaning that half of patients scored below the formal scale cut-off for suspected dementia. In our study cognitive impairment was clearly attributable to glioma and its treatment rather than dementia, however.

The baseline independent clinical and demographic characteristics of participants are shown in Table 14.
### Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>T1 (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years, range; SD)</td>
<td>54.2 (19-76, 12.3)</td>
</tr>
<tr>
<td>Patient sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>89 (57.4)</td>
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<tr>
<td>Female</td>
<td>66 (42.6)</td>
</tr>
<tr>
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<tr>
<td>Married</td>
<td>110 (71.0)</td>
</tr>
<tr>
<td>Cohabiting</td>
<td>19 (12.3)</td>
</tr>
<tr>
<td>Single</td>
<td>26 (16.8)</td>
</tr>
<tr>
<td>Glioma histology</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>113 (72.9)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (27.1)</td>
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<tr>
<td>Glioma WHO Grade</td>
<td></td>
</tr>
<tr>
<td>Low grade glioma (1-2)</td>
<td>22 (14.2)</td>
</tr>
<tr>
<td>High grade glioma (3-4)</td>
<td>133 (85.8)</td>
</tr>
<tr>
<td>Hemispheric laterality</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>72 (46.5)</td>
</tr>
<tr>
<td>Left</td>
<td>72 (46.5)</td>
</tr>
<tr>
<td>Both</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Isolated lobe</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>45 (29.0)</td>
</tr>
<tr>
<td>Other</td>
<td>110 (71.0)</td>
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<td>Extent of resection</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>39 (25.2)</td>
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<td>Debulking</td>
<td>116 (74.8)</td>
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<td>Radiotherapy</td>
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<td>Radical</td>
<td>121 (78.1)</td>
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<td>Palliative</td>
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<tr>
<td>None</td>
<td>16 (10.3)</td>
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<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Temozolomide</td>
<td>77 (49.7)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>None</td>
<td>69 (44.5)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108 (69.7)</td>
</tr>
<tr>
<td>No</td>
<td>47 (30.3)</td>
</tr>
<tr>
<td>Mean dose (mg, range; SD)</td>
<td>2.6 (0-15; 2.7)</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83 (53.5)</td>
</tr>
<tr>
<td>No</td>
<td>72 (46.5)</td>
</tr>
<tr>
<td>Seizures in the preceding month</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (21.3)</td>
</tr>
<tr>
<td>No</td>
<td>122 (78.7)</td>
</tr>
</tbody>
</table>

(Table continues on next page)
I began this chapter by summarising my view of the main areas of deficiency in the current literature on distress and depression in adults with glioma, methodologically and in terms of clinical knowledge.

I then described in detail the methodology of a prospective cohort study designed specifically to improve our understanding of key clinical aspects of this condition.

I next presented basic results relating to study recruitment, follow-up and drop-out, and described the independent clinical and demographic characteristics of participants at each study time-point.

The following five chapters each address an individual clinical area examined in the study.

### Table 14. Demographic characteristics of participants in the main study at T1.

<table>
<thead>
<tr>
<th>KPS</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>25 (16.1)</td>
</tr>
<tr>
<td>90</td>
<td>58 (37.4)</td>
</tr>
<tr>
<td>80</td>
<td>44 (28.4)</td>
</tr>
<tr>
<td>70</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>14 (9.0)</td>
</tr>
</tbody>
</table>

| ACE-R (mean, range; SD)\(^i\) | 86.5 (57-100; 8.7) |
| MMSE (mean, range; SD)\(^i\) | 28.2 (20-30; 1.9) |

| Previous history of depression\(^j\) | 28 (18.1) |

Figures are n (%) except where otherwise indicated.

a. Independent samples t-test (two-tailed) \( p = 0.247 \).
b. \( \chi^2 \) \( p = 0.543 \).
c. \( \chi^2 \) \( p = 0.718 \).
d. \( \chi^2 \) \( p = 0.507 \).
e. Non-participating histology other: Astrocytoma \( n = 8 \), oligodendroglioma \( n = 4 \), oligoastrocytoma \( n = 3 \), gliosarcoma \( n = 1 \), ganglioglioma \( n = 1 \), gliomatosis cerebri \( n = 1 \), ependymoma \( n = 1 \), dysembryoplastic neuro-ectodermal tumour (DNET) \( n = 1 \).
f. Participating histology other: Astrocytoma \( n = 20 \), oligodendroglioma \( n = 12 \), oligoastrocytoma \( n = 3 \), pleomorphic xanthoastrocytoma \( n = 1 \), gliosarcoma \( n = 3 \), primitive neuro-ectodermal tumour \( n = 2 \), DNET \( n = 1 \).
g. Lobe other: temporal \( n = 24 \), parietal \( n = 19 \), occipital \( n = 7 \), mixed lobes/deep structures \( n = 60 \).
h. Chemotherapy other: Gliadel \( n = 8 \), PCV \( n = 1 \).
i. \( n = 137 \).
j. \( n = 133 \).
The frequency, clinical associations, longitudinal course and causes of emotional distress in glioma

8.1 Introduction

In Chapter 1, I noted that glioma can profoundly affect young, previously healthy adults. Treatments are toxic and intensive, and epileptic seizures are common. Prognosis is poor. Among all cancers, glioma is associated with the highest risk for psychiatric hospitalisation in the year prior to cancer diagnosis. (Benros 2010) Clearly, glioma is a potential cause of emotional distress.

In Chapter 4, I reported that in the United States, the National Comprehensive Cancer Network (NCCN) recommends regular screening of all cancer patients using the Distress Thermometer (DT). (NCCN 2010) I presented a review of this instrument, suggesting that clinically significant emotional distress is reported in a median of 44% of systemic cancer patients worldwide.

Although there is good reason to believe that glioma patients may be highly distressed, few studies have examined the use of the DT in glioma. Those that have are small (n < 100) and enrolled patients at differing stages in their illness. (Keir et al. 2008a;Keir et al. 2008b;Kvale 2009) None have measured distress longitudinally. None have conducted multivariable analysis of associations between clinical variables and distress in glioma. Few have described the specific causes of distress that glioma patients report. (Keir et al. 2008b;Kvale 2009) As a result our understanding of the natural extent, course, risk factors and causes of emotional distress in glioma is limited.

I administered the DT to a cohort of consecutively presenting adults with new, histologically-confirmed high-grade glioma. Specific research questions were:

1. What is the frequency of high distress?
2. Which clinical variables are independently associated with high distress?
3. What is its longitudinal course over a 6-month period?
4. Which causes of distress do patients report?

8.2 Methods

This study was contained within the larger study described in Chapter 7. Design, setting, participants and variables were as outlined in that chapter. Variables particularly relevant to the current chapter are outlined again below for convenience.
8.2.1 Outcome variable

The primary dependent variable was severity of emotional distress, as measured by the NCCN Distress Thermometer (DT) (Appendix 9). The DT is a single-item, self-report screening tool on an 11-point Likert scale constructed to look like a thermometer. Scores range from 0 - 10, anchored at point 0 with “no distress” and at point 10 with “extreme distress”. As recommended by the NCCN, I defined a priori a threshold of 4+ as clinically significant. I further subdivided clinically significant distress into “moderate” (DT score 4 - 6) or “high” (DT score 7 - 10).

The secondary dependent variable was the reported causes of distress, as measured by the DT’s accompanying “problem checklist”. This is a list of potentially distressing items which the patient may endorse. We did not attempt to modify the pre-existing DT problem checklist for use in glioma.

8.2.2 Statistical analyses

The frequency of clinically significant distress (threshold 4+) at different time-points was presented as count rates with 95% confidence intervals.

Since DT score data were ordinal, I calculated the median and interquartile ranges at each time-point, and used non-parametric statistical analyses to compare groups.

Univariate associations between independent variables and distress severity were based on a categorisation of the DT score either as ‘low’ [< 4] or ‘high’ [≥ 4]). These were analysed using either Chi Square or Fisher’s Exact Test, as appropriate.

Multivariable associations with clinically significant distress at T1 were then examined using forward and backward conditional logistic regression.

The frequency of distressing problems was presented as count rates.

In a post-hoc analysis, I analysed the significance of longitudinal change in distress prevalence across three time-points using the Friedman Test. I also conducted post-hoc analyses to identify variables associated with higher counts on the problem checklist (Mann-Whitney U Test or Kruskal-Wallis Test as appropriate).
8.3 Results

8.3.1 Recruitment and follow-up

N = 155 patients were recruited to the main study, as described in chapter 7. One patient had an interview but did not complete the DT, as she was too distressed to do so at the time. Therefore in the current analysis, T1 (baseline) n = 154. At T2 (three months post-radiotherapy start) 108 participants could be followed up, of whom 103 completed the DT. At T3 (six months post-radiotherapy start), 88 patients remaining in the study, with DT data available for 83.

8.3.2 Participants

The clinicodemographic characteristics of participants at T1 were as shown previously in Table 14. The sole missing person was a 26 year-old female with a Primitive Neuro-Ectodermal Tumour (PNET, a WHO grade 4 glioma). There were no significant differences between initial participants and non-participants in age, patient sex, glioma grade or histological diagnosis.

8.3.3 Frequency of distress

At T1, 56/154 participants reported clinically significant distress (36.4%; 95%CI 28.8% - 44.0%), with n = 40 (25.8%) being “moderately” and n = 16 (10.3%) being “highly” distressed. At T2, 37/103 participants reported significant distress (35.9%; 95%CI 26.6% - 45.2%; n = 16 [15.5%] “moderate” and n = 21 [20.4%] “high”). At T3, 28/83 participants were significantly distressed (33.7%; 95%CI 23.5% - 43.9%; n = 19 [22.9%] “moderate” and n = 9 [10.8%] “high”).

During the entire study, 80/154 individuals (51.9%; 95%CI 44% -59.8%) reported clinically significant distress (DT score 4 or greater) at least one time-point.

8.3.4 Variables associated with distress

I conducted univariate analyses of associations between distress and clinical parameters at each time-point. Variables demonstrating a statistically significant association with clinically significant distress at any time-point were: younger age (at T1, p = 0.014); being prescribed AEDs (at T1, p = 0.038);
having concurrent major depression (at T1 and T2, $p < 0.001$ for both time-points); having concurrent functional impairment (at T2, $p = 0.013$ and T3, $p = 0.002$); and having had biopsy rather than resection (at T3, $p = 0.047$). Some variables showed a trend to association. These were: having epilepsy (at T1, $p = 0.072$); having had no chemotherapy (at T2, $p = 0.061$); and cognitive impairment (at T2, $p = 0.055$). All other variables showed no association with distress (Table 15).

I needed at least 10 cases of high distress for each variable included in a logistic regression model (Peduzzi et al. 1996). Five significantly associated variables (plus distress as an outcome variable) would require 60 cases of high distress. With only 56 patients reporting high distress at T1, I was unable to control for them all and required to select four variables (plus DT score as an outcome) to test in the model.

The study protocol did not state how to approach this situation. In a post-hoc decision, made after discussion with a supervisor (RG), I selected younger age, functional impairment, Major Depressive Disorder and being prescribed AEDs. Age, MDD and AED prescription were included because they demonstrated a relatively strong univariate association with distress at T1. Functional impairment was included because there was a consistent univariate relationship with distress throughout the whole study. After logistic regression, independent predictors of significant distress at T1 were concurrent major depression, functional impairment and younger age ($\chi^2$ for model $= 39.882$, $p < 0.001$, R Square $= 0.312$).

8.3.5 Longitudinal course of distress

In the whole sample, median DT score did not change over time (T1 = 2, IQR 0 - 4; T2 = 2, IQR 0 - 5; T3 = 2, IQR 0 - 4; Friedman Test $p = 0.891$).

DT score data were available at three time-points for 77 subjects. Those initially reporting “low” distress (T1 median DT score $= 1$, IQR 0 - 2) remained un-distressed throughout the study (T2 median $= 1$, IQR 0 - 4; T3 median $= 1$, IQR 0 - 3). This group, however, did show a statistically significant increase in the distribution of distress scores over time (Friedman Test $p = 0.022$).

Participants reporting “moderate” distress at T1 (median DT score $= 4$, IQR 4 - 6) had a variable course (T2 median $= 3$, IQR 1 - 7; T3 median $= 3$, IQR1 - 4). Although in moderate distress, median distress decreased, the overall effect was not significant (Friedman Test $p = 0.062$).
Subjects with “high” distress at T1 (median DT score = 8; IQR 7 - 9) remained highly distressed on follow-up (T2 median = 8, IQR 6 - 8; T3 median = 7, IQR 5 - 8) (Friedman Test p = 0.304) (Figure 7).

8.3.6 Causes of distress

The frequencies of each problem at each time-point are shown in Table 16. One further patient was unable to complete the problem checklist at any interview, due to a mild learning disability. Therefore the sample size for this analysis at baseline was n = 153. At T1, at least one distressing item was endorsed by 136/153 (87.7%), at T2 by 89/103 (86.4%) and at T3 by 70/83 (84.3%). Median problem count was 4 (IQR 1 - 6, range 0 - 20) at T1, 4 (IQR 1 - 6, range 0 - 26) at T2 and 4 (IQR 1 - 6, range 0 - 17) at T3. At each time-point, the three most common problems included worry and fatigue, with sleep difficulties (at T1/T2) and sadness (at T3) also highly frequently reported causes of distress.

More problems were reported by patients with: DT score ≥ 4 (at all three timepoints, Mann-Whitney U Test Z = -4.747 or more, p < 0.001 throughout); concurrent MDD (at all three timepoints, Mann-Whitney U Test Z = -2.816 or more, p = 0.005 or less); a past history of depression (at all three time-points, Mann-Whitney U Test Z = -2.010 or more, p = 0.044 or less); functional impairment (at T2 and T3, Kruskal-Wallis Test $\chi^2 = 22.012$ or more, p < 0.001 at both points); male sex (at T3 only, Mann-Whitney U Test Z = -2.094, p = 0.036); concurrent steroid use (at T3 only, Mann-Whitney U Test Z = -2.505, p = 0.012); and current epilepsy (at T3 only, Mann-Whitney U Test Z = -2.336, p = 0.019).

8.4 Discussion

8.4.1 Main findings

This study demonstrates the extent of emotional distress in adults with glioma. At each time-point, fully one-third of patients reported significant emotional distress, which often persisted during follow-up. High distress was strongly and independently associated with concurrent major depression. Worry and sadness were consistently top-ranking problems. Although high distress could affect any subgroup, patients who were younger and functionally impaired appeared to be at greater risk. There was also some evidence that patients with epilepsy reported more distress and distressing problems.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportion with high distress (DT score ≥ 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1 (n = 154)</td>
</tr>
<tr>
<td>Age†</td>
<td>-0.197</td>
</tr>
<tr>
<td>Patient sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34/89</td>
</tr>
<tr>
<td>Female</td>
<td>22/65</td>
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<td>Married</td>
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<td>Cohabitng</td>
<td>7/19</td>
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<td>8/26</td>
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<tr>
<td>Histology</td>
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</tr>
<tr>
<td>GBM</td>
<td>38/112</td>
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<td>Other</td>
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<tr>
<td>WHO grade</td>
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</tr>
<tr>
<td>HGG (3-4)</td>
<td>47/132</td>
</tr>
<tr>
<td>LGG (1-2)</td>
<td>9/22</td>
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<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>24/71</td>
</tr>
<tr>
<td>Left</td>
<td>26/71</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6/12</td>
</tr>
<tr>
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<td>Other</td>
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<td>Extent of resection</td>
<td></td>
</tr>
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<td>Biopsy</td>
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</tr>
<tr>
<td>Resection</td>
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<td>Yes</td>
<td>43/107</td>
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<td>AEDs</td>
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<td>No</td>
<td>20/72</td>
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<td>Seizures</td>
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<td>16/32</td>
</tr>
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<td>40/122</td>
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(continued on next page)
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<th>0.020</th>
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<td>7/14</td>
<td>4/8</td>
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<tr>
<td>&lt;70</td>
<td>8/13</td>
<td>9/13</td>
<td>7/13</td>
</tr>
</tbody>
</table>

| Cognitive function† | -0.058 | 0.484 | -0.192 | 0.055 | -0.078 | 0.492 |
| MDD            | <0.001 | <0.001 | 0.173 |
| Yes           | 18/20  | 15/16  | 4/6   |
| No            | 38/134 | 22/87  | 24/77 |

Table 15. Univariate associations with high DT-measured distress in adults with primary cerebral glioma.

Analyses are with Chi Square unless otherwise specified. * Fisher’s Exact Test. † Spearman’s correlation on ordinal data. ‡ Data missing for one person. DT = Distress Thermometer. GBM = Glioblastoma multiforme. HGG = High-grade glioma. LGG = Low-grade glioma. AED = Antiepileptic drugs. KPS = Karnovsky Performance Status. MDD = Major Depressive Disorder.
Figure 7. Glioma patients with low, medium and high distress at T1 and their subsequent levels of distress at T2 and T3.
<table>
<thead>
<tr>
<th>Checklist item</th>
<th>Frequency (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1 (n = 153)</td>
</tr>
<tr>
<td><strong>Practical</strong></td>
<td></td>
</tr>
<tr>
<td>Childcare</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Housing</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Insurance</td>
<td>14 (9.2)</td>
</tr>
<tr>
<td>Transport</td>
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</tr>
<tr>
<td>Work</td>
<td>11 (7.2)</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Dealing with children</td>
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</tr>
<tr>
<td>Dealing with partner</td>
<td>24 (15.7)</td>
</tr>
<tr>
<td><strong>Emotional</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Fears</td>
<td>22 (14.4)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>29 (19.0)</td>
</tr>
<tr>
<td>Sadness</td>
<td>23 (15.0)</td>
</tr>
<tr>
<td>Worry</td>
<td>44 (28.8)</td>
</tr>
<tr>
<td>Anger</td>
<td>33 (21.6)</td>
</tr>
<tr>
<td><strong>Spiritual</strong></td>
<td></td>
</tr>
<tr>
<td>Loss of faith</td>
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</tr>
<tr>
<td>Relating to God</td>
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</tr>
<tr>
<td>Loss of meaning or purpose to life</td>
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</tr>
<tr>
<td><strong>Physical</strong></td>
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<tr>
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<tr>
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<td>18 (11.8)</td>
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</tr>
<tr>
<td>Urination</td>
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</tr>
<tr>
<td>Constipation</td>
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<td>Diarrhoea</td>
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<td>Feeling swollen</td>
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<tr>
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<tr>
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<td>Metallic taste in mouth</td>
<td>27 (17.6)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (11.1)</td>
</tr>
</tbody>
</table>

**Table 16.** Frequency of distressing problems in the six months after starting radiotherapy, reported by adults with primary cerebral glioma.
8.4.2 Limitations of the study

Although I identified a consecutive cohort of glioma patients from the two centres, the final sample accrued to this study was selected. In particular, I excluded functionally and cognitively impaired patients (and a few with very high levels of distress). Functional and cognitive impairment were also common reasons for drop-out as the study progressed. The longitudinal analyses required patients to complete all three interviews, and so were conducted on a highly selected, relatively well-functioning group. These factors would arguably tend to produce conservative estimates of distress frequency, severity and causes, particularly over time.

Another potential mediating factor on the reported frequency of distress (and a particular problem in longitudinal quality of life studies) is response shift. (Sprangers and Schwartz 1999) This is the process by which patients cognitively re-appraise their internal values and conceptualizations of quality of life over time, as they adjust to a diagnosis of serious illness. Again, the impact would arguably be to reduce the observed frequency of distress in later time-points.

I was unable, in multivariable analyses, to fully control for all variables showing a positive univariate association with distress. The findings of independent associations with younger age, functional impairment and major depression could be confounded. I did not measure other important variables, including the extent of family support, individual coping strategies or awareness of prognosis. These factors could be among others that modulate expressions of distress. (Dolbeault et al. 2008) Finally, the extent to which varying degrees of mild cognitive impairment affects the external validity of glioma patients’ self-reports is unclear. The results should therefore be generalised with caution to routine clinical practice.

8.4.3 Results in context

Few studies have examined the frequency of DT-defined emotional distress in patients with a brain tumour. Those that exist are cross-sectional in design. Keir et al. reported data from 75 primary brain tumour patients attending their clinic in December 2006 (Keir et al. 2008a); in a separate paper, the same authors studied 83 patients with GBM attending clinic in December 2007 (Keir et al. 2008b): whether these samples were completely separate is unclear. Kvale et al. administered the DT to 50 patients attending clinic with GBM. (Kvale 2009) Distress was defined in each study as the patient reporting a DT score ≥ 4/10. Frequency of distress in these studies ranged from 29% to 54%. In the current study I found a consistent distress level of approximately 36%. This is therefore in keeping with the general level of emotional distress reported in the brain tumour population, measured using the DT at a threshold of 4+.
At least 16 studies of DT-measured emotional distress have been conducted in other cancer populations using a threshold of 4+ (see Table 4.1 in Chapter 4 for references). The reported frequency of distress using this cut-off ranges from 29% in mixed-site cancer patients (Clover et al. 2009) to 61.6% in lung cancer patients. (Graves et al. 2007) The distress reported by patients in the current study is therefore towards the lower end of the frequency spectrum for DT-measured distress in cancer patients generally. One possible reason for this is that patients in my study were all starting primary treatment, whereas almost all of the studies conducted in systemic cancer patients sampled cross-sectional outpatients. Participants starting my study sometimes voiced hope and desire to overcome the tumour. Many seemed to take courage and belief from receiving aggressive treatment. Perhaps the early stages of glioma treatment (after initial shock and distress at the diagnosis has receded) are characterised by patients taking heart from intensive treatment programmes, leading to relatively low distress compared to cancer patients further along the disease process.

This study is the first to examine independent associations between higher distress and clinicodemographic variables in patients with a brain tumour. The only variable that has so far been associated with a high level of DT-measured distress in glioma is patient sex. In both their 2008 papers, Keir et al. reported a statistically significant univariate association between higher distress and female sex. However, the authors appear to have used t-tests on ordinal data from relatively small samples (n = 75 of whom 28 were female; and n = 83 of whom 33 were female). Nonparametric analyses may have been more appropriate in these circumstances. In her sample of 50 GBM patients (21 female), Kvale found no relationship between distress and patient sex using the nonparametric Wilcoxon Rank-Sum test. In the current study I found no association between a high DT score and patient sex at any time-point. Although my data are relatively strong, I think corroboration from other large studies is necessary on this point.

Like researchers studying systemic cancer patients, I observed an independent relationship between higher levels of distress and younger age (Graves et al. 2007), functional impairment (Hurria et al. 2009; Tuinman et al. 2008) and depression. (Akizuki et al. 2003; Graves et al. 2007) Neither Keir et al., nor Kvale et al. noted a relationship between distress and age, despite recruiting brain tumour patients of similar mean age to those in the current study. However, the correlation between age and distress in the current study was relatively weak. It is possible that the earlier studies had insufficient power to detect a small but significant relationship. It is also important to note that the significant association was only apparent at T1. My study is not directly comparable to the other studies which were conducted in cross-sectional samples of brain tumour outpatients. Overall, the available evidence broadly suggests that younger glioma patients could be at greater risk of distress shortly after starting primary treatment, but not at later time points.

I observed that distress persisted over the follow-up period, in the subset of glioma patients reporting high distress initially. Some patients did ‘buck the trend’ and become highly distressed after being un-
distressed (and vice versa). However, most described similar states of distress over time. These data suggest that distressed glioma patients are likely to remain distressed unless appropriately assessed and managed. Evaluating this result against the other DT literature is difficult because only four studies have administered the DT longitudinally (Gessler et al. 2008; Podnos et al. 2007; Roth et al. 2003; Yamagishi et al. 2009) and of these, only one conducted a similar analysis. Yamagishi et al. administered the DT to 462 adult mixed-site systemic cancer patients at the start of chemotherapy, and at every hospital visit thereafter. The authors used a threshold of 6+, based on their own analyses of the operating characteristics of the DT. At any time point, 165 patients reported high distress. In most of these cases (n = 115, 70%) the high distress had resolved (< 6) after a median of 17 days follow-up. Most of the patients who remained distressed reported significant physical symptoms. (Yamagishi et al. 2009)

There are a number of differences between that study and the current one, including patient population, cultural context, choice of DT cut-off, duration of follow-up and probably also the time-point at which high distress was first identified. These differences may partly account for the authors’ finding, contrary to my study, that high distress generally did not persist.

I observed an association between distress and functional impairment, so it is interesting to note that among Yamagishi’s patients in whom distress persisted, troublesome symptoms were the rule rather than the exception. Unfortunately the authors did not describe the frequency of significant physical symptoms among the patients in whom high distress resolved, so it is difficult to interpret their finding alone. The reported data are consistent with the hypothesis that distress is more likely to persist in patients with ongoing functional impairment. Persisting distress could be a considerable cause of psychological morbidity in glioma patients, who are often functionally impaired. Interventions designed to identify and treat psychological distress in functionally impaired patients could be of great value.

This is also one of the few studies to report causes of distress in glioma (as measured by the NCCN problem checklist). Kvale et al. suggested that ‘Getting around’ (33%), and ‘Insurance/financial concerns’ (28%) were the most common problems reported by GBM patients. (Kvale 2009) However data from the current study supports the observations of Keir et al., who identified ‘Fatigue’ and ‘Worry’ as the most common symptoms. (Keir et al. 2008b) These problems are also often very common in studies of patients with systemic cancers. (Bulli F et al. 2009; Dabrowski et al. 2007; Shim et al. 2008; Zainal 2007) The longitudinal design allowed me to observe an increasing prevalence of sadness over time, which may in part reflect adaptation to the illness and an increasing awareness of prognosis.
8.5 Chapter summary

In this chapter I described the largest and currently the only longitudinal analysis of NCCN DT data in glioma patients. At each study time-point, one-third of patients reported significant emotional distress, which often persisted during follow-up. High distress was strongly and independently associated with concurrent major depression. Worry and sadness were consistently top-ranking problems. Although high distress could affect any subgroup, patients who were younger and functionally impaired appeared to be at greater risk. There was also some evidence that patients with epilepsy reported more distress and distressing problems. These clinical groups may benefit from increased support.
9 How can we screen for Major Depressive Disorder in glioma?

9.1 Introduction

Depression in cancer patients may often be missed by non-psychiatric physicians. (Cepoiu et al. 2007; Fallowfield et al. 2001) Screening for depression could improve its identification (Thekkumpurath, V 2009; Vodermaier et al. 2009) and as a general practice in cancer is supported by several relevant national and international bodies. (National Cancer Institute 2010; NICE 2009a; Stiefel et al. 2001) Several depression screening tools have been validated in cancer and palliative care populations. (Katz et al. 2004; Linden et al. 2005; Lloyd-Williams et al. 2004; Walker et al. 2007)

However none have been validated specifically for use in patients with cerebral glioma. This is important because the reliability of many screening measures may be sample-dependent. (Rouse 2007) Glioma patients have an intracranial tumour, brain surgery, epilepsy, cranial radiotherapy and/or chemotherapy. They are qualitatively different from other cancer patients. (Armstrong et al. 2002a; Arnold et al. 2008; Weitzner 1999)

In this chapter I will examine the validity, in adults with glioma, of three patient-reported depression rating scales, aiming to determine:

1. Their internal consistency;
2. Their operating characteristics compared to structured clinical interview for MDD.

9.2 Methods

This study was contained within the larger study described in Chapter 7. Design, setting, participants and variables were as outlined in that chapter. Variables particularly relevant to the current chapter are outlined again below for convenience.

9.2.1 Outcome variables

The three screening measures were: the National Comprehensive Cancer Network’s Distress Thermometer (DT) (NCCN 2010); the Depression Subscale of the Hospital Anxiety and Depression Scale (HAD-D) (Zigmond and Snaith 1983); and the Patient Health Questionnaire-9 (PHQ-9).
The DT was administered from the beginning of study recruitment. The HADS and PHQ-9 were added after it was clear that the original protocol could be tolerated by the first 20 participants.

9.2.1.1 NCCN DT

The DT is a single-item self-report 11-point Likert scale constructed to look like a thermometer. Scores range from 0-10, anchored at point 0 with “no distress” and at point 10 with “extreme distress”. A threshold 4+ was taken to represent clinically significant distress.

9.2.1.2 HAD-D

The HADS is a self-report distress screening questionnaire designed for use in medical populations. It consists of a 7-item depression subscale and a 7-item anxiety subscale. In this paper, we present data from the depression subscale only (HAD-D). Each item is rated on a four-point scale (0-3), so the maximum score on each subscale is 21. Higher scores indicate greater severity of depressive symptoms over the preceding week. Two possible subscale cut-offs were proposed in the original paper: 8+ (for greater sensitivity) and 11+ (for greater specificity).

9.2.1.3 PHQ-9

The PHQ-9 is a nine-item self-report questionnaire consisting of the symptoms of major depression, as currently defined by the American Psychiatric Association. Each item is scored from 0 (“not at all”) to 3 (“nearly every day”), so the maximum score is 27. In the original validation study conducted in primary care, a threshold of 10+ had 0.88 sensitivity and 0.88 specificity for MDD.

9.2.1.4 SCID

Each patient received the Structured Clinical Interview for DSM-IV (SCID) to diagnose the presence or absence of Major Depressive Disorder (MDD). (First et al. 1996) I administered the screening questionnaires and the SCID. At first, the SCID was given after the questionnaires had been completed by the patient, but before they had been formally scored. In a small number of cases patients required assistance to complete the scales (e.g. patients with hemiparesis who could not hold
a pen responded verbally). I recognized that this could potentially bias the SCID outcome and reversed the order of interventions so that SCID was given first.

9.2.2 Statistical analyses

I examined the internal consistency of the HAD-D and PHQ-9 scales using Cronbach’s alpha (the mean of all split-half coefficients). (Cortina 1993) My a priori threshold was that \( \alpha \geq 0.60 \) would represent acceptable reliability for the total scale. We studied the diagnostic accuracy (sensitivity, specificity, positive predictive value and positive likelihood ratios) of all three scales using ROC curve analysis and classification tables on SPSS.

9.3 Results

9.3.1 Participants

Of 155 patients receiving an interview at T1 in the parent study, 154 completed the DT, 133 completed the HADS and 129 completed the PHQ-9. The baseline clinical and demographic characteristics of main study participants were presented in Table 14 (Chapter 7).

9.3.2 Frequency of high scoring

At T1, the median DT score was 2 (IQR 0 - 4) with 56/154 patients reporting clinically significant distress (36.4% \( \pm \) 7.6%). Median HAD-D score was 3 (IQR 1 - 6); 20/133 patients scored \( \geq 8 \) (15% \( \pm \) 6.8%) with nine patients scoring \( \geq 11 \) (6.8% \( \pm \) 4.3%). Median PHQ-9 score was 5 (IQR 2 - 8) with 26/129 patients scoring \( \geq 10 \) (20.2% \( \pm \) 6.9%).

9.3.3 Prevalence of MDD

At T1, 21/155 patients (13.5% \( \pm \) 5.4%) met criteria for MDD. However, one patient with MDD did not complete any self-rating scales because she was too distressed. For this analysis, MDD was therefore present in 20/154 patients completing the DT, 15/133 patients completing the HAD-D and 15/129 patients completing the PHQ-9.
9.3.4 Internal consistency

9.3.4.1 HAD-D

At T1, for the HAD-D, $\alpha = 0.818$. Internal consistency was similar at the other sampling time-points. Corrected item-total correlations for individual HAD-D scale items were acceptable ($\rho = 0.474 - 0.688$). HADS Item 8 (“I feel as if I am slowed down”) correlated least well with total score ($\rho = 0.418$). Excluding it would not have improved the internal reliability of the HAD-D enough to justify removing it from the current analysis, however.

9.3.4.2 PHQ-9

For the PHQ-9 at T1, $\alpha = 0.814$. Internal consistency was similar at the other sampling time-points. Item-total correlations were mostly acceptable ($\rho = 0.507 - 0.677$). However, Item 6 (“Feeling bad about yourself – or that you are a failure or have let yourself or your family down”) correlated less well with total score ($\rho = 0.417$). Item 9 (“Thoughts that you would be better off dead, or of hurting yourself in some way”) correlated poorly ($\rho = 0.307$). We retained both items in the current analysis because their exclusion would not markedly have affected internal reliability of the PHQ-9.

The internal consistency and item-total correlations for the HAD-D and PHQ-9 are shown in Table 17.

9.3.5 Diagnostic accuracy

9.3.5.1 DT

Across all sampling time-points, the median area under the DT ROC curves (AUC) was $0.882 \pm 0.087$. Overall, the optimal threshold was 5+ (sensitivity = 0.67 - 0.81 and specificity = 0.81 - 0.84 for concurrent MDD). Positive predictive value (PPV) at this threshold ranged from 0.22 to 0.45. Positive likelihood ratio ($LR^+$) ranged from 3.7 to 4.9.
9.3.5.2 HAD-D

The median HAD-D AUC was 0.931 ± 0.074. Overall, the optimal threshold was 7+, due to a slightly better sensitivity (sensitivity = 0.80 - 1.00, specificity = 0.88 - 0.91, PPV = 0.31 - 0.59, LR⁺ = 6.7 - 10.0). However a threshold 8+ had similar specificity and predictive value (PPV = 0.27 - 0.67, LR⁺ = 5.6-12).

9.3.5.3 PHQ-9

The median PHQ-9 AUC was 0.915 ± 0.055. There was no clearly optimal cut-off on this scale. No threshold displayed operating characteristics consistently above 80%. In the largest sample (T1), which would tend to provide the strongest data, the optimal threshold was 10+ (sensitivity = 0.80, specificity = 0.86, PPV = 0.43, LR⁺ = 5.7).

Sensitivity, specificity, PPV and LR⁺ for varying cut-offs at each sampling time-point on the three scales are presented in Table 18. ROC curves for the three methods are shown in Figure 8.
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<td>0.1 (0.4)</td>
<td>0.42</td>
<td>0.864</td>
<td>0.1 (0.3)</td>
<td>0.468</td>
<td>0.856</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 17.** Internal reliability of two depression screening questionnaires at three sampling time-points in adults with glioma.

T1/2/3 = first, second and third sampling time-point. HAD-D = Hospital Anxiety and Depression Scale, Depression Subscale. PHQ-9 = Patient Health Questionnaire-9.
<table>
<thead>
<tr>
<th>Screening tool and cut-off</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
</tr>
<tr>
<td>DT ≥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.900</td>
<td>0.716</td>
<td>0.32</td>
</tr>
<tr>
<td>5</td>
<td>0.800</td>
<td>0.836</td>
<td>0.42</td>
</tr>
<tr>
<td>6</td>
<td>0.600</td>
<td>0.896</td>
<td>0.46</td>
</tr>
<tr>
<td>7</td>
<td>0.500</td>
<td>0.955</td>
<td>0.63</td>
</tr>
<tr>
<td>HAD-D ≥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.933</td>
<td>0.805</td>
<td>0.38</td>
</tr>
<tr>
<td>7</td>
<td>0.933</td>
<td>0.907</td>
<td>0.56</td>
</tr>
<tr>
<td>8</td>
<td>0.733</td>
<td>0.924</td>
<td>0.55</td>
</tr>
<tr>
<td>9</td>
<td>0.733</td>
<td>0.958</td>
<td>0.69</td>
</tr>
<tr>
<td>10</td>
<td>0.600</td>
<td>0.958</td>
<td>0.64</td>
</tr>
<tr>
<td>11</td>
<td>0.400</td>
<td>0.975</td>
<td>0.67</td>
</tr>
<tr>
<td>PHQ-9 ≥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.000</td>
<td>0.675</td>
<td>0.29</td>
</tr>
<tr>
<td>9</td>
<td>0.933</td>
<td>0.746</td>
<td>0.33</td>
</tr>
<tr>
<td>10</td>
<td>0.800</td>
<td>0.860</td>
<td>0.43</td>
</tr>
<tr>
<td>11</td>
<td>0.733</td>
<td>0.868</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 18. Sensitivity, specificity, positive predictive value and positive likelihood ratios for three depression screening tools in adults with glioma.

a. T1 n = 154. T2 n = 103. T3 n = 83.
b. T1 n = 133. T2 n = 91. T3 n = 80.
c. T1 n = 129. T2 n = 87. T3 n = 77.
d. Data not available as no-one scored 9 on this scale at this time.

DT = Distress Thermometer. HAD-D = Hospital Anxiety and Depression Scale, Depression subscale. PHQ-9 = Patient Health Questionnaire-9. T1/2/3 = first, second or third sampling time-point. PPV = Positive Predictive Value (the ratio of true positives to the sum of true and false positives). LR+ = Positive Likelihood Ratio (the ratio of the probability of screening positive when MDD is present [sensitivity], to the probability of screening positive when MDD is absent [1-specificity]).
Clinicians can screen for depression in well-functioning glioma patients using the depression subscale of the HADS. The HAD-D and PHQ-9 appear to have good internal reliability in adults with glioma, shortly after starting radiotherapy. However, the HAD-D displayed superior and more consistent operating characteristics. Psychometrically, the optimal HAD-D cut-off score was 7+, but 8+ had similar clinical utility. The NCCN DT was inferior. To my knowledge this is the first study to examine the validity of depression screening instruments specifically in patients with glioma.
9.4.2 Limitations of the study

An important limitation was the potential for expectation bias. (Greenhalgh 1997) I gave the SCID and the screening questionnaires. Ideally, the criterion standard should be independently rated. Bias is not necessarily definitely present however; the questionnaires were not examined or scored until after the SCID was given, and for most of the study the SCID was administered before any of the other questionnaires (greatly reducing the potential for any bias). However expectation bias could explain some of the apparent discriminatory power of these tests, and the results need cautious interpretation.

Another potential weakness arises from the difficulty of diagnosing depression shortly after a life-threatening illness. It is possible that some patients meeting criteria for MDD were “only” experiencing a normal reaction to their circumstances. This is a philosophical issue as well as medical. I did not set out to determine the aetiology of symptoms. By first interviewing patients after the start of radiotherapy I exceeded the period of one month which researchers are advised to allow to lapse post-operatively before attempting diagnosing depression in cancer patients. (Satin et al. 2009a) This should have helped improve the specificity of diagnoses.

Other limitations include the small number of depressed patients, especially at T3. The sample was selected, and the results generalize only to cognitively intact glioma patients in the 8 months during and after primary treatment. The impact of low-level cognitive impairment on recall bias is unknown and is a potential source of error.

9.4.3 Results in context

In the sample of glioma patients accrued to this study, internal consistency was $\alpha = 0.769 - 0.821$ for the HAD-D and $\alpha = 0.814 - 0.862$ for the PHQ-9. These data are consistent with other studies reporting internal reliability to be $\alpha = 0.67 - 0.90$ (Bjelland et al. 2002; Mykletun et al. 2001) for the HAD-D and $\alpha = 0.83 - 89$ for the PHQ-9. (Cameron et al. 2008; Lowe et al. 2010; Martin et al. 2006) The two depression rating scales therefore appear, generally, no less internally consistent in adults with glioma than in the wide range of previously studied hospital medical, primary care and community samples.

Several authors have also reported HAD-D item-total correlations. They provide some support for the suggestion in the current study that Item 8 (“I feel as if I am slowed down”) may perform less well in medically ill patients. Lloyd-Williams et al. reported that endorsement of this item showed particularly poor specificity for clinical depression (0.12) in patients receiving palliative care. (Lloyd-Williams et al. 2001) Others identified this item as performing the poorest of all the HADS items in
patients with a recent myocardial infarction, or stroke. (Johnston et al. 2000) By contrast, a study in primary care outpatients which recruited only those referred to a mental health service (possibly a sample with a lesser degree of medical co-morbidity) found Item 8 to correlate moderately well with total scale score. (Cameron et al. 2008) My impression was that glioma patients who were clearly not depressed often endorsed HAD-D Item 8. I think the most likely reason for this is that a degree of subjective psychomotor slowing is a frequent consequence of having intracerebral glioma, brain surgery, radiotherapy and/or chemotherapy. Because the item-total correlation remained above the traditionally accepted floor of 0.40, and because its removal would not have significantly improved HAD-D internal reliability in the sample, I do not think there is sufficient evidence to justify removing Item 8 from future studies using the HAD-D in patients with glioma. Instead, I would say there is doubt over its validity which requires further study to resolve.

In this sample, the HAD-D demonstrated marginally better and more consistent sensitivity, specificity and positive predictive value for concurrent MDD than did the PHQ-9. Few others have compared these two scales head-to-head in the same study. We might actually expect the PHQ-9 to perform slightly better than the HAD-D because the symptoms surveyed in the PHQ-9 are identical to those constituting the syndrome of MDD. This is indeed what was reported by a team of authors (which included authors of the PHQ-9) examining the comparative operating characteristics of these scales in German medical and primary care outpatients. (Lowe et al. 2010) Another group found that the two instruments both demonstrated reliability, convergent/discriminant validity and a robust factor structure. However these authors did not report sensitivity and specificity of the two instruments. (Cameron et al. 2008)

One reason why the HAD-D might have ‘outperformed’ the PHQ-9 in glioma patients is the relatively greater likelihood of criterion confounding in the PHQ-9. The high frequency of physical complications therefore made it more likely that the PHQ-9 score would be high in the absence of either of the cardinal symptoms of depression. The SCID would identify these patients as ‘not depressed’. By contrast the HAD-D is designed to minimise somatic confounding, even if some confounding items remain. (Natusch 2006) Another possible reason is that, in my experience, glioma patients found the PHQ-9 harder to complete than the HAD-D. A degree of executive function is necessary to comprehend and navigate the PHQ-9 response grid; the instruments starts with a double negative (No loss of interest, which, anecdotally, confused a considerable number of patients); and the typeface is relatively small. Patient responses may therefore have been less accurate using the PHQ-9, although I did not study this directly.

Clinicians can reasonably use the HAD-D with its existing lower threshold of 8+ to screen for MDD in similar patients. Psychometrically the better threshold was 7+, but slightly and inconsistently. Others have reported that cancer patients may require a lower threshold still than the official lower HAD-D cut-off score of 8+. (Katz et al. 2004) I would rather interpret the data cautiously, given study
limitations. Taking sensitivity, specificity, PPV and likelihood ratios into account, the ‘tipping point’ appeared to be somewhere between a score of 6 and a score of 9 on the HAD-D. There was often relatively little to choose between thresholds of 7+ or 8+. I think a reasonable conclusion is that there is no good evidence to reject the lower HAD-D threshold (8+) as unsuitable. It is familiar to clinicians and, as a suggested threshold, is consistent with the majority of research in other patient groups. (Bjelland et al. 2002) However, the upper HAD-D cut-off (11+) appears to be too insensitive for use in patients with glioma.

I was initially surprised that the optimal cut-off was so low, knowing that most other studies using the HAD-D in glioma had chosen to use the original upper threshold of 11+. I was further surprised to discover that a threshold of 8+ was, in fact, the most frequently identified optimal balance between sensitivity and specificity in a range of medical populations. (Bjelland et al. 2002) The results of this analysis are therefore consistent with most other HAD-D validation studies.

The NCCN DT performed less well, a finding consistent with the conclusions of a well-conducted review of the operating characteristics of ultra-short or single-item screening instruments for depression in cancer. (Mitchell 2007) One possible reason is that the DT may identify anxiety to a greater extent than it identifies depression. (Mitchell et al. 2010)

9.5 Chapter summary

In this chapter I described the first validation of any depression screening instrument for use in adults with glioma. I concluded that clinicians can screen for depression in well-functioning glioma patients using the depression subscale of the HADS. The existing lower threshold of 8+ on the HAD-D would be a reasonable choice. The upper HAD-D cut-off (11+) appears to be too insensitive for use in patients with glioma. The actual value of screening is currently unclear, however.
10 The frequency, clinical associations and longitudinal course of Major Depressive Disorder in glioma

10.1 Introduction

In Chapter 5, I systematically reviewed observational studies of depression in adults with glioma. From these, depression is known to be an important complication of glioma, associated with reduced quality of life and possibly with reduced survival. Yet we know little about several clinically important characteristics of depression in glioma.

First, the frequency of DSM-IV MDD in glioma has not been studied often. It is important to know how common “clinical” depression is likely to be, in order to plan ‘real-life’ services effectively. Only two studies have used any kind of psychiatric interview to diagnose MDD in glioma patients according to DSM criteria. (Siegel et al. 2008; Wellisch et al. 2002) Those that did, report a prevalence ranging from 6% to 28%. Neither of these studies reported precision estimates. Both sampled patients at varying stages in their illness, making their conclusions harder to generalise to clinical practice.

Second, independent predictors of depression in glioma are poorly characterised. Most existing studies are small, enrolling fewer than 100 patients. Many have lacked sufficient power to observe significant univariate associations, and to control for them adequately in multivariable analysis. It is important to understand which patients are at higher risk of becoming depressed, so that they can be targeted more efficiently in screening if appropriate.

Third, the course of MDD in glioma is unknown, but is important to understand. National guidelines recommend antidepressant medication and psychological support for patients with chronic illnesses. (NICE 2009a) Clinicians need an idea of the natural history of MDD in glioma, in order to weigh the potential benefit of interventions. Most studies of depression in patients with glioma have been cross-sectional and no longitudinal study has used DSM-IV criteria in a consecutive cohort of patients with newly diagnosed glioma.

Understanding the frequency, associations and course of DSM-IV MDD would add significantly to the growing literature on depression in glioma. I examined:

1. The frequency of MDD, and of patients scoring highly on two depression rating scales.
2. Univariate and multivariable associations with a diagnosis of MDD at any point in the study.
3. The longitudinal course of MDD.
10.2 Methods

This study was contained within the larger study described in Chapter 7. Design, setting, participants and variables were as outlined in that chapter. Variables particularly relevant to the current chapter are outlined again below.

10.2.1 Outcome variables

The primary outcome variable was Major Depressive Disorder (MDD), diagnosed according to the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. (APA 2000) At each time-point, each patient received the depression module of the structured clinical interview for DSM-IV (SCID). (First et al. 1996) The secondary outcome variables were two self-rated depression screening questionnaires: the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire-9 (PHQ-9). Both of these instruments were described further in chapters 7 and 9.

10.2.2 Procedure

I asked patients to complete the HADS and PHQ-9 themselves. If they did not at first comprehend how to complete the questionnaire I gave them brief guidance. If they could not hold a pen, I completed it for them. If they described their symptoms and asked which response they should give, I asked them to complete the scale as they saw fit and did not advise them further.

The SCID was initially given after the questionnaires had been completed by the patient, but before they were scored. After a period of time I reversed the order of interventions so that SCID was given first.

If MDD was present I informed the patient. The patient’s GP was sent a letter advising them of the diagnosis, requesting simply that they treat the patient as they usually would. If the patient endorsed suicidal ideation in the SCID I conducted a standard risk assessment after the interview was complete, and acted on this as appropriate.
10.2.3 Statistical analyses

The frequency of MDD, and of supra-threshold scores on the HAD-D and PHQ-9, were reported as count rates with 95% confidence intervals. The significance of univariate associations between baseline clinical variables and MDD arising at any point in the study were examined using Chi Square, Fisher’s Exact Test, independent t-test or the Mann-Whitney U Test as appropriate. Multivariable associations with the binary outcome ‘MDD/No MDD’ (occurring at any point) were conducted using forward and backward multiple logistic regression. For the regression analysis, I stated a priori that we would require 10 cases of MDD per variable included in the multivariable model, as outlined in Chapter 7. Anticipating that variables might need selected for inclusion, the protocol listed the order in which they would be added to the multivariable model if necessary (Box 9).

<table>
<thead>
<tr>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Past history of depression</td>
</tr>
<tr>
<td>Tumour grade</td>
</tr>
<tr>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Tumour location</td>
</tr>
<tr>
<td>Tumour laterality</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
</tr>
</tbody>
</table>

**Box 9. Original multivariable model order (see Appendix 2)**

Inter-rater diagnostic agreement with SCID interview diagnoses of MDD was analysed using Cohen’s Kappa.

To examine whether data on MDD might be confounded by steroid use, I conducted a sensitivity analysis. Increased appetite and insomnia were discounted as depressive symptoms in all those with a diagnosis of MDD who were concurrently taking steroids. Frequency and clinical association analyses were re-run on the basis of this more ‘conservative’ estimate of depression prevalence.

To provide some measure of the likelihood of expectation bias (given that, for roughly the first half of the study, I administered the SCID after the HADS) I split the sample into two halves and conducted a chi square analysis of the frequency of MDD diagnosis in both. For the ‘earlier’ half, I excluded MDD outcome data for the first 20 patients because the HADS had never been given to them.

For the course of MDD, I created a flowchart with count rates indicating the proportion of diagnoses changing over time. I examined the significance of within-subjects longitudinal changes in mean rating scale score using the Wilcoxon Rank Sum Test. To analyse whether patients with high
depressive symptoms at T1 followed a different course from those without initial depressive symptoms, I used the Mann-Whitney U Test to examine relevant between-subjects differences at T2 and T3. I used non-parametric tests in these analyses because rating scales collect ordinal data; parametric assumptions are not met.

The study was powered in advance to be able to estimate the frequency of MDD to within 6 percentage points of the true figure with 90% confidence. For this I needed to recruit 141 participants (see Appendix 2 for the power calculation).

10.3 Results

10.3.1 Participants

At T1 n = 155. At T2, n = 108 and at T3 n = 88. We added the HAD-D and PHQ-9 after the first 20 patients had been shown to tolerate the T1 interview. Recruitment, baseline and follow-up figures for the current analysis, and baseline demographic characteristics of the sample were shown in Figure 6 and Table 14 (Chapter 7).

10.3.2 Frequency of major depression and depressive symptoms

Overall, 32/155 (20.6% ± 6.4%) subjects were diagnosed with MDD during six months of follow-up. The frequency of MDD at individual sampling time-points ranged from 13.5% ± 5.4% at T1 to 6.8% ± 5.3% at T3. The lower HAD-D threshold (8+) reflected these frequencies better than the higher threshold (11+). The higher HAD-D threshold tended to under-estimate the proportion of patients meeting criteria for clinical depression (range 5.0% ± 4.8% to 9.9% ± 6.1%). By contrast the PHQ-9 over-estimated depression frequency, identifying at least 20% of patients as supra-threshold (10+) at any one time (Table 19).

Inter-rater diagnostic agreement for MDD was good (κ = 0.81, 95% CI 0.60 – 1.00). From 36 interviews, I agreed with a consultant neuropsychiatrist (AC) on the diagnosis in 33 cases. In two patients, I diagnosed MDD when the consultant did not. I diagnosed one patient as not depressed whom the consultant thought had MDD. In two of the three cases where we disagreed, the consultant made a point of noting significant difficulty in reaching his decision (Box 10). In a further case of a non-depressed patient, on which we agreed diagnostically, he commented on the difficulty of obtaining a full appreciation of the clinical picture on the basis of the recorded interview.
In the three cases where we disagreed diagnostically, reasons for differences were subtle.

In one patient (no. 10, T1) the consultant and I agreed on the presence of four symptoms of depression; the fifth would be crucial (in this case, whether or not appetite change was also present). I judged that it was and the consultant judged that it was not. However we both recognised the presence of significant and persistent sadness and anhedonia in this patient.

In another patient (no. 144, T1) we agreed on the presence of five symptoms of depression. None of them were sadness or anhedonia (one of which is necessary to diagnose MDD). I judged anhedonia as present and diagnosed MDD. In part I was influenced by aspects of non-verbal communication such as the patient’s tired expression and restricted affect, and her relative nodding to corroborate things the patient said. Relying solely on the audio recording, the consultant specifically noted difficulty in making a decision over the presence or absence of anhedonia, ultimately rating it as absent.

In the final patient (no 141, T1) we agreed on the presence of five symptoms, none of which were sadness or anhedonia. The patient consistently denied these two cardinal symptoms of depression so I did not judge them to be present. However, she also stated consistently that her family believed her to be depressed, sad and losing interest. The consultant gave greater weight to this collateral, judging sadness and anhedonia to be present, and diagnosing MDD, but acknowledging that they could also be rated as not present.

These vignettes highlight difficulties in comparing data derived from face-to-face interview with those of audio recordings. Non-verbal communication can play an important role in guiding a clinician to a psychiatric diagnosis. When symptoms are ambiguous it can be difficult to reach a confident judgement about whether they categorically are or are not present. However even in cases where we disagreed diagnostically, there was still considerable agreement on the presence of other, individual symptoms.

**Box 10. Reasons for inter-rater diagnostic disagreement.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sampling time-point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td><strong>SCIDa</strong></td>
<td></td>
</tr>
<tr>
<td>MDD present</td>
<td>21 (13.5 ± 5.4)</td>
</tr>
<tr>
<td><strong>HAD-Db</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 18</td>
</tr>
<tr>
<td>≥ 8</td>
<td>20 (15.0 ± 6.1)</td>
</tr>
<tr>
<td>≥ 11</td>
<td>9 (6.8 ± 4.3)</td>
</tr>
<tr>
<td><strong>PHQ-9c</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.8 (5.6)</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 25</td>
</tr>
<tr>
<td>≥ 10</td>
<td>28 (21.7 ± 7.1)</td>
</tr>
</tbody>
</table>

**Table 19. Frequency of depression according to three diagnostic or screening methods in adults with glioma.**

Figures in table are n (% ± 95%CI) unless indicated. Percentages are of valid data at each time-point. a. T1 n = 155, T2 n = 108, T3 n = 88. b. T1 n = 133, T2 n = 91, T3 n = 80. c. T1 n = 129, T2 n = 87, T3 n = 77.
10.3.3 Clinical associations with MDD

10.3.3.1 Univariate analysis

In univariate analyses, MDD arising at any point in the study was more likely in patients with: a past medical history of depression (12/28 with PMH depression versus 18/105 without, $\chi^2 = 8.367, p = 0.004$); a Karnofsky Performance Status score $\leq 70$ at T1 (11/28 with KPS $\leq 70$ versus 21/127 without, $\chi^2 = 7.248, p = 0.007$) and a dexamethasone prescription at T1 (30/108 with current steroids versus 2/47 without, $\chi^2 = 11.060, p = 0.001$). MDD was also significantly associated with cognitive impairment (Table 20). No other independent variable was associated with a diagnosis of MDD. For example, women were no more likely to be diagnosed with MDD than men (13/66 vs 19/89 respectively, $\chi^2 = 0.063, p = 0.802$).

10.3.3.2 Multivariable analysis

Multivariable analysis was limited by the number of patients receiving a diagnosis of MDD at any time-point. With 32 patients with MDD, two independent variables could be selected for inclusion in the analysis. Among those showing a statistically significant univariate association, only ‘PMH depression’ had been identified a priori as a predictor variable of interest in the study protocol. The other variables had been included as potential confounding variables, but without specifying an order in which they should be selected for multivariable analysis. I therefore had to select (post-hoc) one further variable to include in the multivariable model, from: functional status; cognitive function; and steroid prescription. I reasoned that functional status was the most clinically relevant variable, being simpler to measure than cognition and more stable over time than steroid prescription.

The selected predictor variables were therefore PMH depression (yes/no) and KPS at T1 ($> 70$/ $\leq 70$). The outcome variable was MDD at any time-point (yes/no). A test of the full model versus a model with intercept only was statistically significant ($\chi^2 = 14.13, p = 0.001$). The model correctly classified 99% of those without MDD, but only 17% of those who became depressed, for an overall success rate of 81% ($R^2 = 0.154$). The regression analysis indicated that when holding all other variables constant, a patient with glioma and previous depression was 3.8 times more likely to develop depression in our study than one with no prior history. A patient with KPS $\leq 70$ shortly after starting radiotherapy was 3.6 times more likely to become clinically depressed in the next six months, than one with better physical functioning. Table 21 shows the logistic regression coefficient, Wald statistic and odds ratio for each of these predictors.
<table>
<thead>
<tr>
<th>Variable / Category</th>
<th>Any MDD</th>
<th>Present (n= 32)</th>
<th>Absent (n= 123)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (mean, SD)</td>
<td>55.1</td>
<td>54.0</td>
<td></td>
<td>0.61a</td>
</tr>
<tr>
<td>Patient sex</td>
<td></td>
<td></td>
<td></td>
<td>0.802</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>53</td>
<td></td>
<td></td>
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<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td>0.447</td>
</tr>
<tr>
<td>Married</td>
<td>25</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohabiting</td>
<td>4</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior depression</td>
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<td>0.004</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td>0.233</td>
</tr>
<tr>
<td>GBM</td>
<td>26</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO glioma grade</td>
<td></td>
<td></td>
<td></td>
<td>0.570b</td>
</tr>
<tr>
<td>High-grade (3-4)</td>
<td>29</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade (1-2)</td>
<td>3</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td></td>
<td>0.697</td>
</tr>
<tr>
<td>Right</td>
<td>17</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>13</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobe</td>
<td></td>
<td></td>
<td></td>
<td>0.455</td>
</tr>
<tr>
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</table>

(continues on next page)
Table 20. Univariate associations between baseline study variables and major depressive disorder, at any study time-point (n=155).

Figures are frequency counts and analyses are by Pearson’s Chi Square except where indicated.

a. Independent samples t-test.
b. Fisher’s Exact Test.
c. Mann-Whitney U Test

KPS = Karnovsky Performance Status. ACE-R = Addenbrooke’s Cognitive Examination Revised. MMSE = Mini Mental State Examination.

<table>
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<tr>
<th>Predictor</th>
<th>B</th>
<th>Wald $\chi^2$</th>
<th>P</th>
<th>Odds Ratio (95%CI)</th>
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<td>3.8 (1.5-9.8)</td>
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<tr>
<td>KPS ≤ 70</td>
<td>1.278</td>
<td>6.755</td>
<td>0.009</td>
<td>3.6 (1.4-9.4)</td>
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</tbody>
</table>

Table 21. Logistic regression predicting presence of major depression.

PMH = Past medical history. KPS = Karnovsky Performance Status

10.3.4 Sensitivity analysis

As outlined above, I excluded from diagnostic consideration any symptom of appetite/weight gain and insomnia when occurring in a patient taking steroids. Using this ‘exclusive’ method, five patients ceased to attract a diagnosis of MDD at any point in the study. MDD remained as a diagnosis in 27 patients. At individual time-points, the ‘exclusive’ frequency of MDD at T1 remained similar to that obtained using the ‘inclusive’ approach: T1 = 16/155 (10.3% ± 4.8%); T2 = 14/108 (13.0% ± 6.3%); T3 = 6/88 (6.8% ± 5.3%).

Significant univariate analyses continued to be observed between ‘exclusive’ MDD and past history of depression (MDD present in 11/28 with PMH depression versus 14/105 without, $\chi^2 = 9.754$, p = 0.002) and T1 steroid prescription (MDD present in 25/108 taking steroids versus 2/47 on no steroid, $\chi^2 = 8.126$, p = 0.004). Functional impairment at T1 now showed only a tendency to significance.
(MDD in 8/28 with KPS ≤ 70 versus 19/127 without, $\chi^2 = 2.955$, p = 0.086), as did cognitive impairment (MMSE mean score = 27.2 in patients developing MDD versus 28.2 in those without, Mann-Whitney U test $Z = -1.759$, p = 0.079).

Since fewer than 30 patients now met criteria for MDD, a reliable multivariable analysis could not be performed.

10.3.5 Risk of expectation bias

After excluding MDD outcome data for the first 20 patients, 12/58 patients were diagnosed with MDD in the first split half of the sample. In the second half, roughly after the reversal of the order of interventions, 14/78 patients were diagnosed with MDD (Pearson’s $\chi^2 = 0.16$, p = 0.689). There was therefore no evidence that MDD diagnoses in the first half of the study were unduly influenced by expectation bias arising from administration of the HADS.

10.3.6 Longitudinal course of depression

10.3.6.1 MDD

Of 32 patients diagnosed with MDD, by the routine ‘inclusive’ method, 17 received at least one follow-up interview and provided data on the course of depression (13 patients dropped out of the study before the next interview and another two were first diagnosed with MDD at T3). There was no clear pattern of symptom duration. There was evidence that MDD frequently persisted, being diagnosed in at least two consecutive interviews in 9/17 patients (53%). In eight other patients it resolved before the next interview, however (Figures 9-13).

10.3.6.2 Depressive symptoms

There was some evidence that HAD-D scores changed over time in the whole sample. The direction of change was not consistent. Among the 71 patients who completed the HAD-D at all three time-points, mean score increased significantly from 3.4 (SD 3.1) at T1 to 4.2 (SD 3.9) at T2 (Wilcoxon Rank-Sum Test $Z = -2.859$; p = 0.004). Mean HAD-D score then decreased, again statistically
significantly, to 3.3 (SD 3.3) at T3 (Wilcoxon Rank-Sum Test $Z = -2.377; p = 0.017$). The difference in mean HAD-D scores between T1 and T3 was not statistically significant.

When patients were subgrouped into those scoring highly (HAD-D 8+) or not at T1, mean HAD-D scores between these two groups were not statistically different at the follow-up points (T2 Mann-Whitney U Test $Z = -1.455, p = 0.146$; and T3 Mann-Whitney U Test $Z = -0.958, p = 0.338$). This suggested that high HAD-D scores did not persist in the group initially scoring high, while those initially scoring low tended to remain low HAD-D scorers.

PHQ-9 scores reduced over time in the 66 patients who completed this questionnaire on three occasions. The change between T1 (mean 6.8, SD 5.9) and T2 (mean 6.1, SD 6.0) was statistically insignificant (Wilcoxon Rank-Sum Test $Z = -0.902, p = 0.367$). However, the mean PHQ-9 score dropped by T3 (4.8, SD 5.4). T3 PHQ-9 scores were statistically significantly lower than those at T1 (Wilcoxon Rank-Sum Test $Z = -2.569, p = 0.010$). On average, patients scoring PHQ-9 $\geq 10$ at T1 continued to score statistically significantly more highly than those with a T1 PHQ-9 score < 10 (T2 Mann-Whitney U Test $Z = -3.558, p < 0.001$; and T3 Mann-Whitney U Test $Z = -2.131, p = 0.033$).

10.3.7 Antidepressant treatment of depression

At T1, 14/155 (9.0%) patients were taking an antidepressant with the intention of treating depression. At T2 and T3, these figures were 8/108 (7.4%) and 11/88 (12.5%), respectively.
Figure 9. The course of SCID diagnoses of DSM-IV MDD, over three study time-points (all depressed patients; n = 32).
Figure 10. Patients with MDD were difficult to follow up.
Figure 11. MDD remitted for the duration of the study in a small number of patients.
Figure 12. MDD frequently persisted for at least three months.
Figure 13. New cases of MDD developed over time.
10.4 Discussion

10.4.1 Main findings

Major Depressive Disorder is a significant complication of primary cerebral glioma. MDD was diagnosed in 20% of this large consecutive cohort of adults with a new histological diagnosis, in the six months after starting radiotherapy. At any one time, between 1 in 7 and 1 in 15 patients were depressed. Major depression was between three and four times more likely in those with a past history of depression, or significant functional impairment. When present, it persisted for at least three months in about half of patients. High drop-out of depressed patients made the longitudinal course of MDD harder to study, however. A sensitivity analysis suggested that diagnoses of MDD were generally not confounded by side-effects of current steroid use.

10.4.2 Limitations

DSM-IV provides for a diagnosis of ‘MDD due to glioma’. In this context, the phrase “due to” alludes to the documented presence of a direct biological cause of depressive symptoms, and not to the possibility of an indirect (but otherwise understandable) psychological reaction to stress. Deciding whether steroids, radiotherapy, chemotherapy or surgery directly caused a given symptom was often impossible. Therefore I did not attempt to make the alternative diagnosis of ‘MDD due to glioma’ in the current analysis. Others have taken this approach. (Ring et al. 1998) My analyses, like theirs, describe symptoms rather than implying aetiology.

A second important diagnostic issue concerns the potential for confusing normal grief with MDD. There is no clear definition of ‘normality’ in this context. Some degree of adaptive (and therefore healthy) emotional reaction to the losses associated with glioma is inevitable. I avoided making a value judgement on whether any given symptom was understandable in any given patient’s context. This decision is consistent with DSM-IV guidance. It is important to note that I only interviewed patients after the start of radiotherapy, allowing at least one month from the operation for psychological adjustment to occur. Even then, MDD was diagnosed only if symptoms were multiple, significant, persistent, new and (often) corroborated – i.e., clinically relevant. This limitation is considered in more detail in Chapter 13. The presence of good inter-rater diagnostic agreement lends some support to the diagnosis of MDD.
There is a high likelihood of recruitment bias towards well-functioning, emotionally expressive patients in these analyses. As time passed, poorly-functioning and clinically depressed patients dropped out of the study, further biasing the later data and reducing precision. These factors may have led me to underestimate the true prevalence of MDD among adults with glioma. Multivariable analyses were constrained by relatively low numbers of depressed patients; the result may remain confounded by the impact of steroid prescription or cognitive impairment. I did not measure other potentially relevant variables at all, including: whether there was a family history of depression; the patient’s personal coping style; their social support; their awareness of prognosis; or their drug or alcohol use.

10.4.3 Results in context

Throughout the 6-month period following the start of radiotherapy, the criteria for diagnosing MDD were met in 20.6% of glioma patients. At any given sampling point, the frequency of MDD ranged from 6.8% to 14.8%. Contextualising these findings is difficult because few other authors have diagnosed depression in glioma patients using structured clinical interview. Probably the most in-depth report is that of Wellisch et al., described in more detail in Chapter 5. The authors reported a cross-sectional prevalence of MDD of 28% in a sample of outpatients with a variety of primary brain tumours. They estimated that an additional 7% of patients met criteria for ‘MDD due to a General Medical Condition’ (primary brain tumour). They did not explain how such a difficult judgement was made. Regardless, a clinically significant, diagnosable depressive disorder was evident in over one third of brain patients in their cross-sectional sample. (Wellisch et al. 2002) The high frequency of endorsement of sadness (53%) or anhedonia (49%) in that study is surprising. For a symptom to be endorsed it is expected to be significant, persistent and new. My experience in the current study was that some sadness and a degree of anhedonia were both very common, but truly persistent in only a small proportion of patients.

Wellisch et al. did not report inter-rater reliability of the clinical interviews. The higher prevalence of MDD in that study may reflect a degree of study-specific expectation or other measurement bias. In this thesis, I presented an analysis of inter-rater reliability which suggested good agreement between my diagnoses and those of an experienced consultant neuropsychiatrist blind to outcome.

Elsewhere, a much lower frequency of clinical depression was reported (6%) among patients with DNET or ganglioglioma undergoing epilepsy surgery. Interviews in this study, by Siegel and colleagues, were based on the DSM criteria but may not have been structured. Their recruited population also differs in several ways from the general population of glioma patients. (Siegel et al. 2008) Another cross-sectional study using the observer-rated Hamilton Rating Scale for Depression
identified clinically significant depressive symptoms in 15% of primary brain tumour patients, in the first few years after diagnosis. (Anderson et al. 1999)

In this chapter I presented the first attempted sensitivity analysis of MDD data in glioma by excluding, from diagnostic consideration, characteristic patterns of steroid-induced sleep and appetite disruption. Using this “exclusive” approach, the frequency of MDD at each time-point was unaffected, or only slightly reduced when compared to the “inclusive” method. At each time-point, there was overlap in the frequency precision estimates obtained using the two methods. PMH depression and T1 steroid prescription remained significant univariate predictors of current or subsequent MDD. The associations between MDD and functional impairment weakened, however. This suggests that the stronger association between functional impairment and MDD, seen in the ‘inclusive’ approach, was to some extent mediated by symptoms consistent with the side-effects of steroids. A specific study would be needed to explore this further, since insomnia, in particular, is a characteristic feature of both MDD and steroid use. Generally, the results of this sensitivity analysis strengthen confidence that a genuine depressive syndrome was being diagnosed.

The prevalence of DSM-III or DSM-IV MDD has been studied more often in other cancer populations. Most recent studies of MDD estimate a frequency in cancer patients of between 5 and 15%. (Hotopf et al. 2002; Pasquini and Biondi 2007) The frequency of MDD in the current study is therefore roughly consistent with existing literature on depression in brain tumour patients, such as it is, and is consistent with what is known about its frequency in systemic cancer patients.

Several studies recruiting glioma patients have reported HADS data, often as a dichotomised outcome variable. (Anderson et al. 1999; Grant et al. 1994; Janda et al. 2007; Kilbride et al. 2007; Pringle et al. 1999) All these authors used the upper HAD-D threshold (11+), which in the current study would have under-estimated the true frequency of MDD. However even using this threshold, I observed a lower frequency of supra-threshold scores than most other authors (whose studies reported a range of 0% to 21%, median 16% as detailed in Chapter 5).

Other researchers have reported the mean HAD-D scale score. (Diaz et al. 2009; Feuerstein et al. 2007; Fox et al. 2007; Grant et al. 1994; Gregor et al. 1996; Janda et al. 2007; Pringle et al. 1999; Zbinden et al. 2006) My data are again at the lower end of the literature (Chapter 5 reports HAD-D mean scores ranging from 3.2 – 6.2, median 5.6)

To date, only one other group has used the PHQ-9. (Arnold et al. 2008) In a large cross-sectional sample of 266 glioma patients (out of 363 brain tumour patients) the authors reported that 41% scored above threshold. However, their chosen threshold was 6+, notably low, and not clearly justified. In the current study I found that even a PHQ-9 cut-off ≥ 10 may systematically over-estimate the frequency of clinical depression compared with structured interview.
MDD in glioma was independently associated both with a past history of depression, and the presence of significant functional impairment. The literature suggests stronger associations between depressive symptoms in glioma and functional impairment, cognitive dysfunction and reduced quality of life (see Chapter 5). I prospectively confirmed an independent association with functional impairment and was able to make the first estimate of its effect size (OR = 3.6). Previous research was inconclusive on whether a prior history of depression was an independent risk factor for depression in glioma. The only other multivariable analysis in DSM-IV diagnosed glioma patients found no association between MDD and PMH depression (Wellisch et al. 2002), but univariate analyses from several other authors suggested some kind of association. (Arnold et al. 2008; D'Angelo et al. 2008; Kaplan and Miner 2000; Mainio et al. 2005a) This uncertainty is also present in depression in patients with systemic cancer. (Van't Spijker et al. 1997) My study suggests that patients with a prior history of GP-recorded depression could be nearly four times as likely to experience MDD following glioma diagnosis as those without a previous history.

The logistic regression model correctly categorised 81% of patients, aided by the relative infrequency of MDD. The false negative rate using this model was high (25/30), indicating that other factors play a considerable role in the development of depression. The model would need to be refined before being used to predict the likelihood of developing MDD in clinical practice.

Depressed glioma patients proved surprisingly difficult to follow up. Out of 32 patients attracting a diagnosis of MDD, nearly half (n = 15) dropped out of the study, mostly after the first interview. This may be explained partly by the association between MDD and functional impairment. High attrition is a recognised problem in trials of depression in cancer (Williams and Dale 2006) but has not previously been reported in observational glioma research. Drop-out would tend to make the course seem less persistent, as more severely affected patients left the study.

In the remaining 17 patients, MDD usually persisted between at least two interviews and new cases developed over time. The persistence of MDD is consistent with epidemiological research suggesting that the median duration of a treated episode of major depression is at least 3 months. (Angst 2009) Many longitudinal studies purportedly describing the ‘course’ of depression in cancer simply present mean scale scores at each follow-up time-point, making symptoms in individual patients difficult to track. However Sharpe et al. reported a cross-sectional study suggesting that symptoms of MDD had persisted in 150 systemic cancer outpatients for a median of 6 months at the point of sampling. (Sharpe et al. 2004) It is likely that MDD often persists in glioma, although it is important to recognise that the syndrome resolved after one interview in a minority of patients who could be followed up in the current study.

The HAD-D and PHQ-9 recorded different longitudinal courses. The overall direction of change on the HAD-D was neutral, while PHQ-9 scores reduced over time. The scales also differed in the extent
to which they maintained a distinction between those initially scoring high and those initially scoring low. Unlike the HAD-D, initially high PHQ-9 scorers continued to score more highly over time. The dissociation between these two scales, when given to the same patients, highlights the importance of considering the choice of rating scale when comparing the results of research studies of depression in glioma patients. To some extent it may reflect a greater element of somatic confounding in PHQ-9 scale scores. As more severely ill patients left the study, artificially inflated mean PHQ-9 scores may have been expected to drop.

10.5 Chapter summary

In this chapter I described the largest and most in-depth study yet conducted of the clinical characteristics of MDD and depressive symptoms in glioma patients. MDD appears to affect up to one in five relatively well-functioning glioma patients in the six months after starting radiotherapy. When it develops, clinical depression often lasts for at least three months. Men and women have similar risk of developing MDD. Patients with a previous history of depression, and those with functional impairment (e.g. those who cannot do their normal daily activities, even with effort) are at higher risk. These patients should be routinely assessed for MDD and may benefit from increased support.
11 Observations on current antidepressant drug treatment practices for Major Depressive Disorder in glioma

11.1 Introduction

In Chapter 6 I noted that antidepressants may be suspected of causing epileptic seizures. One broadly hypothesised mechanism of epileptogenesis is that antidepressants may somehow antagonise the anticonvulsant effects of antiepileptic drugs (AEDs). (BNF 2008) Antidepressants and AEDs may also pharmacokinetically interact, leading to toxicity. (Spina and Perucca 2002) Doctors may therefore hesitate to prescribe antidepressants to epileptic patients (Kuhn et al. 2003), including patients with glioma.

The clinical relevance of these concerns is unclear. Some researchers argue that antidepressants do not increase seizure frequency when given in therapeutic doses. (Alper 2008; Jobe and Browning 2005; Salzberg and Vajda 2001) Because MDD is itself a risk factor for epilepsy (Hesdorffer et al. 2006; Kanner 2008), it is theoretically possible that effective antidepressant treatment might actually improve seizure control. In a large meta-analysis of nearly 40 000 participants in licensing trials, certain SSRIs were associated with a statistically significantly reduction in seizure frequency relative to placebo. (Alper et al. 2007) Although most studies of this issue are in epilepsy-free populations, those examining antidepressant use in depressed epileptic patients report no marked increase in seizure frequency either. (Gross et al. 2000; Kuhn et al. 2003)

A difficulty facing clinicians in neuro-oncology is that such studies generally exclude patients with cerebral glioma. As I have argued in the thesis so far, depression is a frequent and important complication of glioma. Yet glioma patients are also at high risk of epileptic seizures. Clinical and theoretical uncertainty over the impact of antidepressants on seizure frequency – while understandable – could delay or prevent the effective treatment of depression in glioma. There is currently no evidence to guide neuro-oncologists treating depression in glioma. Although an RCT is the gold standard, in the absence of previous research I aimed to conduct a simple descriptive study. In this chapter I will examine:

1. Which AEDs and antidepressants are prescribed to glioma patients, and in what doses?
2. Is there any evidence to suggest that naturalistic antidepressant treatment is associated with the presence of seizures?
11.2 Methods

This study was contained within the larger study described in Chapter 7. Design, setting, participants and variables were as described in that chapter. Variables relevant to the current chapter are again outlined or expanded upon below.

11.2.1 Variables

To determine whether the patient had presented with epilepsy, I scrutinised the inpatient clerking and/or the formal outpatient discharge letter. Any mention of seizure (or, in a few cases, of sudden collapse) was recorded as epilepsy.

At each study time-point, I recorded information about epileptic seizures in the immediately preceding month. The main source for this information was patient and/or relative report. I asked every patient “Have you had any seizures in the past month?” Positive responses were explored further, to satisfy me that the patient was describing an epileptic seizure. I asked questions about aura, onset, duration, phenomenology, associated symptoms, awareness during episode and post-ictal symptoms. In practice most patients gave a history clear enough to make a reasonably confident clinical judgement about the presence or absence of epilepsy. Where there was doubt, the patient’s outpatient clinical records were reviewed. Two patients were known to have previous non-epileptic attacks as well as epilepsy, and I did not attempt to distinguish between these kinds of seizure.

Antidepressant and antiepileptic drug prescription data were collected principally through patient and relative report. I asked every patient to list the medicines and doses they were taking, including “medicines for depression” and “medicines for seizures”. If the patient and/or relative were unsure, I corroborated prescription information either from the current clinical records, or a GP prescription record, or direct observation of the medicine packaging.

11.2.2 Statistical analyses

Due to their exploratory nature, most analyses presented in this chapter are descriptive, using count rates and 95% confidence intervals. I identified patients who were first prescribed an antidepressant during the study period and conducted a narrative before-and-after analysis of seizure prevalence. I examined differences in epilepsy prevalence between HGG and LGG patients using Chi Square. I examined potential associations between antidepressant use and epilepsy prevalence using Fisher’s Exact Test.
11.3 Results

11.3.1 Participants

At T1 n = 155. At T2, n = 108 and at T3 n = 88. Basic clinical and demographic characteristics of participants and eligible non-participants were shown in Table 14 (Chapter 7).

11.3.2 Prevalence of epilepsy

Overall, 72/155 (46.5%) patients had originally presented with an epileptic seizure. Epilepsy was a more frequent presenting complaint in LGG (19/22, 86.4%) than in HGG (53/133, 39.8%; $\chi^2 = 16.4$, p < 0.001). This mainly reflected a greater frequency of partial seizures in LGG (10/20, 50%) than HGG (20/128, 15.6%, $\chi^2$ p < 0.001). Generalised tonic-clonic seizures presented with statistically equal frequency in LGG (7/20, 35%) and HGG (30/128, 23.4%, $\chi^2$ p = 0.267).

At T1, 33/155 (21.3%) patients reported having had an epileptic seizure in the preceding month. The reported prevalence of recent epilepsy at T2 and T3 was 25/108 (23.1%) and 17/88 (19.3%) respectively. LGG patients were more likely than HGG to report epilepsy at T1. At later follow-up points, epilepsy prevalence was similar for HGG and LGG patients. This appeared to be due mostly to improved seizure control in LGG patients. Partial seizures were about three times as common as GTC seizures throughout the study (Table 22).

11.3.3 Use of AEDs

83/155 (53.5% ± 7.8%) patients were prescribed an AED at T1, of whom eight (5.2%) required a second AED for adequate seizure control. These figures rose slightly to 58/88 (65.9% ± 9.9%) by T3, with eight patients (9.1%) on two AEDs by this time. The most frequently-prescribed AEDs were Carbemazepine (at T1), and Levetiracetam (at T2 and T3) (Table 23).
11.3.4 **Use of antidepressants**

The frequency of antidepressant prescription was 8.4% ± 4.4% at T1, 7.4% ± 4.9% at T2 and 12.6% ± 6.9% at T3. Almost all prescribed antidepressants were SSRIs. Citalopram was the most frequent choice. Most doses were above the minimum effective dose (Table 24).

During the whole study, 19 (12.3% ± 5.2%) individuals were prescribed an antidepressant (Table 25). Eleven of these patients received a diagnosis of MDD at some point in the study. A further 21 patients were diagnosed with depression but were not prescribed antidepressants at any point. Therefore, only 34% of glioma patients with MDD at any point reported being treated with antidepressants at any point.

Of the 19 patients prescribed antidepressants, only seven provided useable longitudinal data. A further eight patients dropped out of the study before the following interview, and four were first prescribed antidepressants at T3. All seven patients remained on the same antidepressant for at least three months. Anecdotally, all four patients who started an antidepressant after being diagnosed with depression at T2 reported a perception of benefit at T3.

11.3.5 **Associations between antidepressant use and epilepsy**

Antidepressant prescription was not associated with seizure prevalence at any time-point (Table 26). The absence of any association could have been mediated by inter-group differences in AED dose. It was not possible to compare total AED doses between the two groups however. Patients were often taking differing AEDs which do not readily allow for direct dose comparison. Instead, I compared the frequency of any AED prescription in each group. At T1, patients on antidepressants were statistically less likely to be prescribed an AED (3/13) than those on no antidepressant (80/142, $\chi^2 = 5.297, p = 0.021$). There were no differences in AED prescription frequency between the two groups at T2 and T3.

Most patients had been prescribed antidepressants before the study began. Before-and-after data was available on six patients who commenced an antidepressant during the study period. No clear pattern was apparent from this small series. There was however no evidence of a marked increase in seizure prevalence after starting antidepressants (Table 27).
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<tr>
<td>T3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total n at this point</td>
<td>69</td>
<td>19</td>
</tr>
<tr>
<td>Any seizure</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>GTC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 22.** Frequency of epilepsy at each study time-point.

a. GTC and partial seizure data for this time point n = 148 due to missing data. Note that some patients had GTC and partial seizures together, so ‘any seizure’ may be less than GTC and partial combined. Seizure prevalence HGG vs LGG analysed using Chi Square.

b. GTC and partial n = 153/155. P value calculated using Chi Square.

c. GTC and partial n = 107/108. P value calculated using Fisher’s Exact Test.

d. GTC and partial n = 88/88. P value calculated using Fisher’s Exact Test.
Table 23. Frequency of prescription of individual anti-epileptic drugs at each time point.

Note that this table does not describe the longitudinal drug courses of any individual patients - just raw count rates.

a. Patients taking two AEDs are counted twice in these columns.

We did not statistically test longitudinal differences in median dose because data at T2 and T3 were mixed dependent (from the same patient as an earlier time-point) and independent (no prior data, i.e. a new AED had been started).
Any timepoint

<table>
<thead>
<tr>
<th>MDD present, n (%)</th>
<th>T1 (n = 155)</th>
<th>T2 (n = 108)</th>
<th>T3 (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 (20.6)</td>
<td>21 (13.5)</td>
<td>16 (10.3)</td>
<td>6 (6.8)</td>
</tr>
</tbody>
</table>

Any antidepressant use, n (%)  

<table>
<thead>
<tr>
<th>Antidepressant (n)</th>
<th>T1 (n = 155)</th>
<th>T2 (n = 108)</th>
<th>T3 (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Trazodone</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trazodone</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 24. Frequency of prescription of individual antidepressants at each time-point.

Note that this table does not describe the longitudinal drug courses of any individual patients, just raw count rates.

a. One patient had three different antidepressants during the course of the study, so the numbers in this column add up to 21.
<table>
<thead>
<tr>
<th>Study number</th>
<th>Patient sex</th>
<th>Age</th>
<th>Tumour</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>M</td>
<td>70</td>
<td>GBM</td>
<td>Citalopram 20</td>
<td>Trazodone 150</td>
<td>(deterioration)</td>
<td>MDD present at T1. MDD not present at T1 or T2; antidepressant started by oncologist for emotional lability (sudden crying).</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>GBM</td>
<td>Trazodone 150</td>
<td>(patient choice)</td>
<td>Citalopram 20</td>
<td>MDD present at T1. MDD not present at T1 or T2; antidepressant started by oncologist for emotional lability (sudden crying).</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>58</td>
<td>GBM</td>
<td>—</td>
<td>Citalopram 20</td>
<td>(deterioration)</td>
<td>MDD present at T1. MDD not present at T1 or T2; antidepressant started by oncologist for emotional lability (sudden crying).</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>49</td>
<td>Anaplastic astrocytoma</td>
<td>Paroxetine 20</td>
<td>Paroxetine 20</td>
<td>Paroxetine 20</td>
<td>Patient had a longstanding previous history of depression and was on an antidepressant at the time of presentation. MDD present at all three points.</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>52</td>
<td>Astrocytoma</td>
<td>—</td>
<td>Escitalopram 10</td>
<td>Escitalopram 20</td>
<td>MDD present at T2 and T3 only. Longstanding prior history of depression, on antidepressants at presentation. MDD present at T3 only.</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>58</td>
<td>GBM</td>
<td>Fluoxetine (?)</td>
<td>Fluoxetine 20</td>
<td>Fluoxetine 20</td>
<td>History of alcohol misuse. MDD not present at T1.</td>
</tr>
<tr>
<td>41</td>
<td>M</td>
<td>47</td>
<td>GBM</td>
<td>Fluoxetine (?)</td>
<td>(deterioration)</td>
<td>—</td>
<td>Antidepressant started within a week of initial presentation by the surgical team, due to the patient’s tearfulness on the ward. MDD not present at any study time-point.</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>52</td>
<td>GBM</td>
<td>Citalopram 20</td>
<td>Citalopram 20</td>
<td>Citalopram 20</td>
<td>Antidepressant started about one year before glioma presentation. MDD not present at any study time-point.</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>51</td>
<td>Anaplastic oligodendroglioma</td>
<td>Citalopram 40</td>
<td>Citalopram 20</td>
<td>Citalopram 20</td>
<td>Antidepressant started about two months before glioma presentation. MDD not present at T1.</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>74</td>
<td>GBM</td>
<td>Mirtazapine 30</td>
<td>(deterioration)</td>
<td>—</td>
<td>Longstanding prior history of depression. MDD present at all three time-points. On two</td>
</tr>
<tr>
<td>93</td>
<td>M</td>
<td>33</td>
<td>GBM</td>
<td>Duloxetine 60</td>
<td>Duloxetine 60</td>
<td>Venlafaxine 150</td>
<td>—</td>
</tr>
<tr>
<td>ID</td>
<td>Sex</td>
<td>Age</td>
<td>Tumor Type</td>
<td>Antidepressant at T1</td>
<td>Antidepressant at T2</td>
<td>Antidepressant at T3</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>M</td>
<td>66</td>
<td>GBM</td>
<td>–</td>
<td>–</td>
<td>Citalopram 20</td>
<td></td>
</tr>
<tr>
<td>118</td>
<td>M</td>
<td>59</td>
<td>GBM</td>
<td>–</td>
<td>–</td>
<td>Mirtazapine 15</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>F</td>
<td>65</td>
<td>GBM</td>
<td>–</td>
<td>–</td>
<td>Floxetine 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(deterioration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>M</td>
<td>55</td>
<td>GBM</td>
<td>Citalopram 40</td>
<td>–</td>
<td>Paroxetine 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(deterioration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>M</td>
<td>64</td>
<td>GBM</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>142</td>
<td>F</td>
<td>61</td>
<td>GBM</td>
<td>Citalopram 10</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>F</td>
<td>35</td>
<td>Anaplastic astrocytoma</td>
<td>Citalopram 20</td>
<td>Citalopram 20</td>
<td>Citalopram 20</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>M</td>
<td>76</td>
<td>GBM</td>
<td>–</td>
<td>–</td>
<td>Floxetine 20</td>
<td></td>
</tr>
</tbody>
</table>

**Table 25. Patients receiving antidepressants during the study.**

Grey shaded areas indicate loss to follow-up with principal reason for drop-out.
a. Dose not known by patient and not obtained during the course of the study.

MDD present at T2 only. Patient perceived benefit from antidepressant at T3.
MDD present at T2 only. Patient perceived benefit from antidepressant at T3.
Prior history of depression. Date of starting antidepressant not clear.
MDD not present at T1.
MDD present at T1.
MDD present at T1 and T2 only. Patient perceived benefit from antidepressant at T3.
Antidepressant started shortly after starting radiotherapy due to high distress. Patient only participated in study at a later date, when MDD was not present at any time-point.
MDD present at T2 only. Patient perceived benefit from antidepressant at T3.
Table 26. Cross-tabulation of current antidepressant prescription and patient/relative report of epileptic seizures in the preceding month at each time-point.

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Epilepsy at:</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>P</td>
<td>T2</td>
<td>Absent</td>
<td>Absent</td>
<td>P</td>
</tr>
<tr>
<td>Yes</td>
<td>Present</td>
<td>1</td>
<td>1</td>
<td>0.302</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>Absent</td>
<td>32</td>
<td>110</td>
<td>12</td>
<td>0.302</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 27. Before-and-after details of patients first starting antidepressants during the course of the study (n = 6).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>AD first prescribed</th>
<th>Seizure at presentation</th>
<th>Seizures reported pre-AD</th>
<th>Seizures reported post-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>T2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>32</td>
<td>T2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>111</td>
<td>T3</td>
<td>No</td>
<td>Yes (GTC)</td>
<td>No</td>
</tr>
<tr>
<td>118</td>
<td>T3</td>
<td>No</td>
<td>Yes (Partial)</td>
<td>Yes (GTC)</td>
</tr>
<tr>
<td>133</td>
<td>T3</td>
<td>Yes (Partial)</td>
<td>Yes (Partial)</td>
<td>Yes (Partial)</td>
</tr>
<tr>
<td>152</td>
<td>T3</td>
<td>Yes (GTC)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

AD = antidepressant. GTC = generalised tonic-clonic seizure.
11.4 **Discussion**

11.4.1 **Main results**

In this prospective exploratory study, I found no evidence to suggest that antidepressants should be considered to be contraindicated due to fear of precipitating epilepsy in adults with primary glioma. When GPs and clinical neuro-oncology teams were allowed to treat depression as usual, I observed no association between antidepressant prescription and an increased prevalence of epilepsy. Antidepressants were tolerated well by those glioma patients who could be followed up. Several patients also reported a perception of benefit from antidepressant treatment, and in each case their major depression was found to have remitted. However, depression appeared to be under-treated, with only 34% of depressed patients on antidepressants at any point in the study.

11.4.2 **Limitations of study**

There are several important limitations to these results. They stem from the epilepsy–antidepressant interaction being only a secondary focus of the main study. Antidepressant prescription was not controlled. Patients receiving antidepressants may therefore have been selected by their GPs or neuro-oncology teams, for a variety of unknown reasons. AED, antidepressant use and presence and type of epileptic seizures were determined largely by patient self-report and clinical assessment. These are suboptimal methods and may be unreliable. I did not measure patient compliance with prescribed treatment, or other types of treatment for depression that may have had an effect on epilepsy frequency (e.g., St. Johns Wort). The small number of patients eligible for the before-and-after analysis limited the conclusions that could be drawn. These limitations prevent the results from being generalised confidently to clinical practice.

11.4.3 **Results in context**

Only 34% of depressed glioma patients reported taking antidepressants. Recall bias might explain some of the observed discrepancy. The result is consistent with previous research, however, which generally suggests that not all episodes of probable depression diagnosed in the context of a research study are currently treated with antidepressants. The clearest previous evidence in glioma was from the cohort study of Litofşky et al., which was described more fully in Chapter 5. These authors reported clinical (physician-diagnosed) depression in 15% - 22% of patients, but an antidepressant
prescription frequency, respectively, of 5% - 16%. Whether the depressed patients were the same ones taking antidepressants was unclear. (Litofsky et al. 2004) The sample was also highly selected, particularly in the later stages of the study when physicians continuing to complete study forms may also have been more likely to assiduously screen and manage the patient’s symptoms. An implication would be that the ‘unmeasured majority’ may receive less aggressive diagnosis and/or management of depression.

Studies of patients with systemic cancer support this conclusion. Sharpe et al. surveyed 150 cancer outpatients with MDD, only 29% of whom had been offered antidepressants. A fewer proportion was actually taking them, and overall, 85% of depressed cancer patients were not receiving evidence-based treatment for depression. (Sharpe et al. 2004) One possible reason for this is that doctors may miss distress in up to (and possibly more than) 70% of distressed cancer patients. (Fallowfield et al. 2001)

Another possible reason is that clinicians may be dissuaded from prescribing antidepressants through concern over their side-effects. (Gross et al. 2000) The link between routine antidepressant use and fear of epilepsy may be a form of clinical ‘folklore’, stemming from experience with older antidepressants and case reports of antidepressant overdose. (Jobe and Browning 2005; Whyte et al. 2003) Among 30 000 participants in antidepressant licensing trials, Alper et al. found no evidence that most antidepressants cause epilepsy in therapeutic doses (Bupropion and possibly Clomipramine excepted). (Alper et al. 2007) There is however no good evidence on whether antidepressants increase the risk of seizures in the high-risk group of glioma patients (see Chapter 6).

Only a few, small, retrospective studies have previously examined the effect of antidepressants in cohorts of depressed patients with pre-existing epilepsy. Generally they show no marked deterioration in seizure control. Gross et al. conducted an uncontrolled retrospective case-notes review of 57 patients attending a tertiary specialist epilepsy centre who were started on a psychotropic medicine. (Gross et al. 2000) In most cases the psychotropic was an antidepressant. The median seizure frequency in the two month period before psychotropic prescription was 150 seizures (range 0 - 1500). In the two month period after starting a psychotropic medicine, the median seizure frequency was 125 (range 0 - 1500), not significantly different. The authors concluded that the prescription of psychotropic medicines did not appear to affect seizure frequency in patients with epilepsy.

A particular strength of their study was the collection of pre-psychotropic seizure frequency data, which provided a useful baseline. However, their results do not necessarily generalise to glioma patients. The authors specifically excluded patients undergoing a brain operation within the two month period prior to psychotropic treatment. Seizure disorders typical of the population of patients attending a specialist epilepsy centre may also differ to those of patients with glioma. The authors acknowledged selecting psychotropic drugs and doses with the explicit intention of minimising seizure risk.
Kuhn et al. conducted a post-hoc analysis of clinical data from 75 specialist epilepsy centre inpatients. (Kuhn et al. 2003) Each patient had major depression and a baseline Hamilton Depression Rating Scale score ≥ 15. The authors pseudo-randomised each depressed patient to citalopram, mirtazapine or reboxetine, and followed them up for 20-30 weeks. Depressive symptoms reduced equally in the three groups, although dropout was significantly higher in patients receiving mirtazapine. Choice of antidepressant was not related to the number of AEDs prescribed at final follow-up. According to the authors’ clinical judgement, seizures did not increase in frequency or severity during the study. However, the absence of a control group of depressed patients receiving placebo was a particular weakness.

Most antidepressants are not enzyme inducers, and none are known to reduce serum AED levels (St John’s Wort is an important over-the-counter exception). (BNF 2008;Taylor et al. 2007) Drug interactions are therefore more likely to contribute either to AED toxicity or to lack of antidepressant efficacy. The SSRIs fluoxetine and fluvoxamine are potent CYP inhibitors. They could contribute to AED toxicity if prescribed together with either carbamazepine or phenytoin, both of which have a narrow therapeutic index. Carbamazepine and phenytoin are enzyme inducing AEDs and may decrease the serum level of paroxetine, mirtazapine, mianserin and other tricyclic antidepressants. (BNF 2008;Salzberg and Vajda 2001) In theory therefore, these various combinations of drugs may be best avoided. One patient was prescribed fluoxetine (20mg) concomitantly with carbamazepine (200 mg daily) and tolerated it well, however. The most frequently prescribed AED in this study – levetiracetam – has no known pharmacokinetic interactions with antidepressants, while the most popular antidepressant – citalopram – is only a weak cytochrome P450 system (CYP) inhibitor.

11.5 Chapter summary

In this chapter I found no apparent association between antidepressant prescription and an increased prevalence of epilepsy. There are a number of important limitations to this observation. However in the context of a total absence of glioma-specific evidence, it is initially reassuring to observe the apparent lack of a severe risk of seizures among a cohort of glioma patients who are prescribed antidepressants in a naturalistic fashion. Patients who reported taking an antidepressant also usually remained on the same drug throughout follow-up, suggesting more generally that side effects were tolerable.
12 What GP and patient-related barriers exist to the effective management of depression in glioma?

12.1 Introduction

Potential barriers exist to the effective diagnosis and treatment of depression in patients with systemic cancer. They include: a doctor’s lack of confidence distinguishing between normality and disorder; lack of time in clinic; physician reluctance to broach emotionally difficult topics; and assumptions that patients will spontaneously disclose any problems. (Greenberg 2004; Hoffman and Weiner 2007; Lloyd-Williams 2000; Maguire 1985) Possible barriers to treatment include: under-diagnosis; assumptions that treatment is not required because depression is somehow normal in the circumstances; concern over side-effects of antidepressant medications; and patient resistance. (Lloyd-Williams 2000; Maguire 1985; Nutting et al. 2002; Priest et al. 1996)

Depression in patients with glioma is a particularly complicated case of depression in cancer. The poor prognosis and frequent functional impairment may make doctors inclined to expect depression to occur, perhaps even to regard it as a normal event. The high prevalence of epilepsy could raise anxiety about precipitating a seizure by prescribing an SSRI. Although these factors could influence the management of depression in glioma, the attitudes of patients and doctors towards depression and its treatment in glioma are unknown.

I therefore conducted a basic study to begin identifying the barriers to the diagnosis and treatment of depression by General Practitioners (GPs) of adults with primary cerebral glioma. I surveyed GP views about the nature of depression and its diagnosis. I recorded their depression treatment preferences and linked them with those of their glioma patients.

12.2 Method

This study was contained within the larger study described in Chapter 7. Design, setting and glioma patient participants were as outlined in that chapter. Other variables and those particularly relevant to the current chapter are outlined below.
12.2.1  Materials

I used two data collection forms: a GP questionnaire and a patient questionnaire. These were both developed in discussion with supervisors. Psychometrically validating the questionnaires would have been impractical in the time-frame. Instead they were designed to have satisfactory face validity by making the questions as clear and as unambiguous as possible. I tried to avoid leading the respondents and did not adopt any position on which answers were correct.

The GP and patient questionnaires are presented in Appendix 12a and Appendix 12b.

12.2.2  Procedure

The GP questionnaire was posted to every named GP of the patients enrolled in the parent study. I identified each patient’s GP through a combination of asking the patient, checking hospital clinical records and telephoning GP practices directly. The questionnaire was only posted after each patient had completed the entire study protocol (or else had dropped out). This avoided influencing GP management of any depression while the observational study was ongoing. One reminder letter was sent to non-responding GPs a month later. Patients completed their questionnaire during their first study interview, shortly after the start of radiotherapy.

12.2.3  Statistical analyses

Data are presented as count rates with 95% confidence intervals. I identified a priori hypotheses of special interest. These were: (1) that GPs who considered depression to be mainly a psychological reaction would be more likely to state a preference for psychotherapy as primary treatment; (2) that GPs regarding depression as ‘a normal reaction’ would be more likely to state that it did not always need treated and (3) that GPs reporting concern over provoking epileptic seizures with an SSRI would be more likely to favour psychotherapy as primary treatment of depression. These hypotheses, and univariate associations between patient sex, years of practice (GP) or age (patients) and response, were tested using Chi Square analyses or Mann-Whitney U tests as appropriate.
12.3 Results

12.3.1 Participants

N = 155 patients were recruited to the parent study. However GPs for three participating patients were excluded because they were already the GP for another patient in the study. One other patient was visiting from the USA and had no GP. Therefore, 151 GP questionnaires were posted out. Responses were received from 105 GPs. Six did not provide any useable data, as follows: three indicated they would not complete the questionnaire because the patient had died; one stated that the patient’s original GP had now left the practice; one stated simply “I cannot answer these questions” and one did not provide a reason for returning an empty questionnaire. Data were therefore available for analysis on 99/151 GPs (response rate 65.6%). All patients completed the patient questionnaire, but in order to link patient and GP attitudes directly, patients whose GP did not respond were excluded from this analysis. Clinical and demographic data are presented in Table 28.

<table>
<thead>
<tr>
<th>GP data (n = 99)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sex n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58 (58.6)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (41.4)</td>
</tr>
<tr>
<td>Years in practice</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>19 (9.5)</td>
</tr>
<tr>
<td>Range</td>
<td>1 - 35</td>
</tr>
<tr>
<td>Glioma patients seen</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
</tr>
<tr>
<td>IQR</td>
<td>1-20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient data (n = 99)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sex n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58 (58.6)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (41.4)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.4 (12.1)</td>
</tr>
<tr>
<td>Range</td>
<td>19 - 72</td>
</tr>
<tr>
<td>Prior antidepressants n (%)</td>
<td>28 (28.3)</td>
</tr>
<tr>
<td>Prior counselling n (%)</td>
<td>14 (14.1)</td>
</tr>
</tbody>
</table>

Table 28. Relevant clinical and demographic information on GPs and their patients.
12.3.2 GP data

12.3.2.1 Demographics

58/99 GPs were male (58.6%). GPs had been registered for a mean of 19 years (SD 9.5, range 1 - 35). Responding male and female GPs were similarly experienced (independent samples t-test $t = 1.012$, $p = 0.314$).

12.3.2.2 Previous glioma patients

GPs had cared for a median of 2 glioma patients (IQR 1 - 3, range 1 - 20). As expected, number of previous glioma patients correlated with increasing years of experience (Spearman’s $\rho = 0.546$, $p < 0.001$). Data suggested that on average a GP would see one new glioma patient every 10 years.

12.3.2.3 Questionnaire responses

GP responses are shown in Table 29. Most GPs (78.4% ± 8.2%) thought that most depression was a normal reaction to having glioma, and that it was mainly psychological, rather than biological in origin (83.0% ± 7.6%).

Most (81.1% ± 7.9%) thought it quite hard to distinguish between normal sadness and depression in glioma. Most (72.7% ± 8.8%) stated that they would routinely ask a glioma patient about their mood during the GP surgery. Fewer GPs (43.6% ± 10.0%) recalled their glioma patients spontaneously volunteering information about their mood. Nearly all (90.8% ± 5.7%) would review a glioma patient at least once before treating them for depression.

Most GPs (60.8% ± 9.7%) thought that depression should always be treated. About half (55.3% ± 10.1%) favoured antidepressants over psychotherapy, and half (50.5% ± 9.9%) would worry about provoking an epileptic seizure if they prescribed an SSRI. Most (75.0% ± 8.7%) would prefer to treat a depressed glioma patient themselves rather than referring to a specialist.
12.3.2.4 Associations between variables and response

GPs who reported being concerned about the possibility of causing epileptic seizures by prescribing an SSRI were significantly more likely to favour primary treatment with psychotherapy (Table 30).

Female GPs were also more likely to favour psychotherapy (22/38, 58%) than men (20/56, 36%; \( \chi^2 = 4.506, p = 0.034 \)). There were no significant associations between treatment preference and number of years as a qualified GP.

GPs regarding depression mostly as a normal reaction to having glioma were just as likely to state that it should always be treated (48/75) as those regarding depression as mostly abnormal (10/21, \( \chi^2 = 1.841, p = 0.175 \)) This suggested that GPs may have interpreted the phrase ‘normal reaction’ (Q1) to mean an empathically understandable reaction, rather than a biologically harmless reaction.

GPs regarding depression as psychological in origin were equally likely to prefer antidepressants over psychotherapy (41/75) as those regarding depression as biological in origin (5/15, \( \chi^2 = 0.733, p = 0.392 \)).

12.3.3 Patient data

12.3.3.1 Previous treatment for depression

28/99 patients (28.3%) indicated that they had taken antidepressant medicines previously. 14/99 patients (14.1%) had received counselling for low mood. Patient report of previously having received antidepressants for low mood showed moderate agreement with GP records indicating a past history of depression (Spearman’s \( \rho = 0.590, p < 0.001 \); Cohen’s \( \kappa = 0.58 \)).

12.3.3.2 Attitudes towards future treatment

When asked how they would feel if their doctor suggested taking an antidepressant in the future, 42 patients (42.4%) would probably have refused, 44 (44.4%) would not want to decide immediately and 13 (13.1%) would probably have accepted. When asked how they would feel if their doctor suggested attending counselling in the future, 28 (28.3%) would probably have refused, 50 (50.5%) would not
Most depression is a normal reaction to having glioma. 76 (78.4)
Most depression is an abnormal reaction to having glioma. 21 (21.6)
It is mainly psychological in origin (due to the stress of having a brain tumour). 78 (83.0)
It is mainly biological in origin (due to disruption of neural circuits involved in emotion). 16 (17.0)
I’d find it quite hard to distinguish between normal sadness and depression, in glioma. 77 (81.1)
I’d find it quite easy to distinguish between normal sadness and depression, in glioma. 18 (18.9)
I’d routinely ask a glioma patient about their mood in surgery. 72 (72.7)
I’d not routinely ask a glioma patient about their mood in surgery. 27 (27.3)
My glioma patient(s) volunteered information about their mood in surgery. 41 (43.6)
My glioma patient(s) did not volunteer information about their mood in surgery. 53 (56.4)
In glioma, depression should always be treated. 59 (60.8)
In glioma, depression should not always be treated. 38 (39.2)
I’d generally treat depression in a glioma patient on the basis of one consultation. 9 (9.2)
I’d generally review a glioma patient at least once before treating them for depression. 89 (90.8)
I’d be worried about provoking an epileptic seizure if I prescribed an SSRI. 50 (50.5)
I’d not be worried about provoking an epileptic seizure if I prescribed an SSRI. 49 (49.5)
I’d favour psychotherapy over antidepressants for depression in glioma. 42 (44.7)
I’d favour antidepressants over psychotherapy for depression in glioma. 52 (55.3)
I’d prefer to refer a depressed glioma patient to a specialist for treatment. 24 (25.0)
I’d prefer to treat a depressed glioma patient in primary care. 72 (75.0)

Table 29. GP questionnaire responses.
Missing data n: a = 1; b = 2; c = 3; d = 4; e = 5

<table>
<thead>
<tr>
<th>Worried about epilepsy?</th>
<th>Favours psychotherapy</th>
<th>Favours antidepressants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>28</td>
<td>19^a</td>
<td>47</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>Totals</td>
<td>42</td>
<td>52</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 30. Cross-tabulation of GP responses suggesting that those concerned about epilepsy were less likely to favour antidepressants in treating a depressed glioma patient.
a. \( \chi^2 \ p = 0.004 \)
want to decide immediately and 21 (21.2%) would probably have accepted. These data suggested that
counselling was significantly more acceptable to patients (Wilcoxon Rank Sum Test $Z = -3.092$, $p =
0.002$).

12.3.3.3 Associations between variables and response

The attitudes of men were no different from the attitudes of women towards receiving antidepressants
(Mann-Whitney U Test $Z = -1.400$, $p = 0.161$) or counselling in future (Mann-Whitney U Test $Z =
-0.264$, $p = 0.792$). Patient age was not associated with attitude towards either future antidepressants
($Z = -0.930$, $p = 0.353$) or future counselling ($Z = -0.930$, $p = 0.353$). Likewise, whether a patient
reported having previously received counselling or antidepressants made no difference to their attitude
towards receiving counselling ($Z = -0.368$, $p = 0.713$) or antidepressants ($Z = -0.734$, $p = 0.463$) in
future.

12.4 Discussion

12.4.1 Main findings

This was a basic survey of GP and patient opinions on a number of issues surrounding depression in
glioma. It identified a number of possible barriers to the diagnosis and treatment of depression in
glioma patients. Nearly 80% of GPs regarded major depression as a normal reaction to having glioma,
and almost 40% believed that some major depression did not require treatment. Half would worry
about causing an epileptic seizure when prescribing an SSRI, and these GPs were more likely to
favour psychotherapy as primary treatment of depression.

GPs expressed difficulty distinguishing between normal and excessive sadness in a patient following
diagnosis of glioma. This difficulty may be compounded by the infrequency with which a GP may see
such patients. Whereas GPs had no preference for how to treat depression, their glioma patients
appeared to express a preference for counselling. Most patients expressed resistance to any kind of
future depression treatment, however.
12.4.2 Limitations of the study

Several limitations must be considered. Although the response rate was better than similar GP surveys (Arean et al. 2003; Jorm et al. 1997), questionnaire surveys are especially prone to response bias. Bias in the current study would arguably result from receiving more responses from GPs with a particular interest in depression. One might expect these GPs to be more likely to identify and treat depression where present. The validity of forcing GPs to choose from categorical responses can also be debated. It is a less sensitive method than qualitative interview or direct observation. However it is quick and simple, and to some extent reflects clinical reality where the decision is often between one or other courses of action. The questionnaires were not validated, despite efforts to make them as clear as possible.

Another important caveat is that GP attitudes may not predict their actual behaviour. (Dowrick et al. 2000) Similarly, some patients reported difficulty imagining how they would feel in future: they could therefore be more or less likely to accept treatment for depression in reality. The study illustrates only how patients and GPs currently think they would act. I was unable to compare these attitudes with actual practice (e.g. whether the GP prescribed antidepressants to a patient with MDD).

12.4.3 Results in context

GPs frequently believed that depression is a “normal reaction” to glioma. The reasons and assumptions underlying this result remain unknown. “Normal” could be interpreted variously to mean frequent, understandable or physiological. Equally, GPs may have interpreted “depression” to mean clinical depression, or simply colloquial sadness. Regardless, such an expectation is a potential barrier to the effective management of depression in glioma. Others have linked the under-recognition of depression in cancer patients partly to clinicians dismissing it as ‘understandable’. (Passik et al. 1998)

GPs acknowledged difficulty in distinguishing sadness from depression. This could be especially troublesome when a GP might only see a new glioma patient once every 10 years, as our demographic data suggested was the case. Although major depression is a wider concept than just severe sadness, there is no clear demarcation between normal and disordered sadness. Distinguishing between the two states is a well-recognised problem in cancer patients. ‘Borderline’ cases require clinical judgment. In such situations, psychiatric opinion-leaders recommend doing what GPs already do: reviewing patients at least once before making diagnoses. (Spitzer 2001) However this presents another potential barrier: diagnostic delay, especially if patients miss follow-up appointments.
A major potential barrier to treatment was the belief of a substantial minority of GPs that depression should not always be treated in a glioma patient. We did not study their reasons for stating this. The questionnaire referred explicitly to “major depression”. UK national guidelines recommend treatment with antidepressants in all depressed adults with chronic illnesses. (NICE 2009a) Guideline non-adherence could occur as a result of several factors, including lack of guideline awareness and/or disagreement with the guideline itself (Smith et al. 2004) and concern about the likely efficacy or adverse effects of medication. (Andersson et al. 2001; Nutting et al. 2002)

The lack of GP preference for antidepressants or psychotherapy perhaps fairly reflects the lack of evidence on their efficacy in treating depression in glioma. (Rooney and Grant 2010) However I found some evidence that anxiety about provoking epilepsy could influence a GPs preferred treatment strategy. The finding that half of GPs would worry about epilepsy when prescribing SSRIs is clinically significant. In the UK, psychotherapy wait times may be too long to be of practical use in glioma. Anxiety about antidepressants (the other mainstay of depression treatment) could sway GPs against treatment, especially if they already believed that not all depression should be treated anyway. A major difficulty in addressing such anxiety is the current lack of evidence to support or refute the concern about provoking epilepsy.

These results suggest a number of interventions. GP recognition of depression could benefit from education on the importance of even moderate depressive symptoms in glioma. ‘Best practice’ advice and clinical tips on differentiating normal from disordered sadness could be prepared and disseminated. The question of seizures requires careful management due to the potential risks. An appraisal of the current literature would however include the observation that there is currently no good evidence that antidepressants are dangerous in patients with glioma, but reasonable evidence that depression is a considerable burden.

Patients expressed resistance in anticipation of the idea of depression treatment generally, and treatment with antidepressants in particular. In keeping with previous studies (Priest et al. 1996), counselling appeared to be more appealing to patients. Patient attitudes towards antidepressant prescription may be influenced by many factors including: the frequent belief that antidepressants are addictive (Priest et al. 1996; Stone et al. 2004); the perceived stigma of requiring medication to treat low mood (Garfield et al. 2003); non-acceptance of diagnosis (Badger and Nolan 2006; Nutting et al. 2002); and/or poor previous personal or family experiences of treatment. (Badger and Nolan 2006) Others have reported that cancer patients do not always accept the offer of antidepressants even if it is made. (Sharpe et al. 2004) The fact that most patients expressed a degree of resistance to any kind of future treatment for depression represents another important barrier to its effective management.

Doctors should avoid assuming that glioma patients will seek treatment for depressive symptoms. Most GPs reported that their patients did not spontaneously volunteer information about their mood in
surgery, highlighting the need to ask them directly. The potential for reluctance of some cancer patients to disclose depressive symptoms is well-recognised. (Passik et al. 1998) Possible causes include the patient’s concern about “bothering the doctor”, fear admitting to difficulty coping and/or expectation that such symptoms must be normal. (Maguire 1985)

12.5 Chapter summary

In this chapter I presented data from a survey linking glioma patient and GP attitudes towards aspects of depression. I identified barriers to the effective diagnosis of depression in glioma, including the difficulty of distinguishing normal from abnormal sadness and patient reluctance to volunteer information about their mood. There is a need to educate GPs on how to distinguish sadness from depression in glioma, to encourage them to ask about mood every time, and to continue their practice of reviewing patients in difficult cases. The infrequency of glioma suggests value in obtaining a specialist diagnosis of depression where necessary, with GPs following the patient up routinely after that. Barriers to treatment include GP perception that not all depression needs treated, concern over the possible epileptogenic effects of SSRIs and patient resistance to depression treatment, particularly antidepressants.
13 Main findings and limitations of the thesis.

13.1 Introduction

In Chapters 7 - 12 I described the methodology and results of a prospective observational cohort study with 6 months follow-up, conducted to examine a number of important clinical issues relating to MDD and depressive symptoms in glioma. In each chapter I discussed some limitations of the analyses presented, and contextualised chapter-specific results. In this Chapter I will briefly summarise the main findings from the entire project, before discussing methodological limitations which I think are relevant to the whole study. I then appraise some practical and theoretical problems relevant to researchers studying glioma patients generally, and depression in glioma particularly. I close this Chapter with a summary of the main strengths of the study, which should be set against the limitations.

13.2 Thesis findings

General emotional distress has been poorly studied in glioma. Few studies have examined the use of the NCCN Distress Thermometer, and none have studied DT-measured emotional distress longitudinally. When depression is considered specifically, most observational studies in glioma have been small, cross-sectional and/or retrospective. Only one group previously used the SCID to diagnose MDD in these patients. There are no high-quality studies of the benefits or harms of antidepressant medicines when prescribed to treat depression in adults with glioma.

To improve our knowledge, I studied the largest cohort of consecutively presenting glioma patients yet to be assessed with either the NCCN distress thermometer, or a structured clinical interview for depression. In this twin centre study, I approached over 200 glioma patients, consenting and serially interviewing 155 in the six month period following the start of radiotherapy.

DT-defined emotional distress was present in at least one third of patients at any time-point, particularly those who were younger or functionally impaired. Distress persisted in patients who reported high distress initially. Worry and sadness were frequent causes of distress throughout the study. High distress was also strongly and independently associated with MDD.

I partially validated two multi-item depression rating scales to help clinicians who may wish to screen for major depression. The Hospital Anxiety and Depression Scale (Depression Subscale) and Patient Health Questionnaire 9 both had good internal reliability, but the HAD-D had marginally better and
more consistent sensitivity, specificity and positive predictive value. Clinicians can reasonably use a threshold of 8+ when screening for major depression using the HAD-D.

Screening instruments do not substitute for clinical interview, however. Using structured clinical interview diagnoses, MDD was present in 6.8% - 14.8% of patients at any one time-point, particularly those with a previous history of depression or significant functional impairment. MDD persisted in a clinically significant proportion of patients, and new cases developed over time. Depressed glioma patients were hard to follow longitudinally as they frequently dropped out of the study.

One of the recommended treatments for MDD is antidepressant medication. Yet depression appeared to be under-treated in glioma. Only 34% of depressed patients reported taking antidepressants. I found no evidence to suggest that antidepressants should be considered to be contraindicated in glioma. In particular, there was no apparent association between antidepressant prescription and an increased prevalence of epilepsy, in patients managed routinely by their usual team.

I identified a number of possible attitudinal barriers, among GPs and their patients, to the effective diagnosis and management of depression in glioma. These included: a tendency among GPs to regard depression as a “normal reaction”; difficulty distinguishing between normal and excessive sadness; a frequent belief that major depression sometimes did not need treated in glioma; and concern over provoking an epileptic seizure when prescribing an SSRI. Patients expressed resistance to depression treatment generally and to antidepressants in particular.

13.3 Thesis limitations

13.3.1 Sources of theoretical uncertainty

13.3.1.1 General limitations of the DSM system

The DSM model of operationalised diagnosis of mental disorder has been criticised. I will note four broad criticisms. First, in sacrificing the historical requirement for depressive symptoms to be disproportionate to the circumstances, the authors of DSM risked reframing normal sadness as a psychiatric illness, causing “diagnostic inflation”. (Horwitz and Wakefield 2007) I have come to wonder if the origin of this problem lies partly in historical changes to psychiatrists’ roles. In the 19th century psychiatry had been concerned only with the management of severe mental illnesses. The early 20th-century shift towards psychological and psychodynamic approaches added patients with
relatively mild distress. When the biomedical model was reasserted with the advent of DSM-III, patients with mild distress remained within psychiatry’s remit. However, the biomedical model does not necessarily fit them to the same extent.

Second, DSM scarcely acknowledges a continuum of disorder, thereby implying that normal sadness is qualitatively distinct from MDD. This assumption may be false, as in much of medicine (hypercholesterolaemia and hypertension are two examples of ‘continuous’ diseases). However the DSM compounds the difficulty by providing no clear criterion of demarcation between normality and disorder. It:

“…evades the question central to its logical structure, the difference between normality and pathology… [and] masks uncertainties about how much intrinsically continuous variables vary from an ill-defined norm by using vague modifiers such as ‘significant’”. (Galatzer-Levy and Galatzer-Levy 2007)

I think that this failure to clearly differentiate between states while asserting a dichotomous model ironically introduces subjectivity to a system that was specifically designed to eliminate it.

Third, the method of selecting symptoms to the syndromes operationalised in DSM was open to bias. No systematic literature review was undertaken during the development of DSM-III. Decisions on inclusion and exclusion criteria were made on the basis of individual expert opinion. This allowed data potentially to be overlooked or even wilfully ignored. (Rounsaville et al. 2002) The DSM edifice has been attacked as a largely political exercise, representing a white male American psychiatric consensus. In creating diagnostic categories, concessions were made to prevailing social conventions, special-interest groups, professional needs, and the demands of research funders and insurance companies. (Callahan and Berrios 2005)

Fourth, the boundaries between the diagnostic categories are arbitrary and may not reflect natural distinctions. The efficacy of many psychotropic medications cuts across different DSM diagnoses. (Kupfer et al. 2002) The correlation of diagnoses with biochemical findings is poor. (Galatzer-Levy and Galatzer-Levy 2007; Goodwin 2009) DSM-IV states that symptoms must have been present for at least two weeks, and in sufficient number – but these criteria are also arbitrary. There is no good evidence to support either the choice of two weeks as a cut-off for duration of symptoms or for a total of five symptoms being required to diagnose MDD. (Kendler and Gardner 1998) Callahan and Berrios argue that:

“…the [DSM] categories are actually just hypotheses regarding how emotional disorders might be distinct diseases..” (Callahan and Berrios 2005)
Blazer concurs:

“[DSM] diagnostic categories are simple concepts, justified only if they provide a useful framework for [making] inferences about outcome and… decisions about treatment”. (Blazer 2005)

The authors of DSM acknowledge many of these criticisms, stating that:

“…reification of DSM-IV entities, to the point that they are considered to be equivalent to diseases, is more likely to obscure than to elucidate research findings”. (Kupfer et al. 2002)

Therefore, it is important to remember that MDD is not necessarily a single disease. Rather it is a syndrome, the constituent symptoms of which were selected by consensus on the basis of a non-systematic review of patchy epidemiological evidence. In another sense, MDD is a convention: the particular term agreed, adopted and used mainly to denote the presence of symptoms which 30 years ago were hypothesized to co-vary together by a committee of psychiatrists under considerable political pressure.

13.3.1.2 Questions raised by the “bereavement exclusion”

One of the concessions made in this process was that symptoms attributed by the patient to bereavement would not count towards a diagnosis of MDD. The ‘bereavement exclusion’ is understandable and appropriate. However, some have argued that there may be little qualitative difference between grief experienced in response to loss of a loved one and grief experienced in response to loss of a cherished object. (Wakefield et al. 2007) Examples of possible losses, relevant to glioma, abound and include: health; future plans; driving license; identity; independence; professional and familial roles; physical function; and a sense of personal security. Why exclude sadness due to loss of life but not sadness due to loss of health – or even the perceived future loss of life? The bereavement exclusion is something of an arbitrary convention (see Box 11 for more detail).
Wakefield et al. argue that restricting the ‘bereavement exclusion’ to bereavement is of questionable validity. These authors re-analysed the first National Comorbidity Survey (NCS, n = 8098) and identified 1308 cases of DSM-III-R MDD, of which 710 were judged to have been triggered by a loss (including serious medical illness) other than bereavement. The authors labelled 536 of these cases as “complicated MDD”. They defined “complicated” as the presence of two or more of: a morbid preoccupation with worthlessness; suicidal ideation; suicide attempt; symptom duration longer than 12 weeks; functional impairment sufficient to stop the person from working or seeing friends; or marked psychomotor retardation. Patients meeting criteria for MDD, but without these particular symptoms, had “uncomplicated MDD”. The authors stated that:

“our overarching view is that [our] “uncomplicated” vs “complicated” distinction reflects likely nondisorder vs disorder.”

Therefore these authors would only regard “complicated” MDD, when occurring following a loss (as it did in 536/710 cases) as disorder. I did not replicate their approach in this thesis. I did not assess patients for symptom duration > 12 weeks and did not formally assess the presence of worthlessness (as opposed to guilt). I think that the psychomotor retardation and ‘functional impairment sufficient to stop work’ criteria would be less relevant, often being confounded by the normal consequences of glioma.

Wakefield et al. proceeded to show that the 174 patients with “uncomplicated MDD” diagnosed following some other loss event were no different from a subgroup of 56 patients with “uncomplicated MDD” diagnosed specifically following bereavement, in eight out of nine clinical outcomes (e.g., melancholic features, or whether antidepressants were prescribed). They concluded DSM-IV’s ‘bereavement’ exclusion clause should be extended to other kinds of loss, including the loss of health secondary to the onset of serious medical illness. This would have the effect of preventing MDD from being diagnosed following glioma diagnosis, unless “complicating” features were present.

One of the problems with Wakefield’s methodology, however, is their choice of outcome. Some of their Disorder Indicators (e.g., suicide attempt and duration of episode) had already been used to define whether MDD was complicated or uncomplicated in patients suffering bereavement and loss. I was therefore not particularly surprised that these factors did not differ between ‘MDD with uncomplicated bereavement’ and ‘MDD with uncomplicated loss’. These patients had already been defined as ‘uncomplicated’ on the basis of the very clinical variable that was subsequently presented as an outcome – creating a circular argument.

An alternative would be to use the same methodology of Wakefield et al, but rather than transcribing the NCS methodology, transcribe the existing DSM-IV criteria for complicated bereavement (which differ to the NCS criteria) to other forms of loss.

**Box 11. Issues raised in a study of the bereavement exclusion.**

13.3.1.3 Advantages of DSM

Yet, it is necessary to offset these weaknesses against the important advantages of the DSM system. It improves reliability of diagnosis, allows clinicians of different theoretical backgrounds to communicate clearly and reflects the symptoms in historical syndromes of low mood. (Spitzer 2001) DSM-IV is also internationally accepted. Its approach to diagnosing major depression in medical illness is endorsed by several relevant national and international bodies including the European Association for Palliative Care (Stiefel et al. 2001) and the National Institute for Health and Clinical
Excellence. (NICE 2009a) Applied in a face-to-face interview, the DSM-IV criteria remain the internationally recognised criterion standard method of diagnosing major depression.

MDD is essentially a hypothesis that certain symptoms co-vary together. A stated aim of the DSM model is to stimulate research into the suitability of the diagnostic categories themselves. (Spitzer 2001) It is surely appropriate to apply these criteria in studies of new populations. For me this is a key argument. The symptoms may be consensual, arbitrary, subjective and potentially confounded – but they were always intended to be studied and refined in an iterative process of hypothesis testing. It is acceptable to study how well MDD performs as a construct in different clinical populations.

13.3.1.4 Implications of theoretical uncertainty

The various limitations of the DSM system mean that the results of my study should be interpreted on the understanding that MDD may or may not be a valid construct in glioma patients. This does not necessarily imply that my methodology was weak, but rather that results must be viewed in the context of theoretical uncertainty as to the nosological validity of MDD in glioma.

My understanding of this was initially basic. I did not set research questions designed to study the validity of DSM-IV MDD itself. As I suspect many doctors do, I assumed at first that MDD was a specific condition, a single illness, and used the SCID as the ‘gold standard’ against which other tools could be validated. In doing so I followed many other researchers who have studied depression in cancer.

This problem is therefore relevant to much of the literature on depression in cancer. In the absence of disease-specific evidence, its interpretation can only be a matter of personal judgment. There may be a ‘conspiracy of the willing’, by which I mean that the question of the validity of MDD in cancer is broadly recognised, but collectively ignored by many in the psycho-oncology research community. The problem may be regarded as too difficult (or possibly too threatening) to engage with in a meaningful manner. I once suggested to an experienced researcher the possibility of studying the validity of DSM-IV symptoms in cancer patients. The idea was dismissed with a terse, “Tiger country”.

Yet, my patients’ symptoms were a profound burden upon them. In nearly every case, symptoms of MDD were severe enough to interfere with daily life and persistent enough to be present for most of the time. In every case, either sadness and/or loss of interest were prominent among the symptoms reported. As I showed in chapter 5, there is reasonably good evidence that moderate depressive symptoms are significantly and independently associated with reduced quality of life. The burden of
symptoms necessary to trigger a SCID diagnosis of MDD might reasonably be at least as great as those experienced by patients in previous studies, which mostly relied merely on rating scales. By extension the consequences would be at least as meaningful for the individual concerned. The WHO defines health as:

“…a state of complete physical, mental and social well-being…” (WHO 1948)

By this measure, no patient attracting a diagnosis of MDD in the current study could be said to have been mentally healthy.

The burden experienced by ‘depressed’ patients in my study represents precisely the kind of psychological suffering which doctors can and should identify and treat. The high level of inter-rater agreement with a consultant neuropsychiatrist, who rated randomly selected interviews in a random order and blind to the outcome, strengthens this position.

I think the major alternative argument here is that the kind of psychological suffering experienced by supposedly “depressed” glioma patients ought to be regarded not as an illness, but as adaptive: an evolutionary mechanism which developed in order to ease the process of adaptation to loss. In this view, even quite severe depressive symptoms, occurring after the diagnosis of glioma, could be considered a normal reaction and simply observed. This position is more reflective of the historical view of depression/melancholia, which was rarely diagnosed after a loss. Adherents to this view argue coherently against the medicalisation of sadness. (Horwitz and Wakefield 2007) However, the evolutionary biology of sadness, and its natural limit with regards to distinctions between normality and disorder, is still largely a theoretical concept. (Kupfer et al. 2002) I do not believe that it is necessarily “medicalising sadness” by attempting to diagnose and treat severe and persistent suffering.

13.3.2 Lack of alternative psychiatric diagnoses

One of the alternative DSM-IV diagnoses available to researchers is to attribute Major Depressive Disorder as “due to a General Medical Condition” (GMC; in this case glioma). This may be diagnosed when the mood disturbance is judged to be due to the direct physiological effects of glioma. Examples could include tumour destruction of emotional-regulatory neuronal networks, cerebral oedema, or radiation-induced damage to critical areas (all rather vague concepts and themselves difficult to precisely measure).

Some researchers have described MDD in epileptic patients without any reference to the ‘due to GMC’ clause at all. Although patients in their study could have suffered fatigue and concentration
difficulties due to AED use or epilepsy, the authors deliberately reported “the phenomenological nature of the psychiatric state” without inferring aetiology. (Ring et al. 1998)

Initially, I attempted to diagnose competing diagnoses of ‘MDD due to GMC (glioma)’ but found it difficult. In theory, it sounds reasonable to accurately judge the cause of a given symptom. In practice as others have noted, it is often impossible. (Hoffman and Weiner 2007) Even using a proforma based directly on notes in the DSM-IV, I found that the process relied heavily on subjective judgement. For example, one of the key judgements required is that the presentation is not better accounted for by a primary psychological reaction to the stress of diagnosis. If symptoms are due to a primary mood disorder or adjustment reaction, the ‘GMC’ clause falls. Since every patient in the study had a perfectly valid reason to be stressed and sad, I began to feel that this particular judgement was impossible to make confidently. A second “clue” to the diagnosis is said to be if the development of mood symptoms are contemporaneous with the onset of glioma. Most patients did indeed report feeling extremely sad contemporaneously with being told they had terminal brain cancer. Psychosocial stressors often continued to present during the follow-up period, confounding attempts to attribute depressive symptoms wholly to the direct effects of glioma or its treatment.

At one point in the training video of the SCID, an author of DSM-IV considers this problem. He concludes – not entirely helpfully – that:

“…unfortunately this is the kind of difficult clinical judgment we have to make”. (First et al. 1996)

Given these uncertainties I decided that conducting a sensitivity analysis would be useful, automatically discounting symptoms of insomnia and increased appetite in patients currently receiving dexamethasone. Although this also requires a degree of judgement (e.g. over which particular symptoms to exclude in the analysis) it is more easily reproducible by other researchers. In this sensitivity analysis, only five of 32 patients moved from having a diagnosis of MDD, to not having that diagnosis. Estimates of the frequency of MDD using both methods (inclusive and exclusive) were similar, and precision estimates overlapped. Clinical association analyses were slightly, but not markedly altered. Taken together, this pattern suggests that the side effects of steroid use were, at worst, a limited factor contributing to diagnostic inflation, and that the diagnosis of MDD appeared often to be made relatively independent of the most common steroid side-effects.

I also originally planned to record the competing psychiatric diagnosis of Adjustment Disorder. At the time of writing the protocol I did not appreciate the difficult judgements required in accurately assigning patients to these diagnoses. In the hierarchical convention of DSM, Adjustment Disorder is by definition a residual, sub-threshold condition (i.e. the criteria for MDD are not met). It may therefore be interpreted in one of two ways: an insufficient number of symptoms (fewer than 5) or their insufficient severity (present, but not severe enough to warrant categorically endorsing). The
DSM-IV does not clearly state the correct interpretation and this confused me. It is also a characteristic of adjustment disorder that the level of distress either causes significant functional impairment, or is “in excess of what would be expected given the nature of the stressor”. (APA 2000) The latter imperative is a subjective judgement with no clear frame of reference. Finally, in the rubric of DSM-IV, Adjustment Disorder is partly a retrospective diagnosis, which by definition resolves within six months of onset. The course of symptoms is difficult to confidently predict at the start of a prospective study. I therefore stopped attempting to diagnose it, choosing instead to focus solely on MDD and to revisit Adjustment Disorder in another study.

I did not consider other important conditions. One example is the possible melancholic subtype of depression. This is potentially important because the risk factors and clinical course of (hypothesised) melancholic depression could vary. If it was a valid entity, forcing unity with data from patients with ‘reactive’ depression could yield misleading results. I also did not specifically exclude bipolar affective disorder (BPAD) in patients meeting criteria for MDD. BPAD is a distinct illness and another potential source of depressive symptoms with a different clinical course to ‘unipolar’ MDD. Although the review of GP records identified no participants with a prior diagnosis of bipolar disorder, it would have strengthened the study to formally exclude BPAD.

Obtaining formal psychiatric supervision throughout the entire period of the project (rather than from approximately half-way through) may have strengthened this general area of the study. Planning a proper period to pilot data collection may also have identified some of the diagnostic difficulties in advance.

I do not believe that the tight focus on MDD renders the study invalid. The process of reporting and analysing symptoms does not require competing ‘diagnoses’ (themselves largely hypotheses) to be confirmed or excluded. Like Ring et al., I made no assumptions about the aetiology of depressive symptoms. Several distinct pathophysiological entities may be contained within the group of patients labelled as having MDD. Given the hypothetical nature of the whole DSM system, this would have been the case whether I excluded other DSM-IV diagnoses or not. Instead, this general limitation means that my findings should be replicated if possible, in future populations of glioma patients, including those studied more closely for a range of psychiatric disorders.
13.3.3 Sources of bias

13.3.3.1 Recruitment centre bias

There was an Edinburgh bias to recruitment. This could have been due to differences in: the method of approach to patients; the environment for recruiting patients; my apparent integration within the treating team; the encouragement given by the treating team to the patient for them to participate and patients’ willingness to talk about their feelings.

In Edinburgh I was usually present in the room during the clinic appointment in which the study was introduced by the treating clinician. It was also usually easier to find a free room to explain the study to the patient in more detail. By contrast, in Glasgow rooms were scarce and I often had to speak to patients in the waiting room. More patients were approached by clinical staff without me being present, and often they declined any further information. There is an anecdotal tradition of west-coast stoicism that may not be present to the same degree among patients from in south-east Scotland.

Although the twin-centre design is a strength of the study, differences in the methods of approach and possibly in patient characteristics make it important to avoid assuming that the results automatically generalise to glioma patients in other locations.

13.3.3.2 Selection bias

Beyond local recruitment biases, selection biases were inherent in the study eligibility criteria. I recruited patients with relatively good physical and cognitive function. This was a pragmatic recognition that physically and cognitively impaired patients would be very difficult to study. Questionnaire completion would by hindered by physical disability and responses rendered potentially unreliable by cognitive impairment. We anticipated also that patients receiving supportive care only would be less likely to remain in the study, due to clinical deterioration or death within the follow-up period. However, these exclusions mean that the results of this study cannot be confidently generalised to glioma patients receiving only best supportive care.
13.3.3.3 Attrition

Even focusing on well-functioning patients, attrition was high. By far the main reason was death/clinical deterioration. This highlights a real difficulty inherent in following glioma patients longitudinally, even immediately following the start of radiotherapy. Drop-out of functionally impaired patients is also suggested by the apparent improvement in KPS scores observed over time, and may account partially for the lower frequency of MDD observed at T3. A possible strategy to minimize drop-out in future may be to design shorter, more intensive follow-up periods (e.g., monthly for three months), perhaps focused on recognized distressing points in the illness process. A second strategy could be to study the validity of proxy reports, with a view to adopting them when patients are unable to respond themselves. This may entail recruiting the patient-carer dyad to future studies, rather than the patient alone.

13.3.3.4 Expectation bias

Expectation bias (bias toward the result expected by the experimenter) is possible in analyses of the screening validity of the HAD-D, PHQ-9 and DT for MDD. I administered all these measures, largely because of the pragmatic difficulties of recruiting and employing a second researcher. Approximately halfway through the study I recognized the risk of expectation bias and moved the screening questionnaires to the end of the study interview, minimizing this particular problem. However, expectation bias could still have played a role in influencing patient responses to the screening questionnaires, perhaps after discussing the presence or absence of symptoms of MDD with their partner in the SCID interview.

Expectation bias cannot fully explain the HAD-D operating characteristics because I was surprised that the optimal cut-off turned out to be so low. From my review, I was already aware that most studies in glioma had chosen to use a threshold of 11+ to represent clinical depression. Had I been highly influenced by expectation bias, one might have expected the optimal threshold discovered in my study to be closer to 11+ than to 8+.

Therefore I am not sure to what extent expectation bias was a problem in this thesis. The ideal approach would have been to minimize the risk by administering the screening tools and SCID independently of one another, for example by using two researchers. Alternatively, patients could have completed the questionnaires at home shortly before attending for interview and brought them to interview in a sealed envelope.
13.3.3.5 Recall bias

Recall bias may have affected several variables in the current project including MDD, HADS, PHQ-9, DT and the presence of seizures. I would generally expect such bias to be in the direction of minimizing the extent of symptoms. There are also considerable methodological difficulties involved in determining whether an individual has ever had a lifetime episode of major depression. (Joyce 2009) Although we obtained and reviewed GP records for patients in this study, it is possible that records were incomplete or inaccurate, introducing a degree of uncertainty to analyses involving this variable.

13.3.4 Sources of error

13.3.4.1 Tumour location

Tumour location proved to be surprisingly difficult to measure well, for several reasons. Firstly, I recorded information from pre-operative scans, occurring approximately two months before the first study interview. The limits of the surgical resection cavity may have been a more appropriate measure given that I first interviewed patients post-operatively, but not all patients received a post-operative MRI. Secondly, although most scans were contrast enhanced-MRI scans, some were CT scans. CT results may be less reliable and are not necessarily directly comparable with MRI scan results. Thirdly, where contrast was given, I recorded only the location of the enhancing portion of tumour. Tumour may however extend well beyond the margins of enhancement seen on a contrast-enhanced scan. By extension, I effectively ignored the impact of tumour-associated oedema. Finally, even though we used consultant radiologist reports, the possibility of inter-observer variability remains, especially with masses that intersect several lobes deep in white matter. The tumour lobe location analysis may be unreliable if reporting methodology differed between patients.

I think this is a good example of how a study that is not designed to address a specific question may fail to firmly answer that question. The question of tumour location and depressive symptoms needs to be studied specifically, precisely because of the complexity of interpreting these data. For example, to examine this question all patients should probably receive pre-operative and post-operative contrast-enhanced MRI scans, reported by the same consultant radiologist. A priori-defined anatomical limits should be used in the demarcation of different lobes, with anatomical margins reported for both the contrast-enhancing portion of tumour and any surrounding oedema.

However, the data which was gathered does provides a rough approximation of tumour location.
13.3.4.2 Chemotherapy

I recorded chemotherapy at the start of treatment (i.e. the planned course of primary treatment). Patients on adjuvant Temozolomide (TMZ) receive monthly ‘pulses’ which can lead to fatigue and loss of appetite. I did not record the timing of the follow-up interviews relative to an individual’s TMZ schedule. I did not record the total amount of chemotherapy given. Some patients completed the full 6 month adjuvant course; others stopped it after a few weeks. Not knowing much about the practicalities of glioma treatment, I did not anticipate these issues when designing the study. Associations between chemotherapy and outcome variables should be interpreted cautiously.

13.3.4.3 Lack of proxy report for each patient

Patients with subtle or clinically mild-moderate cognitive impairments may inaccurately report the presence or absence of symptoms. I did not fully appreciate this risk when designing the protocol, partly because I was relatively unfamiliar with the clinical features of glioma. As a result we did not specify that all patients should attend for interview with an informant. This would have improved the quality of the SCID data. However, my clinical impression was that almost all patients could remember their recent health and daily activities in general conversation. I generally did not get the impression that patients struggled to remember the immediately preceding two weeks. If I perceived a significant difficulty remembering such recent events, I stopped the interview and dropped the patient out of the study at that point. Nevertheless including a proxy report for each patient would have improved the quality of the data collection.

13.3.4.4 Timely recruitment and follow-up

In a similar study conducted among patients receiving radiotherapy for malignant glioma, Davies et al. reported considerable difficulty recruiting patients in a timely manner. (Davies et al. 1996) In that study only 75/91 patients could be seen within the first three months after radiotherapy. I also found some glioma patients difficult to recruit in a timely manner. The workload associated with recruiting and interviewing patients in two centres, combined with difficulties coordinating interviews around the schedules of hospital transport services, was one reason for a small number of patients being missed. Patients receiving short courses of radiotherapy (only 6 sessions) were difficult to recruit, and LGG patients did not attend hospital regularly. In a longitudinal study of depression in cancer patients, Sharpe et al. accept that:

“…the practical screening of large numbers of patients with limited resources is inevitably an imperfect process.” (Sharpe 2004)
This difficulty was both a source of bias and a source of error. It biased recruitment against patients with poorer-prognosis tumours, e.g. those receiving short duration radiotherapy, and introduced error because patients eventually included at a later stage in their disease process may have experienced a greater or lesser amount of distress depending on their circumstances, relative to those recruited on time. The number of patients approached as ‘late entrants’ was however small (16 patients, 10.3% of all participants).

13.3.4.5 Polythetic error

The polythetic nature of diagnostic criteria for MDD means that different patients can attract the same diagnosis with different symptoms. The pattern of symptoms experienced by patients in any given study could therefore differ greatly from that of patients in another. This is equally the case for diagnoses based on rating scales and those based on clinical interview.

I am not sure if this specific problem has been articulated before. I think of it as ‘polythetic error.’ The potential for inter-study variability of syndromes (such as MDD) which are based on polythetic criteria weakens confidence in the reproducibility and generalisability of the results of any given study. I would expect this effect potentially to be greater in smaller samples, where the distribution of symptoms may be less reflective of the true population. Other than recruiting a larger sample size, one way of minimising the potential for this error would be for authors to report the frequency of individual symptoms in each study. Readers could then make an informed judgement as to whether the sample of patients in a given study was representative of their own clinical population. Recruiting patients with a single disease (e.g., glioma) may also help generalisability to specific populations. Therefore, cancer-specific studies may be useful.

13.3.5 Sources of confounding

13.3.5.1 Unmeasured variables

A number of unmeasured variables remain as potential confounders of the analyses. These include alcohol misuse, tumour size, extent of social support, extent of social deprivation, presence of family history of depression, patient and carer coping strategies and the patient’s awareness of their prognosis.
13.3.5.2 Response shift

Recent research has suggested that longitudinal analyses of self-reported quality of life outcomes may be prone to confounding by the phenomenon of ‘response shift’. This is a process of cognitive re-appraisal through which the patient comes to evaluate their circumstances differently over time. (Sprangers and Schwartz 1999) This could cause difficulty interpreting longitudinal change in a self-reported outcome measure (e.g., level of distress).

Whether response shift does occur, and to what extent as regards distress and depression in glioma, is unclear. In one prospective study of fatigue in 99 patients receiving radiotherapy, only 11% displayed a pattern of responses consistent with the hypothesis of response shift. (Sprangers et al. 1999) Others have criticized the phrase for being an insensitive descriptor of several potentially separate and distinguishable processes. (Ubel et al. 2010)

13.4 General practical difficulties

I encountered a number of practical difficulties in the course of this research. Together they illustrate how hard it could be to study glioma patients in a similar kind of study:

- Glioma is a relatively rare cancer. Approximately 400 new cases may be expected every year across the whole of Scotland (population approx. 5 million). Multi-centre studies are necessary to boost recruitment, and these are more complicated and expensive to run.

- The diagnosis of glioma can only be secured on histopathological grounds. There is inevitably a degree of uncertainty about the nature of the intracerebral lesion at and around the time of operation. The patient may not always be told, explicitly, that they are thought to have a brain tumour at this time. They may instead be informed of a ‘lesion’ or ‘abnormality’ necessitating a diagnostic operation. If patients are to be approached peri-operatively, the wording of the study patient information leaflet (PIL) must be considered carefully. The design of my study was altered after the local ethics committee objected to the phrase ‘brain tumour’ in the PIL. Ethically, researchers must consider what they will do with data collected peri-operatively from patients who turn out to be ineligible.

- Glioma patients, without exception, are unable to drive. This limits their flexibility in attending study interviews. Particularly for patients receiving hospital transport to attend radiotherapy, time pressures occasionally made conducting hour-long interviews impractical. We minimised this problem by conducting follow-up interviews in the patient’s home.
Although this was more enjoyable for patients (and me!) it was a time-consuming and expensive method. Others have administered diagnostic interviews by telephone (Strong et al. 2007) and this could be a future avenue to explore in glioma.

- Palliative radiotherapy may be given in a small number of fractions (e.g., six). Patients receiving it are often older or frail and may be more likely to use hospital transport. Recruiting them to a study can therefore be impractical, because clinical research is often lower down the list of clinical priorities in this context.

- Relatively high rates of cognitive impairment and dysphasia must be taken into account when calculating recruitment projections. High rates of attrition due to clinical deterioration should be anticipated.

- Cognitive impairment may theoretically impair patient self-report. Systematic collection of additional proxy reports may improve reliability.

- Although not all glioma patients will be disabled, a significant proportion will have difficulty physically completing questionnaires. It is not just an issue of whether the tumour is in the dominant hemisphere: questionnaires generally need two hands to hold and complete. Hemianopia and neglect are frequent neurological signs and will further hinder data collection. The potential consequences of workaround strategies (e.g., expectation bias due to the researcher reading the questions out) should be anticipated and thought through before starting the study.

- Because glioma patients can deteriorate quickly, it is ethically important to determine that they are still alive and well before telephoning them to arrange a follow-up interview. The patient’s GP is usually able to provide this information, but obtaining it adds another layer of work.

### 13.5 Depression-specific difficulties

With regard specifically to depression in glioma, several problems arise:

- The literature on depression in glioma is distributed across several sectors including neurosurgical, neuro-oncological, general cancer, psychiatry, palliative care and nursing. It is therefore important to consider whether a systematic search strategy ensures total coverage of
the entire literature. For example, in the current study I exhaustively searched for terms covering glioma, depression and cancer, but neglected terms covering the more general palliative care population.

- My clinical experience is now that most symptoms of MDD in glioma lie on a spectrum of severity, at least in terms of how they are described by patients. Although the categorical classificatory nature of DSM provides a framework that is easy to understand, analyse and communicate, in practice it can be very difficult to allocate patients to the category of ‘symptom present’ or ‘symptom absent’. Inevitably this leads to some uncertainty about ‘borderline’ cases in either category. In a research study, perhaps the best way to deal with this problem is to examine inter-rater agreement for diagnostic interviews. Alternatively, a continuous rather than categorical approach to symptom scoring could be adopted.

- There is no external criterion standard of the ‘appropriate’ amount of sadness patients ought to feel following a diagnosis of terminal brain cancer. The DSM system does not necessarily require one. However, researchers choosing to adopt the position that “if it is severe, it counts” should anticipate i) the possibility of diagnostic inflation and ii) a degree of patient and carer resistance to being informed of a diagnosis of MDD. It can be difficult to communicate the interview result in a sensitive manner. I found it particularly hard to explain the limitations of the DSM system to patients and carers in terms that I think they fully understood.

- ‘MDD due to GMC [glioma]’ can be a difficult judgement to make. In order to make this particular diagnosis it is necessary to judge that the symptoms are not primarily a reaction to psychosocial stress. This can seem like a redundant question since in nearly every case, several highly plausible causes of psychosocial stress are self-evident. The possible exception is patients with anhedonia but minimal sadness. Even then patients can report losing interest in activities because, due primarily to functional impairment, they are now unable to do anything they consider meaningful. Like MDD itself, ‘MDD due to GMC’ may or may not a meaningful diagnostic distinction and deserves further study.

Reflecting on these difficulties I have compiled a list of potential improvements to any future, similar studies of depression in glioma (Box 12).
Conduct a pilot study to test out diagnostic procedures and suitability of exclusion criteria.

Entertain a wider spread of psychiatric diagnoses (those relevant to depression – “due to GMC”, bipolar disorder, the presence of melancholic features etc).

Widen the theoretical base to include adjustment disorder – softening the message for distressed patients: avoid insisting on MDD when explaining interview outcome to patients and GPs.

Rigorously review data collection mechanisms after a few months.

Have a shorter period of total follow-up (e.g. 3 months) to minimize attrition.

Study a specific ‘stress point’ for psychological distress rather than arbitrary time-points.

Have a researcher in each centre of a multi-centre study, if funding allows.

Measure a greater number of relevant confounding variables (based on a literature review of depression in cancer, and also on depression in general).

Consider quantifying response shift in any longitudinal study.

Make a formal follow-up appointment with patients at the time of leaving previous appointment.

Obtain a proxy report of depressive symptoms each time.

Compile a ‘patient pack’ diary to record seizures, medication changes, chemotherapy course etc.

Uncouple the “tool being validated” from “the gold standard” (or conduct gold standard test first).

Consider measuring distress in carers too.

Box 12. What I’d do if I was doing it again: some thoughts.

13.6 Strengths of the study

There were a number of important strengths to this study. I recruited the largest consecutively-presenting cohort of glioma patients to be studied for depression to date, anywhere in the world. This was the first longitudinal study to use structured clinical interview to diagnose clinical depression in patients with glioma. It was the first either to validate any depression screening measure, or to systematically explore barriers to the management of depression in this population. As regards the study of emotional distress this was the first longitudinal study utilising the DT in glioma patients, and the sample is larger than the other two studies of the DT in glioma, combined. I believe that the twin-centre, prospective and longitudinal design, large sample and relatively rigorous methodology mark this as a high quality study of depression in glioma conducted.
In this chapter I summarized important limitations or caveats to this thesis. These include: theoretical uncertainties about the psychometric validity of depression in glioma; the lack of alternative psychiatric diagnoses; selection bias, expectation bias, recall bias and attrition; the potential for measurement error in a number of variables including tumour location, chemotherapy and depressive symptoms; difficulty co-ordinating timely interviews, and potential confounding from unmeasured variables and response shift. I also outlined the major strengths of the study, which is the largest and methodologically strongest study of depression in glioma yet conducted.
14 Implications and summary

14.1 Introduction

I will lastly consider some of the main clinical and academic implications of the study results, in light of the limitations outlined in Chapter 13. Their context – comparing my results to those of other groups – formed part of the discussion in each individual results chapter. I will firstly summarise what I think the current study means for clinicians, before outlining potential avenues of future research. Within each section I will briefly consider general emotional distress, before focussing more fully on depression. Finally I will close the entire thesis with a short summary of the main points.

14.2 Implications for clinical practice

14.2.1 ‘Practice points’ for emotional distress in glioma

Younger cancer patients, women, those in psychosocial adversity and the functionally impaired may report higher distress. These clinical groups may therefore benefit from more detailed evaluation. Clinicians may also anticipate providing them with increased support services. Any patient screening sufficiently highly for distress should be assessed specifically for the presence of pain, depression and anxiety.

Emotional distress is common, affecting at least one-third of adults with primary cerebral glioma at any time-point. High distress persisted over time. These patients should therefore be actively managed. Distress was independently associated with major depression, younger age and functional impairment. These clinical groups particularly may benefit from screening and increased support.

14.2.2 ‘Practice points’ for depression in glioma

Clinicians might intuitively expect depression to be more common in women, younger patients, high-grade glioma patients and those with frontal lobe tumours. However my systematic review of observational studies suggested that this is not the case. Men, older patients, those with low-grade glioma and those with a tumour elsewhere than a frontal location appeared to be at equal risk of
depression. The index of clinical suspicion should therefore remain high in all these patient groups. However, patients with cognitive or functional impairment could be at higher risk of depression.

The literature review also helped reveal the impact of depression in glioma, and why it is important to identify and treat in clinical practice. Depression was associated with reduced quality of life, reduced work productivity and (potentially) reduced survival in glioma.

There is currently no evidence that pharmacological treatments for depression in patients with any kind of primary brain tumour are effective, or harmful. Best clinical practice would suggest that doctors treating depressed brain tumour patients discuss the lack of evidence with the patient, document their views and use their clinical judgement. If any drug treatment was started, close follow-up was advised to help detect any adverse effects.

How can we screen for depression in glioma? The HAD-D and PHQ-9 are both internally consistent but the HAD-D appears marginally to be the better instrument. A threshold of 8+ on the HAD-D would be a reasonable choice when screening for MDD in glioma. This threshold would identify roughly one false positive for every true positive in patients with glioma. A key question that clinicians need to consider is whether the burden of false positive diagnoses (on the patient/family and clinical services) outweighs the benefit (to the same stakeholders) of identifying and successfully treating depression.

I found that MDD may affect up to one in five well-functioning glioma patients in the six months after starting radiotherapy. If it develops, MDD often persists and individuals may continue to develop depression as time passes. Men and women appear to be at similar risk. The odds of developing MDD were increased three- to four-fold in patients with a previous history of depression, or functional impairment. Such patients may benefit particularly from screening and increased psychological support.

Two-thirds of glioma patients attracting a diagnosis of MDD reported not being prescribed antidepressants during the study period. However, I found no evidence to suggest that antidepressants should be contraindicated in adults with primary glioma. Antidepressants appeared to be reasonably well tolerated by those who did receive them.

Many GPs reported difficulty distinguishing normal from abnormal sadness in glioma, so clinicians may consider obtaining specialist opinions where necessary. There also is a frequent perception that depression is a normal reaction to glioma and/or that it does not always need treated, so the consequences of depressed mood should be highlighted to clinicians. There is a frequent concern that SSRIs may cause epilepsy in glioma. Clinicians should discuss the potential benefits and harms of
antidepressants with every depressed glioma patient, documenting the clinical decision in each case and offering close follow-up.

Patients may, however, be reluctant to volunteer information about their mood or take antidepressant medication. Clinicians should ask about mood at every review of a glioma patient, and review patients serially in difficult cases. Newly-diagnosed glioma patients also expressed resistance to depression treatment, particularly antidepressants. Psychological therapies could be more appropriate for some patients.

14.3 Implications for research

14.3.1 Emotional distress

More studies are needed to better understand the course and risk factors for distress in glioma. Most of the reported independent associations need to be corroborated by future research. The relationships between age, patient sex and distress remain unclear, and since these independent variables are so easily and reliably measured, merit further study.

The precise nature and validity of the concept of ‘emotional distress’ in cancer patients could be studied further. In particular, serious questions can perhaps be asked of the value and generalisability of self-reported distress data in any population, where these data rely on relatively open-ended scales.

Future studies of emotional distress should include those that are cancer-specific, longitudinal and conducted in settings other than outpatient departments. It will also be important to study which interventions are effective in treating distress associated with longer-term problems (such as functional impairment).

14.3.2 Depression

Researchers should report observational studies in accordance with the STROBE guidelines. (von Elm 2007) In particular, explicit definition of certain independent variables may help comparison between studies. Such variables include marital status, past psychiatric history, physical function, cognitive function, ethnicity, tumour lobe, tumour histology, tumour size, EOR, radiotherapy, chemotherapy, steroids, epilepsy, QOL and the definition of medical complications.
Detailed prospective studies and randomised controlled trials of the risks and benefits of antidepressants are vital. Important questions include whether antidepressants are effective in treating depression and whether they have side-effects of epilepsy, fatigue and cognitive impairment. The presence or extent of clinically significant pharmacokinetic interactions between antidepressants and antiepileptic drugs or chemotherapy also remains to be studied in glioma.

Although the HAD-D and PHQ-9 were partially validated in the current project, other aspects of validity (such as the factor structure, test-retest reliability and sensitivity to change over time) remain unknown. More study is needed on the optimal HADS threshold for use in adults with glioma. The operating characteristics of other rating scales could also be researched. The value of screening for depression in glioma generally has not been determined.

Larger samples of depressed glioma patients are needed to control sufficiently for myriad confounding variables in analyses of the independent predictors of depression. The longitudinal course of MDD in glioma, in particular its stability over time, should be studied in more detail.

It is difficult to study clinical relationships between antidepressants, AEDs, depression and epilepsy. Even after controlling the prescription of drugs, considerable barriers will remain. They include the possibility of bidirectional pharmacokinetic interactions between drug treatments (Spina and Perucca 2002), the potential for pharmacokinetic modulation by genetic polymorphisms or lifestyle factors (Lin and Lu 1998), and uncertainties about patient compliance. (Gross et al. 2000) However, future studies of whether antidepressants have a clinically significant effect on epilepsy in glioma should aim to record seizure frequency using a seizure diary, and to monitor medication adherence. Antidepressant and antiepileptic prescription needs to be controlled where possible, as do drug doses, rate of titration and rate of withdrawal. The patient should be asked specifically about use of St John’s Wort. (Gross et al. 2000)

It would be interesting to explore reasons why nearly half of GPs regard major depression in glioma either as a normal reaction or as appropriate not to treat. Among patients, a greater understanding is needed of which factors influence antidepressant acceptability, including how patients and carers view the concept of depression in glioma.

Looking beyond the current study, other broadly important areas of research in glioma may include the aetiology of depression, whether MDD is a valid construct and the course of normal sadness. Broadly the same questions addressed in this thesis could be asked about anxiety, personality change, anger and a range of other emotional reactions. Everything could be repeated in carers of glioma patients too, who have been completely ignored in this study but who are often more highly distressed than the patient.
Such a wide-ranging program of research as outlined above would need many different studies, recruiting many thousands of glioma patients. The relatively low incidence of glioma, with an estimated depression prevalence of 10%, encourages multi-centre collaboration. To facilitate this, it would be useful to develop a network of researchers with an interest in psychological neuro-oncology.

The potential for polythetic error suggests that studies of depression need replicated in order to be more confidently accepted as generalisable to clinical practice. Cancer-specific studies would aid comparison of study findings. Researchers should report the relative frequency of symptoms in their sample, to further aid direct comparison of findings. Authors using rating scales to measure depressive symptoms could present mean scores for each scale item.

### 14.4 Conclusion

My thesis has been focused on learning about emotional distress and major depression in adults with a new diagnosis of cerebral glioma. It is a challenging area of study, both for reasons of theoretical uncertainty and practical difficulty. However I am convinced that it is important. A great deal of psychological morbidity accompanies the personally catastrophic diagnosis of glioma. Very little indeed is currently known about the precise causes, risk factors, protective factors, clinical course and effective treatments for distress and depression in these patients.

After reviewing current knowledge, I reported what is methodologically the strongest study of distress and depression yet conducted in glioma. Partly because it was my first research project there are a number of important weaknesses to the study, but I have clear ideas about how these could be addressed in future.

In summary, the main findings in this thesis are that:

- Most previous observational studies of DT-measured distress and MDD in glioma are small, cross-sectional and/or retrospective. No high-quality studies exist of the benefits or harms of antidepressant medicines, when prescribed to treat depression in adults with glioma.
- DT-defined emotional distress may be present in at least one third of glioma patients in the 6 months following the start of radiotherapy, particularly in the younger, the depressed or the functionally impaired. Distress may persist in patients reporting high distress initially.
- When used to screen for MDD in glioma, the HAD-D and PHQ-9 have good internal reliability. The HAD-D has marginally better and more consistent sensitivity, specificity and
positive predictive value. Clinicians can reasonably use a threshold of 8+ when screening for major depression using the HAD-D.

- MDD may be present or develop in up to one-fifth of glioma patients in the six months after starting radiotherapy (6.9% - 14.8% of patients at any one point). It is more likely in those with a previous history of depression or significant functional impairment. MDD persists in a clinically significant proportion of cases, and new cases developed over time.

- Only 34% of depressed glioma patients reported taking antidepressants. There was no association between antidepressant prescription and an increased prevalence of epilepsy, in a cohort of depressed glioma patients managed routinely by their treating team. Antidepressants appeared to be well-tolerated when prescribed.

- Many GPs regard depression as a “normal reaction” to glioma and believe that it does not always need treated. Glioma patients express resistance to depression treatment generally and to antidepressants in particular.
15 References


16 Appendices
APPENDIX 1. Cochrane review search strategies.

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1950 to Present (July week 2 2009)

(exp depressive disorder OR *Depressive Disorder, Major OR *Dysthymic Disorder OR Depression, involutional.mp. OR Depress$.ab,ti. OR Affective disorder$.ab,ti. OR Mood disorder$.ab,ti.) AND (exp Glioma OR exp Brain Neoplasms OR brain tumor$.ab,ti. OR astrocytoma$.ab,ti. OR meningioma$.ab,ti. OR oligodendroglioma$.ab,ti. OR glioblastoma$.ab,ti.) AND (exp Antidepressive Agents OR exp Serotonin Uptake Inhibitors OR exp Monoamine Oxidase Inhibitors OR exp Drug Therapy OR Antidepress$.ab,ti OR TCA$.ab,ti. OR MAOI$.ab,ti. OR SSRI$.ab,ti. OR Antidepressive Agents, Tricyclic OR Antidepressive Agents, Second Generation) NOT (animals not [humans and animals]).sh.

(n=57)

EMBASE 1980 to 2009 Week 29

(exp Depression OR exp Mood Disorder OR "Depress*".ti,ab. OR "Affect*".ti,ab. OR "Dysthym*".ti,ab.) AND (exp Glioma OR exp Brain Tumor OR Astrocytoma OR Meningioma OR [glioma* or brain tumor* or astrocytoma* or meningioma*].ti,ab.) AND (exp Antidepressant Agent OR Monoamine Oxidase Inhibitor OR Tricyclic Antidepressant Agent OR Serotonin Uptake Inhibitor OR [antidepress* or SSRI* or MAOI* or TCA* or tricyclic*].ti,ab.) NOT (animal not [human and animal]).sh

(n=287)

PsycINFO 1806 to July Week 2 2009

(exp Endogenous Depression OR exp Reactive Depression OR exp Major Depression OR exp Mental Disorders OR exp Affective Disorders OR [depress$ or mood$ or affective$ or dysthym$].ab,ti.) AND (exp Brain Neoplasms OR brain tumo?:r.mp. OR Oligodendroglioma$.mp. OR Astrocytoma$.mp. OR Meningioma$.mp. OR [glioma$ or brain tumo$ or astrocytoma$ or meningioma$ or oligodendroglioma$].ab,ti.) AND (exp Drug Therapy OR pharmacotherapy.mp. OR exp Antidepressant Drugs OR exp Tricyclic Antidepressant Drugs OR exp Monoamine Oxidase Inhibitors OR exp Serotonin Reuptake Inhibitors OR [antidepress$ or SSRI$ or MAOI$ or TCA$ or tricyclic$ or drug therap$ or pharmacotherap$].ab,ti.)

(n=39)
British Nursing Index and Archive 1985 to July 2009

(exp depression OR exp psychiatric disorders OR [depress$ or mood$ or affectiv$ or dysthm$].ti,ab.) AND (exp cancer OR [glioma$ or brain tumo$ or astrocytoma$ or meningioma$ or oligodendrogioma$].ti,ab.) AND (exp Drug Therapy OR exp Psychiatric disorders OR Drug Therapy OR SSRI$.mp. OR MAOI$.mp. OR Tricyclic.mp. OR [antidepress$ or SSRIS or MAOIS or TCA$ or drug therap$ or pharmacotherap$].ti,ab.)

(n=20)

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2009

(Glioma OR exp Brain Neoplasms OR Astrocytoma OR Meningioma OR [glioma or brain tumo$ or astrocytoma$ or meningioma$ or oligodendrogioma$].ti,kw,ab.) AND (exp Antidepressive Agents OR exp Antidepressive Agents, Second-Generation OR Antidepressive Agents, Tricyclic OR Serotonin Uptake Inhibitors OR Monoamine Oxidase Inhibitors OR [antidepress$ or SSRI$ or MAOI$ or TCA$ or drug therap$] .ti,kw,ab. OR exp Drug Therapy OR pharmacotherapy.mp.) AND (exp Mental Disorder OR Depression OR Affective Symptoms OR [depress$ or mood$ or affectiv$ or dysthm$].ti,kw,ab.)

(n=8)

LILACS 22/07/2009

(Depression OR Depressive OR Mood OR Affect) AND (Glioma OR Glioblastoma OR Meningioma OR Brain neoplasm) AND (Antidepressant OR Antidepressive OR SSRI OR MAOI OR TCA)

(n=0)

Psycindex 22/07/2009

(Depression OR Depressive OR Mood OR Affect$) AND (Gliom? OR gehirntumo? OR Krebs OR Astrocytom? OR Oligodendrogliom? OR Meningiom?) AND (Antidepress OR Serotonin OR SSRI OR MAOI OR TCA OR Pharmacotherap?)

(n=1)

National Research Register 22/07/2009 (Database was only active until 2007)

(Glioma)
Database of Abstracts of Reviews of Effectiveness 3rd Quarter 2009

((depress or affective disorder$ or mood disorder$).ab,ti.) AND ((brain tumo$ or astrocytoma$ or meningioma$ or oligodendroglialoma$ or glioblastoma$).ab,ti.) AND ((antidepress$ or TCA$ or Tricyclic$ or MAOI$ or SSRI$).ab,ti.)

(n=0)

www.isiknowledge.com (22/07/2009)

Topic=(depression OR depressive disorder OR major depression OR mood disorder OR depress* OR affectiv* OR dysthym* OR mood*) AND Topic=(antidepress* OR SSRI OR MAOI OR TCA) AND Topic=(brain neoplas* OR brain tumo* OR glioma OR astrocytoma OR oligodendroglialoma OR meningioma)

(n=306)
## ADDENBROOKE’S COGNITIVE EXAMINATION - ACE-R

**Final Revised Version A (2005)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Date of testing: …… / …… / ……</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth</td>
<td>Tester’s name: …………………………</td>
</tr>
<tr>
<td>Hospital no.</td>
<td>Age at leaving full-time education: ……………</td>
</tr>
<tr>
<td>Addressograph</td>
<td>Occupation: …………………………</td>
</tr>
<tr>
<td>Handedness</td>
<td>Gloved hand:…………………………</td>
</tr>
</tbody>
</table>

### ORIENTATION

- **Ask:** What is the Day: ……  Date: ……  Month: ……  Year: ……  Season: ……  
  - Score 0-5
- **Ask:** Which Building: ……  Floor: ……  Town: ……  County: ……  Country: ……  
  - Score 0-5

### REGISTRATION

- **Tell:** ‘I’m going to give you three words and I’d like you to repeat after me: lemon, key and ball’. After subject repeats, say ‘Try to remember them because I’m going to ask you later’. Score only the first trial (repeat 3 times if necessary). Register number of trials ……
  - Score 0-3

### ATTENTION & CONCENTRATION

- **Ask the subject:** ‘could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 86, 79, 72, 65). ……  ……  ……  ……  ……  
  - Score 0-5
- **Ask:** ‘could you please spell WORLD for me? Then ask him/her to spell it backwards: ……  ……  ……  ……  ……  
  - Score 0-5

### MEMORY - Recall

- **Ask:** ‘Which 3 words did I ask you to repeat and remember?’ ……  ……  ……  
  - Score 0-3

### MEMORY - Anterograde Memory

- **Tell:** ‘I’m going to give you a name and address and I’d like you to repeat after me. We’ll be doing that 3 times, so you have a chance to learn it. I’ll be asking you later’
  - Score 0-7
  - Score only the third trial

<table>
<thead>
<tr>
<th>Name</th>
<th>1st Trial</th>
<th>2nd Trial</th>
<th>3rd Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harry Barnes</td>
<td>……</td>
<td>……</td>
<td>……</td>
</tr>
<tr>
<td>73 Orchard Close</td>
<td>……</td>
<td>……</td>
<td>……</td>
</tr>
<tr>
<td>Kingsbridge</td>
<td>……</td>
<td>……</td>
<td>……</td>
</tr>
<tr>
<td>Devon</td>
<td>……</td>
<td>……</td>
<td>……</td>
</tr>
</tbody>
</table>

### MEMORY - Retrograde Memory

- **Name of current Prime Minister** …………………………
- **Name of the woman who was Prime Minister** …………………………
- **Name of the USA president** …………………………
- **Name of the USA president who was assassinated in the 1960’s** …………………………

---

copyright 2000, John R. Hodges
ADDENBROOKE’S COGNITIVE EXAMINATION - ACE-R

VERBAL FLUENCY - Letter ‘P’ and animals

- Letters
  Say: ‘I’m going to give you a letter of the alphabet and I’d like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You’ve got a minute and the letter is P’

- Animals
  Say: ‘Now can you name as many animals as possible, beginning with any letter?’

LANGUAGE - Comprehension

- Show written instruction:
  [Score 0 - 1]
  Close your eyes

LANGUAGE - Writing

- Ask the subject to make up a sentence and write it in the space below:
  Score 1 if sentence contains a subject and a verb (see guide for examples)
  [Score 0 - 1]

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**LANGUAGE - Repetition**

- Ask the subject to repeat: **'hippopotamus'; 'eccentricity'; 'unintelligible'; 'statistician'**
  
  Score 2 if all correct; 1 if 3 correct; 0 if 2 or less.

- Ask the subject to repeat: **'Above, beyond and below'**

- Ask the subject to repeat: **'No ifs, ands or buts'**

**LANGUAGE - Naming**

- Ask the subject to name the following pictures:

  - Pencil
  - Watch
  - Kangaroo
  - Penguin
  - Anchor
  - Camel
  - Harp
  - Barrel
  - Crown
  - Crocodile
  - Accordion

**LANGUAGE - Comprehension**

Using the pictures above, ask the subject to:

- Point to the one which is associated with the monarchy
- Point to the one which is a marsupial
- Point to the one which is found in the Antarctic
- Point to the one which has a nautical connection
LANGUAGE - Reading

- Ask the subject to read the following words: [Score 1 only if all correct]

  sew
  pint
  soot
  dough
  height

VISUOSPATIAL ABILITIES

- Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1]

- Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2]

- Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5]
Ask the subject to count the dots without pointing them
### Recall

> Ask “Now tell me what you remember of that name and address we were repeating at the beginning.”

<table>
<thead>
<tr>
<th>Harry Barnes</th>
<th>73 Orchard Close</th>
<th>Kingsbridge</th>
<th>Devon</th>
<th>[Score 0-7]</th>
</tr>
</thead>
</table>

### Recognition

> This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling “ok, I’ll give you some hints: was the name X, Y or Z?” and so on. Each recognised item scores one point which is added to the point gained by recalling.

<table>
<thead>
<tr>
<th>Jerry Barnes</th>
<th>Harry Barnes</th>
<th>Harry Bradford</th>
<th>recalled</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>73</td>
<td>76</td>
<td>recalled</td>
</tr>
<tr>
<td>Orchard Place</td>
<td>Oak Close</td>
<td>Orchard Close</td>
<td>recalled</td>
</tr>
<tr>
<td>Oakhampton</td>
<td>Kingsbridge</td>
<td>Darlington</td>
<td>recalled</td>
</tr>
<tr>
<td>Devon</td>
<td>Dorset</td>
<td>Somerset</td>
<td>recalled</td>
</tr>
</tbody>
</table>

### General Scores

<table>
<thead>
<tr>
<th>MMSE</th>
<th>ACE-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

### Subscores

<table>
<thead>
<tr>
<th>Attention and Orientation</th>
<th>Memory</th>
<th>Fluency</th>
<th>Language</th>
<th>Visual Spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>/18</td>
<td>/26</td>
<td>/14</td>
<td>/26</td>
<td>/16</td>
</tr>
</tbody>
</table>

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% sensitivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

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Edinburgh Centre for Neuro-Oncology
Western General Hospital, Crewe Road, Edinburgh, EH4 2XU

Nurse Specialist: Shanne McNamara Direct Line: 0131 537 2656
Co-ordinator: Claire Oliver Direct Line: 0131 537 3266
Direct Fax: 0131 537 2659

Neurology: Dr R Grant (CAR)
Oncology: Dr Anna Gregor
Onco coordinator: Dr Sara Erridge

Neurosurgery: Professor I R Whittle (Brain)
Mr P F X Statham (Pituitary)
Mr J M Steers
Mr T Russell
Ms Lynn Myles
Mr M O Fitzpatrick

Website: http://www.den.ed.ac.uk/ecno/

12th March 2008

Dear Prof. Lees,

Re: 07/MRE00/55

Clinical aspects of DSM-IV depression and anxiety in cerebral glioma: a 6-month descriptive, prospective cohort study

Thank-you for the favourable opinion for this study, which is going well with 18 patients having been interviewed since we began recruitment.

With your permission we would like to add two further questionnaires, which are attached with this letter. Despite our initial concerns that our glioma patients would find participation too tiring, we have consistently observed that they tolerate the current questionnaire burden without difficulty. Their relatives likewise have found that the length of the first assessment, which generally takes between 40 and 60 minutes depending on the patient, is acceptable.

Scale 1

The Hospital Anxiety and Depression Scale (HADS) is commonly used to provide a measure of mood disorder in clinical research. It is validated and particularly useful in cancer patients as it largely excludes physical symptoms of depression, which would potentially confound any diagnosis of depression in concurrent physical illness. It is a 14-item self-report questionnaire that takes no more than 5 minutes to complete.

We are keen to add it to bolster any conclusions about the frequency and nature of mood disorder in glioma. It would definitely benefit our study by allowing us to report the extent to which physical symptoms contribute to the likelihood of depression in these patients. Such a comparison has not been reported before.
Scale 2

The Patient Health Questionnaire 9 (PHQ-9) is a validated, commonly used 9-item self-report questionnaire that also takes a few minutes to complete. It covers the same question headings as the Structured Clinical Interview for DSM-IV (SCID), which we are using already in the study. Unlike the PHQ-9, the SCID allows for gentle probing and testing of responses before a decision is made about whether a particular symptom is present.

It is important to know if the PHQ-9 is as accurate as the SCID in patients with glioma because the time cost involved in conducting a structured interview is considerable. We would like to know if the self-report questionnaire could diagnose depression as consistently as a formal interview. This will inform future decisions on potential screening methods, helping us improve the psychological care of this vulnerable group.

As well as these useful benefits, adding both scales will potentially enable us to combine future data with other researchers in the field, often disadvantaged by low numbers of patients and a high dropout rate.

We hope that you agree with our suggestions and look forward to hearing from you.

With best wishes,

Yours sincerely

Dr. Robin Grant
Consultant Neurologist

Dr. Alasdair Rooney
Neuro-oncology research fellow
Dear Prof. Lees,

Re: 07/MRE00/55

Clinical aspects of DSM-IV depression and anxiety in cerebral glioma: a 6-month descriptive, prospective cohort study

As originally planned, we are in the process of extending this study to include patients referred to the Beatson West of Scotland Oncology Centre in Glasgow. As you may know their internal Clinical Trials Executive Committee (CTEC) must pass all proposals for research studies in the Beatson before proceeding to LREC/R&D.

CTEC requested that changes be made to our protocol before they would approve it. These were mainly cosmetic, but included a request for a more detailed summary of the statistical analysis of our data. We made the changes to their satisfaction and the study has now passed to their R&D for approval. However, R&D require MREC to have reviewed the latest version of the protocol.

We hereby include a summary page of changes made, and the new protocol (version 3.2). While we were compiling this document it became apparent that MREC, which reviewed our original protocol (v3.0) did not see the updated protocol (v3.1) that was created in response to changes required by MREC. We have discussed this with Walter Thomson and arranged to include a copy of the (now old) protocol v3.1 for your records.

The included summary page therefore lists changes between v3.1 and v3.2, for your review. No changes have been made to the way the study is run from the perspective of research participants. Accordingly we submit the protocol alterations as non-substantive amendments.

With best wishes (and apologies for the slightly complicated scenario),

Yours sincerely

Dr. Robin Grant
Consultant Neurologist

Dr. Alasdair Rooney
Neuro-oncology research fellow
APPENDIX 12a. Questionnaire of patient attitudes to the treatment of depression.

Att v1.1 27/02/08

ATTITUDES QUESTIONNAIRE

Patient Number: [Blank]  
Visit: 1 only

There are no right or wrong answers to this short questionnaire. Everybody has different opinions and we would just like you to answer as honestly as you can. Your answers will be anonymous.

1. Have you ever taken antidepressant medicines in the past?
   Yes [ ] No [ ]

2. Have you ever had counselling for low mood in the past?
   Yes [ ] No [ ]

3. How would you most likely feel if your doctor suggested taking an antidepressant in the future? (tick one)
   [ ] I’d probably refuse
   [ ] I’d think about it but not want to decide right away
   [ ] I’d probably accept

4. How would you most likely feel if your doctor suggested attending counselling in the future?
   [ ] I’d probably refuse
   [ ] I’d think about it but not want to decide right away
   [ ] I’d probably accept
APPENDIX 12b. Questionnaire of GP attitudes to depression in glioma.

Depression in glioma: short questionnaire

**First some basic questions about yourself:**

- Male  Female
- Year of registration as a GP:______________________
- How many glioma patients have you ever been responsible for (approx)?_____________

**Now here are some opposing statements about major depression in patients with glioma.** For each pair, please tick the box that most closely matches your opinion. If you agree with both statements please tick the one you agree with more strongly.

- Most depression is a normal reaction to having glioma.
- Most depression is an abnormal reaction to having glioma.
- It is mainly psychological in origin (due to the stress of having a brain tumour).
- It is mainly biological in origin (due to disruption of neural circuits involved in emotion).
- I’d find it quite hard to distinguish between normal sadness and depression, in glioma.
- I’d find it quite easy to distinguish between normal sadness and depression, in glioma.
- I’d routinely ask a glioma patient about their mood in surgery.
- I’d not routinely ask a glioma patient about their mood in surgery.
- My glioma patient/s volunteered information about their mood to me in surgery.
- My glioma patient/s did not volunteer information about their mood to me in surgery.
- In glioma, depression should always be treated.
- In glioma, depression should not always be treated.
- I’d generally treat depression in a glioma patient on the basis of one consultation.
- I’d generally review a glioma patient at least once before treating them for depression.
- I’d worry about provoking an epileptic seizure by prescribing an SSRI.
- I’d not worry about provoking an epileptic seizure by prescribing an SSRI.
- I’d favour psychotherapy over an antidepressant for depression in glioma.
- I’d favour an antidepressant over psychotherapy for depression in glioma.
- If treated, depression in glioma should be treated mainly by a specialist.
- If treated, depression in glioma should be treated mainly by the GP.

**Thanks! Please fax this page back to 0131 537 2659.**

The results will be made available to you later in 2010.
APPENDIX 2. Main study protocol.

Clinical aspects of DSM-IV depression and anxiety in cerebral glioma: a 6-month descriptive, prospective cohort study.

Protocol (version 3.2, 5th Feb 2008)

Dr. Alasdair Rooney  Researcher, MD student
               a.rooney@nhs.net  0131 537 3266

Dr. Robin Grant   Chief investigator (Edinburgh)
Prof. Roy Rampling Principal Investigator (Glasgow)
1. BACKGROUND

Brain and Central Nervous System (CNS) tumours are a relatively uncommon but devastating form of cancer, occurring worldwide with a median age-standardised rate in adults of 7.6/100 000 (men) and 5.1/100 000 (women) (Parkin 2005). Primary tumours of the brain can be categorised according to standard World Health Organization (WHO) criteria (Louis 2007), reflecting their histological origin and level of malignancy.

Gliomas are the most common kind of primary brain tumour (Wrensch 2002). Seventy to eighty percent of gliomas are aggressive, diffusely infiltrating "high-grade" tumours with a median survival of between 9 and 12 months (Bleehen 1991). They are more common in men, in Caucasians and with increasing age (Barnholtz-Sloan 2003). The remaining 20 to 30% of gliomas are "low-grade" and confer a relatively good prognosis, although still with a median survival of only seven years (Van den Bent 2005). Low-grade gliomas are particularly associated with epileptic seizures (Pace 1998). Several factors appear to predict survival in low-grade glioma: older age, astrocytoma histology, tumour size > 6cm and tumour crossing the midline at presentation are all associated with a poorer outcome (Pignatti 2002). Due to the wide spread of cancer cells within the brain at the time of diagnosis, both high-grade and low-grade gliomas in adults are often considered incurable by surgery.

Depression is a common syndrome characterised by the triad of emotional symptoms, psychomotor abnormalities and negative beliefs (Gelder 2000). It is associated with reduced quality of life following the onset of neurological illnesses, including stroke (Moon 2004) and epilepsy (Tracy 2007) as well as glioma (Mainio 2006a). It is a recognised risk factor for suicide (Rihmer 2007) and may even be associated with reduced survival in patients with glioma (Mainio 2006b). In patients with Parkinson's Disease, depression has been associated with a recognisable (and potentially treatable) syndrome of cognitive dysfunction over and above that associated with the neurological illness alone (Stefanova 2006).

Reported prevalence rates of depression in cancer vary depending on the population, the diagnostic method and at what point in their illness journey subjects are assessed, but major depression is present in up to 27% of systemic cancer patients (Strong 2007) – considerably higher than in the general population. Patients with glioma may meet diagnostic criteria for depression even more frequently than those with systemic cancer (Litofsky 2004, Welisch 2002) and are commonly prescribed steroids, which have been associated with mood disturbance (Brown 1998). Despite the suspected frequency and profound consequences depression is commonly overlooked in cancer patients (Greenberg 2004), even when identified is often inadequately treated (Sharpe 2004) and has been poorly studied in glioma.

Researching depression in cancer is complicated by the possibility of criterion contamination; that symptoms apparently due to depression might be caused by something else. The gold-standard for diagnosis is a structured clinical interview (SCID, First 2002), but this requires a judgement to be made that each depressive symptom is not better accounted for by the direct effects of a general medical condition (e.g. glioma), and also that the depression (if mild) is not simply a psychological reaction to a recent stressor. These clinical judgements are inevitably contentious in patients with glioma, who are terminally ill with an established brain disorder.

To circumvent these problems, some cancer researchers combine depression and anxiety in a category of general emotional "distress". Although there is no evidence that screening for depression improves outcome by itself (Gilbody 2005), the usefulness of short screening measures of distress, for example the distress thermometer, has been a focus of recent research (Patrick-Miller 2004). To date the validity of this tool for distress in glioma has been unreported.

Other researchers use rating scales that exclude somatic symptoms (e.g., Zigmond 1968). Established cut-off levels roughly correspond to the likelihood of suffering from depression
and high scores are often used to define depression in clinical trials. However, somatic symptoms have long been recognised as robust features of major depression and excluding them risks overlooking or minimising the severity of some genuine depressive illnesses. This could disadvantage the more severely affected patients who have potentially the most to gain from treatment. Rating scales are also known for their relatively low specificity (i.e. they often falsely identify patients as depressed) and although useful for excluding depression, are not designed to confer a definitive diagnosis.

Formally diagnosing depression is essential if potentially harmful treatment is to be justified. Antidepressants are recommended as a first-line treatment for moderate to severe depression in several national guidelines (APA 2000; NICE 2004). Meta-analyses of randomised controlled trials have shown antidepressants to be effective in the depressed elderly (Mottram 2006), and those with both a more chronic, low-level depression (Lima 2005) and a severe/psychotic depression (Wijkstra 2005). Side-effects include a lowered seizure threshold (Montgomery 2005), impaired cognition (Peretti 2000) and fatigue (Cassano 2004); complications commonly associated with brain tumours and therefore potentially worsened by antidepressant treatment.

It is currently unknown whether the benefits of anti-depressants appear to outweigh the risks in patients with glioma. The frequency of, and relationships between antidepressant treatment, epileptic seizures and depression have not yet been prospectively described. Although a future randomised controlled trial will be required to answer the question of efficacy, data to help power and safely conduct it is currently lacking. A better understanding of the frequency, characteristics and predictors of depression and distress in glioma could also allow the more efficient targeting of high-risk patients, which could lead to improvements in care.

2. DESIGN

Prospective cohort study with 6-month follow-up.

3. AIMS / RESEARCH QUESTIONS

In adults attending a tertiary outpatient Neuro-Oncology service with a new diagnosis of primary supratentorial glioma and receiving active or expectant management:

3.1 Describing depression

1. What is the 0, 3 and 6-month prevalence of DSM-IV Major Depressive Disorder (MDD), Minor Depressive Disorder (mdd) and Anxiety NOS?
2. What is the 6-month incidence of each of these disorders?
3. What proportion of patients with MDD could alternatively be considered depressed as a direct effect of glioma?
4. What proportion of patients with mdd (i.e., subthreshold depression) could alternatively be considered as suffering from an adjustment disorder?
5. How commonly is each symptom from the depressive syndrome endorsed by those with MDD?

3.2 Predicting depression

6. What clinical and demographic characteristics are associated with the presence of MDD/mdd, and anxiety at 0, 3 and 6 months?
7. Does age, sex or a past history of GP treatment for depression or anxiety independently predict either MDD/mdd or anxiety at 0, 3 and 6 months?

8. How sensitive and specific are the first two questions of SCID for predicting concurrent MDD?

9. How sensitive and specific is each cut-off on the NCCN distress thermometer for predicting concurrent MDD, mdd or anxiety?

10. What psychosocial factors listed on the NCCN distress tool do patients report contributing to subjective ‘emotional distress’ at 0, 3 and 6 months?

11. Are there any obvious baseline clinical or demographic differences between a case series of patients whose mood disorder follows a relatively favourable course, compared to those whose mood disorder does not improve or worsens?

3.3 Treating depression

12. What proportion of subjects with MDD (at 0 and 3 months) has been prescribed appropriate drug treatment by their GP at 3 and 6 months?

13. Of those subjects prescribed antidepressants at any point, what proportion have treatment of ‘adequate’ dose and duration, as defined by the Maudsley guidelines?

14. In what proportion of all subjects with MDD does the disorder remit over the 6-month period?

15. What are the common side-effects reported by glioma patients who are taking antidepressants? How does this compare to the side-effects they reported prior to starting antidepressants?

3.4 Impact of seizures

16. Of those subjects without a history of seizures and started on an antidepressant, in what proportion do seizures commence by 3 and 6 months? How does this proportion compare with the seizure-onset rate in those not prescribed antidepressants?

17. Of those subjects with baseline seizures, what proportion are prescribed antidepressants and what happens to seizure frequency thereafter? How does this compare to the seizure frequency in those with baseline seizures and no antidepressant?

3.5 Attitudes to treatment

18. How acceptable, at baseline, is the idea of either antidepressant treatment or counselling to patients?

19. How acceptable is the idea of prescribing antidepressants for MDD to their GPs, and what issues do they consider?

3.6 Confounders

20. Are reported rates of MDD likely to be confounded by any of the following: mean steroid dose, general cognitive impairment and reduced functional status?
4. **SUBJECTS**

4.1 *Eligibility criteria*

- Adults aged 18 or over with a histologically proven diagnosis of primary glioma, getting some form of active management including watchful waiting.
- Able to speak English.
- Able to provide informed consent.

4.2 *Exclusion criteria*

- Patients referred but refused expectant treatment on grounds of poor prognosis.
- Not fluent in English.
- Dysphasia making reasonable verbal communication impossible.
- Cognitive impairment impairing capacity to consent.

4.3 *Approach to subjects*

Patients will initially be recruited from two centres in Scotland, and the approach will differ slightly between them.

**NHS Lothian**

All eligible adult outpatients with histologically-proven supratentorial glioma will be identified through the weekly multidisciplinary team (MDT) meeting of the Edinburgh Centre for Neuro-oncology (ECNO), and via liaison with a dedicated Neuro-oncology Nurse. A member of their usual team will hand over the Patient Information Leaflet (PIL) after the patient has been given their diagnosis at the clinic.

**NHS Greater Glasgow and Clyde**

Eligible patients will again be identified via the MDT meeting and Specialist Nurse of the Beatson West of Scotland Cancer Centre (BWOSCC), but the initial approach will be made during a routine telephone follow-up call approximately one week after the diagnosis is given to the patient. During this call the Specialist Nurse will ask permission to post the PIL out to the patient.

4.4 *Consenting subjects*

The process of obtaining informed consent will follow the same pattern in both sites but will differ depending on the management strategy chosen for each patient.

Patients receiving radiation therapy (RT) attend their local unit (either the Edinburgh Cancer Centre or BWOSCC) for RT planning. A researcher will see the patient, answer questions and obtain their written consent to participate in the study when they attend for planning.

Patients allocated ‘watchful waiting’ will be telephoned at home in the week after they have been given the PIL to answer questions and check verbal consent. The researcher will then arrange a meeting specifically to obtain written consent and conduct the first interview. Where this meeting occurs will depend on the location and preferences of the patient: those referred through NHS Lothian will be offered the choice of returning to the Western General Hospital Wellcome Trust Clinical Research Facility (WTCRF) or being visited at home; those referred via NHS Greater Glasgow & Clyde will be offered a choice between a home visit or being seen at BWOSCC.

The WTCRF building has bookable rooms and dedicated car parking. In both centres travel expenses incurred by the patient will be reimbursed, if they are attending a hospital site solely to participate in this study.
5. **METHOD**

At all points meetings will be arranged to coincide with scheduled appointments if possible. Where this is not possible specific meetings will be booked in consultation with the subject.

5.1 **Data Collection Point 1 – at ‘0 months’**

Subjects attending for RT will be interviewed in the site of their treatment after they have begun their course. A specific meeting will be arranged by telephone with patients who are not receiving RT, as described above.

Subjects will be able to have their relatives present during the interview if they would prefer.

Data collected:

- Baseline demographic and clinical information
- SCID interview
- NCCN tool
- Attitudes to antidepressants – questionnaire
- Timed 10-metre walk
- Addenbrooke’s cognitive examination
- Current seizure, steroid and antidepressant information

If a DSM-IV mood disorder is present the patient will be informed. The GP will be sent a letter advising them of the diagnosis. If the patient endorses suicidal ideation (from other studies this would be expected in about 10% of subjects) a standard risk assessment will be conducted separately and acted on appropriately in keeping with Good Clinical Practice. Often this will mean a letter being faxed to the GP surgery to alert them.

The next meeting (3 months) will be arranged at the end of the first meeting.

5.2 **Data Collection Point 2 – at ‘3 months’**

- SCID interview
- NCCN tool
- Timed 10-metre walk
- Addenbrooke’s cognitive examination
- Current seizure, steroid and antidepressant information

Arrange next meeting for 6 months.

5.3 **Data Collection Point 3 – at ‘6 months’**

- SCID interview
- NCCN tool
- Timed 10-metre walk
- Addenbrooke’s cognitive examination
- Current seizure, steroid and antidepressant information

After this final interview the patient’s GP will be contacted by telephone and asked to participate in a short interview about their experience of and attitudes towards prescribing antidepressants for patients with glioma.

5.4 **Data collection phase**

24 months.
6. VARIABLES

6.1 Predictor

The number of independent predictor variables that can be tested for depends on the number of cases of the condition under study. It is likely that case numbers will be relatively small; predictor variables will be tested in the following order until no longer appropriate:

- Age
- Sex
- Past history of depression (yes/no)
- Tumour grade (HGG/LGG)
- Radiation therapy (yes/no)
- Tumour location (frontal/temporal/parietal/occipital/deep)
- Tumour laterality (left/right/both)
- Adjuvant Chemotherapy (yes/no)

6.2 Outcome

- MDD at 0, 3 and 6 months (yes/no)
- ‘mdd’ at 0, 3 and 6 months (yes/no)
- Anxiety at 0, 3 and 6 months (yes/no)
- NCCN thermometer scale score at each interview (0-10)
- Had MDD and was prescribed adequate antidepressant treatment (yes/no)
- Seizure control (worse/improved/unchanged)

The optimal cut-off of the NCCN for association with MDD will be determined (see statistical methods).

6.3 Confounding

- Mean daily steroid dose in last 4 weeks (0/1-4/5-8/9-12/>13)
- Cognition (ACE score >88/ACE score <88)
- Function (Timed 10-metre walk <8 seconds/timed 10m walk>8 seconds)
- Proportion of subjects meeting criteria for MDD who also meet criteria for ‘MDD due to General Medical Condition’
- Proportion of subjects meeting criteria for ‘mdd’ who also meet criteria for ‘Adjustment disorder with depressed mood’

To address the issue of ‘criterion contamination’ we will report our data in two separate analyses – firstly where anyone meeting the diagnostic criteria is assumed to have the relevant mood disorder without regard to aetiology, and then again using a ‘filter’ of prospectively defined criteria for ‘Mood disorder due to GMC’/’Adjustment disorder with depressed mood’.

7. STATISTICAL ANALYSIS

7.1 Summary

Statistical support is available.

- For much of the data – the purely descriptive component including the prevalence and incidence data – count rates will be presented and confidence intervals will be calculated.

- Independent predictors will be analysed by logistical regression.
• Sensitivity and specificity of the NCCN thermometer will be calculated using a ROC curve.

Due to the limited sample size and the absence of a randomisation procedure statistical testing needs to be used sparingly to avoid lending the results a legitimacy they may not warrant.

7.2 **Sample size calculations**


**Prevalence of depression**

How many adults should be included in the sample so that the prevalence may be estimated to within 6 percentage points of the true value, with 90-95% confidence, if it is known that the true rate is unlikely to exceed 25%?

| Anticipated population proportion | 25% |
| Confidence level | 90% - 95% |
| Absolute precision (19%-31%) | 6 percentage points |

141 subjects would be required for 90% confidence and 200 subjects for 95% confidence.

**Prevalence of anxiety**

| Anticipated population proportion | 10% |
| Confidence levels | 95% |
| Absolute precision | 6 percentage points |

138 subjects would be required.

**Incidence of depression or anxiety**

How large a sample of patients should be followed up to determine the incidence rate of depression to within 16% of its true value with 95% confidence?

| Relative precision | 16% |
| Confidence level | 95% |

151 subjects would be required.

**Clinical and demographic predictors of depression**

A formal sample size calculation has not been conducted for logistic regression. Instead (following Peduzzi et al.1996) we have estimated that 10 cases of depression will be required for every variable included in the model: if prevalence is 30% and sample n = 150 we will be able to test four variables.

7.3 **Flowcharts of possible numbers in 12 months**

**Edinburgh**

*Source: informal conversation with a Neuro-oncology nurse; 6-month mortality figures may be an under-estimate according to Neuro-oncology consultant. Accurate case/mortality figures are not currently available in Edinburgh.*
<table>
<thead>
<tr>
<th>All new Gliomas (120)</th>
<th>Low Grade (36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>High Grade (84)</td>
<td>No RT (17) – exclude (palliation)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>RT (67)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2-week course (27)</td>
<td>6-week course (40)</td>
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<td></td>
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<tr>
<td>Dead 6/12 (20)</td>
<td>Alive 6/12 (7)</td>
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<td></td>
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<tr>
<td>Dead 6/12 (13)</td>
<td>Alive 6/12 (27)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. REFERENCES


Hackett ML, Anderson CS, House AO. Interventions for treating depression after stroke. Cochrane Database of Systematic Reviews 2004; 3


Lima MS, Moncrieff J, Soares BGO. Drugs versus placebo for dysthymia. Cochrane Database of Systematic Reviews 2005; 2


Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database of Systematic Reviews 2004; 1


Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. Cochrane Database of Systematic Reviews 2006; 1


Peretti S, Judge R, Hindmarch I. Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin re-uptake inhibitors (Antidepressant selection:


Wijkstra J, Lijmer J, Balk F et al. Pharmacological treatment for psychotic depression. Cochrane Database of Systematic Reviews 2005; 4


Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta PsychiatriScandinavia 1968; 67:361-70
What are the possible benefits to me?

Your responses will help us better understand the areas you have difficulty with. At the moment we do not regularly ask questions about a person’s distress. Taking part would help us detect any significant mood changes that might benefit from advice or treatment.

By taking part you would also help us understand what services we need to develop to support patients and so improve the future care of people with brain tumours in Scotland.

What are the possible disadvantages?

Meeting us three times might be inconvenient or tiring for you. You might be someone who does not really like talking about their feelings, or you might find that the study is not what you thought it was.

Further information and contact details

Independent advice
Prof. Ian Whittle
0131 537 2102

Questions about the study
Dr. Alasdair Rooney (Edinburgh and Glasgow)
07775 802136
Dr. Robin Grant (Edinburgh)
0131 537 2088
Prof. Roy Rampling (Glasgow)
0141 301 7067

Thank-you. Please read the second leaflet for more information about this study.
What is the purpose of this study?

This is a study designed specifically to help improve our brain tumour services here in Edinburgh and Glasgow.

We know that having a brain tumour, and sometimes its treatment, can cause a person emotional distress. Some people find that they become more anxious. Others might feel sad and tired. Some people do not notice any changes in their emotions.

We don't know how many people with a brain tumour experience significant levels of distress, nor how they are currently treated. Sometimes it is hard to talk about it. Yet it is important that serious distress is identified as it can have a big impact on a person’s life.

So, we are asking our patients about symptoms of sadness and anxiety and will record how they are currently managed. This will help us to plan better treatments in the future.

We are not testing a new treatment. We simply want to gather knowledge about what is already happening so we can work to make our care of people with brain tumours better.

Why have I been approached?

Because you are going to get treatment for a brain tumour.

We hope to enlist the help of at least 100 people with brain tumours.

What will happen if I take part?

We will ask you to sign a consent form.

We will then meet you three times in the next 6 months. The first meeting should take one hour at the most. The second and third interviews will take about half an hour and will take place at three months and six months after the first.

Exactly when and where we meet is flexible and can be arranged to suit you best. With your permission we may phone you at home to arrange interviews. If you choose to come to hospital specially to see us, we will refund your travel expenses.

After 6 months your involvement in the study will cease, although you will continue to be followed up by our usual clinic and via your GP. Taking part in this study will not affect your normal treatment in any way.

Do I have to take part?

No. This information sheet tells you all about the study. If after reading it you do not wish to take part, simply decline our invitation. Your decision will not affect any future care you receive.

What will I have to do?

During the interviews we will ask you some questions about how you are feeling, and about any medicines you are taking. If your answers show that you have very low mood or marked anxiety we will write and inform your GP. If you are not distressed we will simply see you again in three months.

We will ask for your permission to audio-record part of the interview. Another Doctor involved in the study will listen to the interview to check that we are doing it properly. If you would rather we did not record part of the interview, we will not. You can still take part.

We will do some simple memory tests, and will also assess your walking speed over 10 metres. Together, these extra tests should take no more than 10 minutes.
What will happen to the results of the research study?

The results of this research will be written up as scientific papers and published for other doctors to read. They may be presented at medical conferences.

They will also be used to design future studies into this topic and hopefully improve future patient care. Your usual doctor will be told of the results and you would be able to get information from him/her.

You will not be identified in any published material. We will offer you and your relatives the option of receiving a summary of our findings when results are analysed in a few years.

Further information and contact details

Independent advice
Prof. Ian Whittle
0131 537 2102

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Dr. Alasdair Rooney (Edinburgh and Glasgow)
07775 802136
Dr. Robin Grant (Edinburgh)
0131 537 2088
Prof. Roy Rampling (Glasgow)
0141 301 7067

Thank you for taking the time to read these leaflets and consider entering the study.

We will contact you in the next few weeks to ask your thoughts on taking part.
Would my taking part in this study be kept confidential?
Yes. Any information you give us will be collected on paper and entered into a secure database. When we are doing this we create a unique number for each patient and use this instead of a name. The code for this system and all paperwork for patients’ answers are stored in a secure place.

Any digital recording of the interview will be kept in a secure place. The only other people who hear it will be people directly connected with running the study. It will be used only to check that we are correctly following the interview procedure and will be destroyed at the end of the study.

We will not share your name (or any other information that may be used to identify you) with anyone out-with the study.

Will my GP be involved?
Yes, in some ways. We will contact your GP to say that you are taking part in a study. We would also write to tell them if you were found to have significantly low mood or anxiety. We would let them decide about any treatment.

Part of the study involves us asking GPs for their own attitudes towards management of distress in someone with a brain tumour. We will therefore also contact your GP after you have left our study and ask them about aspects of your care.

What happens when the research study stops?
We will meet you three times over six months. After that, we will not contact you directly again. If we have found that you have very low mood your usual doctor will follow you up in the usual way.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to a researcher who will do their best to answer your questions. The contact telephone numbers are listed at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. You can get details of this from the hospital.

What will happen if I don’t want to carry on with the study?
You can withdraw at any time without having to give a reason. Deciding to withdraw will have no impact on your usual care. The information you will have given us up to that point will be analysed at the end of the study.

Who has reviewed this research?
An independent group called a Research Ethics Committee looks at all research in the NHS. This process protects your safety, rights, well-being and dignity.

This study has been reviewed and approved by the Scotland A Multi-centre Research Ethics Committee.

The study has also been reviewed by, and designed with the help of local research doctors knowledgeable about brain tumours and distress.

Who is organising and funding the research?
It is being funded by the Lothian NHS Endowment Fund. The researchers are all employed full-time by the NHS.
CONSENT FORM

DISTRESS IN PEOPLE WHO HAVE A BRAIN TUMOUR

CENTRE NUMBER

STUDY NUMBER

I confirm that I have read and understood the information sheet dated ............... (Version .................) for the above study.

I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care or legal rights being affected.

I understand that a researcher and other NHS employees involved in monitoring research may look at relevant sections of my medical notes and data collected during the study, where this is directly relevant to the research. I give permission for these individuals to have access to my records.

I agree to my GP being informed of my participation in the study and for him/her to provide the researchers with relevant clinical information from my GP records.

I understand that parts of the interviews will be audio-recorded and securely stored, and that a senior researcher will listen to a random sample of recordings to ensure proper conduct of the study. I give permission for this recording to occur.

I agree to take part in the above study.

Name of participant  Date  Signature

Name of researcher  Date  Signature

If required
Name of witness  Date  Signature

One copy to researcher, one copy to patient, one copy into medical notes
Clinical aspects of DSM-IV depression and anxiety in primary cerebral glioma: a six-month descriptive, prospective cohort study

Date…………………………

Dear Dr…………………………. ………………...

Your patient:

DOB:

Address:

Has agreed to take part in an ethically-approved observational study of mood disorders in patients with glioma. We are not testing a particular treatment.

Your patient has given informed consent for us to contact you now, and for you to provide us with relevant clinical information from their GP records.

We enclose a copy of the patient information leaflets and will interview your patient three times in the next six months. We may contact you for further information, and will ask you to complete a follow-up survey.

We ask that you manage this patient as you usually would.

If you would like any further information or if you have any reason to be concerned about your patient’s welfare, please contact us using the details below.

Yours sincerely,

Dr. Alasdair Rooney
Research Fellow

Tel 0131 537 3266
Fax 0131 537 2659
Email a.rooney@nhs.net

For

Dr. Robin Grant
Consultant Neurologist

Prof. Roy Rampling
Professor of Neuro-oncology
APPENDIX 5b. Letter to GPs informing them of a patient's diagnosis of Major Depressive Disorder.

Dear Dr.…………………………………………………:

Your patient:

DOB:

Address:

Has been screened in a clinical diagnostic interview as part of a research study, and has symptoms suggestive of:

- [] Major Depressive Disorder
- [] Minor Depressive Disorder
- [] Anxiety Disorder

Further assessment does not indicate any significant suicide risk.

We are currently conducting an ethically-approved, epidemiological study of depression and anxiety in patients who also have glioma. We are not testing a particular treatment. **We therefore ask that you manage this patient as you usually would.**

If you would like any further information or if you have any reason to be concerned about your patient’s welfare, please contact us on 07775802136.

Yours sincerely,

Dr. Alasdair Rooney
Research Fellow

For
Dr. Robin Grant
Consultant Neurologist

Tel 07775802136
Fax 0131 537 2659
Email a.rooney@nhs.net

Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
Scotland G12 0YN

Edinburgh Centre for Neuro-oncology
Western General Hospital
Crewe Road (South)
Edinburgh
Scotland EH4 2XU

Clinical aspects of DSM-IV depression and anxiety in primary cerebral glioma: a six-month descriptive, prospective cohort study
SCID QUESTIONS: DEPRESSION

I am going to ask some questions about your mood. Let’s concentrate on how you have been feeling during the past month. (focus on worst two weeks)

Has there been a period of time when you were feeling depressed or down?

Do you ever feel sad or empty?
Do you ever get tearful?
How long did it last?
As long as two weeks?
Does this low mood last most of the day, nearly every day?

What about losing interest or pleasure in things you usually enjoyed?

When did you last really enjoy yourself?
Is there anything that you CAN do now that you still enjoy?
How much of the time have you felt like that?
Was it for most of the day, nearly every day?

During this two-week period, how was your appetite?

What about compared to your usual appetite?
Have you been eating less/more than usual?
Did you have to force yourself to eat?
Was that nearly every day?
Did you lose/gain any weight? (How much?)
Were you trying to lose/gain weight?

How have you been sleeping?

What is your normal sleeping pattern?
How many hours a night have you been getting compared to usual?
Do you have trouble falling asleep?
Do you have trouble staying asleep?
Do you wake earlier than usual? (How much earlier?)
Are you sleeping too much?
(Are you taking sleeping tablets?/how long)
Have you been so fidgety or restless that you were unable to sit still?

Was it so bad that other people noticed it? (What did they notice?)
Can you sit and relax, for example in front of the television?
Or have you felt the opposite – talking or moving more slowly that is normal for you?
Was that nearly every day?

Over this period of time, what was your energy like?

Have you been feeling tired all the time?
What times of the day? Nearly every day?

I’m interested in how you feel about yourself at the moment. During this time, has the way that you feel about yourself changed in any way?

Is your self-esteem different from usual?
Do you ever feel bad about yourself?
(Ever feel so bad that you feel worthless?)
Are you feeling guilty or blaming yourself for things?
Have you felt like this for most of the day, nearly every day?

Have you been having trouble thinking or concentrating?

Does your mind ever wander?
What kinds of things do you have trouble concentrating on?
What about watching TV or reading a book?
Do you find it difficult to make decisions?
(What times in the day do you feel like this? How many days in the week)?

I know it might be difficult, but can you give me an idea of the worst that you have felt?

Have you ever felt that it’s not worth carrying on?
Were things so bad that you thought you might be better off ending your life?
What about hurting yourself?

IF ENDORSES LAST QUESTION – move to RISK PROFORMA

REMEMBER TO WRITE IN NOTES
### SCID SCORE SHEET – DEPRESSION

**Patient Number**

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Depressed mood most of the day, nearly every day, as indicated either by subjective report or observation made by others.

   - Y
   - N

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

   - Y
   - N

3. Significant weight loss when not dieting, or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day.

   - Increase
   - Decrease
   - Same

   - ?

4. Increase
   - Weight
   - Appetite

5. Decrease

6. Insomnia or hypersomnia nearly every day.

   - Insomnia
   - Hypersomnia
   - n/a

7. Psychomotor agitation or retardation nearly every day.

   - Agitation
   - Retardation
   - n/a

8. Fatigue or loss of energy nearly every day.

   - Y
   - N

9. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.

   - Y
   - N

10. Diminished ability to think or concentrate, or indecisiveness, nearly every day.

   - Y
   - N

11. Recurrent suicidal ideation with or without a specific plan, or a suicide attempt.

   - Y
   - N

### DIAGNOSIS

<table>
<thead>
<tr>
<th>MDD</th>
<th>mdd</th>
<th>No</th>
</tr>
</thead>
</table>

1st visit only:

1. Depression at time of glioma diagnosis?

   - Yes
   - No

2. Present >4 weeks?

   - Yes
   - No
APPENDIX 7. The Hospital Anxiety and Depression Scale.

HADS v1.0 12/03/08  Office use: A_________ D_________ Total ______________

HADS Questionnaire

Patient Number ________  Visit 1 2 3

Instruction
Please read each item and tick the box opposite the reply which comes closest to how you have been feeling IN THE PAST WEEK. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

I feel tense or 'wound up':
- Most of the time
- A lot of the time
- Time to time, occasionally
- Not at all

I still enjoy the things I used to enjoy:
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly
- Yes, but not too badly
- A little but it doesn't worry me
- Not at all

I can laugh and see the funny side of things:
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind:
- A great deal of the time
- A lot of the time
- From time to time but not too often
- Only occasionally

I feel cheerful:
- Not at all
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed:
- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down:
- Nearly all the time
- Very often
- Sometimes
- Not at all

I get sort of frightened feelings like 'butterflies in the stomach':
- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance:
- Definitely
- I don't care as much as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I had to be on the move:
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things:
- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic:
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I can enjoy a good book or radio or TV programme:
- Often
- Sometimes
- Not often
- Very seldom
# APPENDIX 8. The Patient Health Questionnaire-9.

**PATIENT HEALTH QUESTIONNAIRE (PHQ-9)**

**NAME:** ____________________________________________________________

**DATE:** ___________________

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use “✓” to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**add columns:** __ __ __

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card.)

**TOTAL:** 

<table>
<thead>
<tr>
<th></th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.
2. If there are at least 4 ✓s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

3. Consider Major Depressive Disorder
   —if there are at least 5 ✓s in the blue highlighted section (one of which corresponds to Question #1 or #2)

   Consider Other Depressive Disorder
   —if there are 2 to 4 ✓s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients’ files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION
for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9

For every ✓:
Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Minimal depression</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>
THERMOMETER

HIGH DISTRESS

0 1 2 3 4 5 6 7 8 9 10

NO DISTRESS

First please circle the number (0-10) that best describes how much distress in general you have been experiencing over the past week, including today.

Second, if any of the following has been a problem for you over the past week, including today, please tick the box next to it. Leave it blank if it does not apply to you. Then rank your top 4 difficulties (1 would be the biggest problem, 4 would be your fourth biggest concern).

Practical Problems
- Child care
- Housing
- Insurance
- Transportation
- Work/school

Family Problems
- Dealing with children
- Dealing with partner

Emotional Problems
- Depression
- Fears
- Nervousness
- Sadness
- Worry
- Anger

Spiritual/religious concerns
- Loss of faith
- Relating to God
- Loss of meaning or purpose of life

Physical Problems
- Appearance
- Bathing/dressing
- Breathing
- Changes in urination
- Constipation
- Diarrhoea
- Eating
- Fatigue
- Feeling swollen
- Fevers
- Getting around
- Indigestion
- Mouth sores
- Nausea
- Nose dry/congested
- Pain
- Sexual
- Skin dry/itchy
- Sleep
- Tingling in hands/feet
- Metallic taste in mouth

Other Problems: ____________________________________________

_________________________
<table>
<thead>
<tr>
<th>Highest ranking concerns</th>
<th>Description and history of problem</th>
<th>Plan of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signed by staff member: ____________________________

Today’s Date: ____________________________

Diagnosis: ____________________________