Depression in glioma: a primer for clinicians and researchers

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ABSTRACT
Depression is one of the leading causes of global disability, and a considerable hidden morbidity among patients with glioma. In this narrative review, we summarise what is currently known about depression in glioma, the main unanswered questions and the types of studies that should be prioritised in order to find out. We conclude by calling for a prospective Phase II study of antidepressants in depressed glioma patients, to test methodologies for a multicentre randomised controlled trial.

INTRODUCTION
The incidence of primary cerebral glioma is approximately 8/100 000/year.1 Headache is the most common first symptom, but by the time of presentation, there is usually evidence of focal symptoms including hemiparesis, hemisensory loss, visual field loss, dysphasia and seizures. There may alternatively be other more poorly localising symptoms, such as unsteadiness, cognitive impairment, personality change or mood disturbance.2 Whereas patients who present with focal neurological problems present early to medical attention and are investigated, those with poorly localising changes commonly present late.

When the diagnosis of brain tumour is made on brain imaging, headache and neurological impairment are treated symptomatically with steroids. There are, however, several reasons why depressive symptoms may pass without further investigation and treatment. Initial changes in mood may be attributed directly to headache (itself often associated with changes in sleep pattern, fatigue, apathy and lack of enjoyment of activities). Treating clinicians may believe that depression is an understandable reaction to the diagnosis of glioma. Later in the course of disease, depression may be considered a natural reaction to surgery, radiation or chemotherapy, loss of the driving license, concerns about future employment and existential fears.

Depression
The WHO estimates that depression affects 350 million people worldwide and is one of the leading causes of global disability.3 Population studies in Westernised countries suggest a point prevalence of clinical depression of between 2% and 5%.4 5 Major risk factors for the development of depression include female sex, a family history of affective disorder, low socio-economic status, poor social support, physical illness and stressful life events.6 The impact of depression on a person’s biological and social functioning lies on a spectrum of severity ranging from mild to devastating. Equally profound is the impact on society, with the indirect costs of depression dwarfing health service costs: in England in 2010, the total economic cost was estimated at nearly £11 billion.7

But what exactly is it? It can be tempting to think that the term ‘depression’ denotes a discrete illness with a specific cause, for example, as a neurologist might speak of ischaemic stroke or a neurosurgeon of subdural haemorrhage. To psychiatrists, however, it is only a descriptive label for a heterogeneous clinical syndrome of cognitive, affective and physical symptoms co-occurring with low mood and/or anhedonia. No aetiology is implied in the diagnosis; the fundamental mechanisms of depression are largely unknown.8 The hypothesis underlying its identification as a syndrome (that co-varying symptoms reflect a unifying pathophysiology) is currently unproven. Even the research criteria standard diagnosis of Major Depressive Disorder (MDD)9 (box 1: Symptoms of MDD)

HAD-D or the Patient Health Questionnaire-9 (PHQ-9))11 12 or by treating clinicians (eg, the Hamilton Rating Scale for Depression). Rating scales are popular in research for reasons of cost and practicality but are less rigorous than interview.

CURRENT KNOWLEDGE
How often do patients with glioma suffer from depression?
We previously reviewed 42 observational studies of depression in glioma. Most were cross-sectional, of small sample size (n<100) and tended to enrol younger and better functioning patients than is representative of glioma. Younger, fitter patients are more able to participate in research; they are also more likely to receive active treatment and therefore be readily available for hospital study. Correspondingly, we know little about depression in glioma patients with very poor functional status or in those receiving palliative care.

Direct between-study comparison of depression prevalence was hampered by the use of 25 distinct diagnostic methods in the 42 studies. Most used some kind of self-reported rating scale, with suprathreshold ‘prevalence’ rates varying widely (range 0–93%, median prevalence 27%). More robust data from clinical interviews gave a narrower range and lower prevalence (range 6–28%, median 15%). Across studies, depression was most consistently associated with functional impairment and reduced quality of life.

In the largest consecutively presenting cohort studied to date (n=155), 20% of patients became clinically depressed in the 8 months after glioma diagnosis. After controlling for confounding variables, patients with severe functional impairment or a past history of depression were at higher risk.

Taken together, available data suggest that most glioma patients fit enough to receive active treatment cope relatively well with the diagnosis, but that a sizeable minority (in the order of 15–20%) will become clinically depressed. There is a need for studies of depression in palliative care and severely functionally disabled patients.

How can clinicians diagnose depression in glioma?
The process of diagnosing depression in cancer is complicated because some symptoms of apparent depression could be due in fact to the cancer or its treatment. So-called criterion contamination presents a considerable problem for clinicians attempting to diagnose depression in glioma. With the general exception of suicidal thoughts, every symptom of MDD could plausibly be explained by direct or indirect consequences of the tumour, its treatment or both.

Common approaches to this problem include the Inclusive (count all symptoms if present), Exclusive (exclude from diagnostic criteria any symptoms frequently caused by cancer), Substitutive (use different diagnostic criteria) and Etiologic (only count symptoms if clearly caused by depression). None of these different approaches to diagnosing depression in cancer are clearly superior to the others.

The etiologic model sounds appealing, but is difficult to apply in glioma. For example, where a symptom is likely due to treatment (eg, insomnia arising shortly after starting high-dose dexamethasone), it may seem reasonable to discount it from the depressive syndrome. However, this may be misleading. Insomnia is also a common symptom of depression, and the relationship between steroids and sleep may not be straightforward in glioma. For example, of 108 local patients taking dexamethasone shortly after primary surgery, most (n=73, 67.6%) reported either no sleep changes (n=56) or hypersomnia (n=17) on clinical interview. (Rooney 2010, unpublished data; explanations could include fatigue and somnolence from chemotherapy, radiotherapy, cerebral oedema or depression). The safest conclusion may be that in glioma, with multiple confounding influences, it is often impossible to confidently attribute causality to individual depressive symptoms.

In the absence of a notably better alternative, we therefore suggest taking an inclusive approach and counting depressive symptoms if clearly present. This approach is simple, sensitive and supported by many researchers in the field. It risks over-diagnosing depression, but since disabling sadness or
anhedonia must be present for a diagnosis, anyone meeting
diagnostic criteria will arguably be experiencing the kind of suf-
ferring that doctors should identify and treat.

Similarly to taking a history of epilepsy, the best way to clinic-
ically diagnose depression in glioma is by face-to-face interview,
with additional collateral history from an informant. Carers
acting as proxy informants tend to report more depressive
symptoms than patients report for themselves. Proxies appear to
be more reliable in reporting observable behavioural symptoms
in particular.

Depressive symptoms can also be screened for in clinic using
the HAD-D (threshold 8+) or PHQ-9 (threshold 10+). Both
instruments have been partially validated for use in glioma, with
good internal validity and acceptable sensitivity and specificity,
although their positive predictive value is low (0.55 and 0.43,
respectively). Patients scoring highly should receive a more
detailed assessment.

Some clinical diagnostic tips are suggested in box 2.

UNANSWERED QUESTIONS
Isn’t depression a normal reaction to having glioma?
It may be natural to think ‘I’d be depressed if I had a brain
tumour’. It is, however, important to distinguish between collo-
quial and medical meanings of ‘depressed’: while nearly every
glioma patient will feel understandably sad, the evidence sug-
gests that most do not become clinically depressed. Whether
depression should be viewed as an abnormal reaction in the
remaining 20% can be debated.

Such a debate highlights different philosophical positions about
the nature of psychiatric disorder. Is it right to affirm the presence
of mental illness in face of the many losses of glioma? Horwitz
and Wakefield argue that, historically, depression/melancholia was
rarely diagnosed after an obvious loss and that doing so is a
modern phenomenon. They regard depressive symptoms occur-
rning after loss as an evolutionary mechanism designed to ease the
process of adaptation. Others respond that the evolutionary
biology of sadness remains largely a theoretical field. Despite dif-
fferences in ‘where to draw the line’, both sides of the debate affirm
that clinical depression can develop following a decline in health.

It matters in practice because (often unspoken) attitudinal dif-
ferences between treating clinicians may lead to differences in
care. We previously conducted a survey of 105 Scottish consult-
ant neurosurgeons, neurologists, oncologists, psychiatrists and
GPs to explore this question. Participants received a vignette of
a glioma patient with symptoms meeting criteria for MDD, with
each symptom also having a plausible alternative explanation in
the context of recent surgery and chemoradiotherapy. For the
same clinical information, there was marked disagreement on
diagnosis. Sixty-four consultants (61%) diagnosed MDD while
41 (39%) thought the symptoms were better framed simply as
‘an understandable reaction’. Choice of diagnosis strongly influ-
cenced choice of management: only 2/41 consultants diagnosing an
‘understandable reaction’ prescribed antidepressants com-
pared to 38/64 diagnosing MDD (p<0.001). The

The question is unlikely to be resolved without further study on
the normal response to multiple losses. We support a prag-
amatic approach. Depression severe and persistent enough to
justify a clinical diagnosis is invariably associated with consider-
able, potentially treatable suffering. The WHO defines health as
“a state of complete physical, mental and social well-being”.
If depressive symptoms are clearly interfering with this balance, it
seems right for doctors to view them as a clinical issue.

What causes depression in glioma?
Some neuro-ontocology researchers explain depression in primar-
ily biological terms. Aetiological hypotheses include neuro-
chemical imbalance and the direct destructive effect of glioma or
surgery on critical emotional pathways. Others view depres-
sion more in terms of an abnormal psychological reaction to
overwhelming stress and loss. Others favour a combination of
biological and psychological causes.

It is tempting to imagine that a brain tumour or its treatment
must somehow ‘cause’ depression directly. Yet observational
studies show a relatively consistent lack of association between
depression and most tumour-related variables, including WHO
tumour grade, histology, location and laterality, radiotherapy,
chemotherapy or extent of surgical resection. Tumour size may
be an exception, with increasing size generally associated with
an increased frequency of depression, although this relation-
ship could be mediated by other factors (eg, psychological dis-
tress at greater disability). Methodological limitations in the
current literature prevent many inferences being drawn. For
example, nearly all studies attempting unsuccessfully to link
tumour location with depression have bluntly described tumour
location by the main affected lobe, rather than at the more fine-
grained level of cortical–subcortical circuitry.

To our knowledge, only one study has focussed specifically on
the question of depression aetiology in this population. Armstrong
et al studied 57 adults with low-grade primary brain

Do glioma patients respond to treatment for depression?
Depressive symptoms impose a great burden on glioma patients
and their carers and are clearly associated with reductions in
quality of life. In such an aggressive disease as glioma, quality of
life is a valuable outcome, and identifying safe and effective
treatments for depression would be of great clinical benefit. The
mainstays of treatment for clinical depression in the general
population are antidepressants and psychotherapy.

In physically ill people, antidepressants are effective in treat-
ing depression in the absence of underlying structural brain
disease. Antidepressants are also considered first-line treatment
in depressed patients with functional neurological disorders for
example, epilepsy. It is, however, completely unclear whether
antidepressants are effective in the presence of a tumour pro-
gressively invading, distorting and destroying brain pathways. It
is possible that antidepressants would do nothing at all to improve
mood in these circumstances. There are currently no
published peer-reviewed randomised controlled trials (RCTs) of
antidepressant treatment of depression in glioma. Existing treat-
ment studies are few and have either treated depression as a sec-
ondary outcome or studied mixed populations of patients with
different types of cancer.

Brain cancer, surgery, chemotherapy and radiotherapy may all
impair cognitive functioning, particularly the domains of
executive function, memory and insight. Whether psychotherapy is an effective treatment for depression under these challenging conditions is unknown. Neuro-oncology researchers in the Netherlands are currently recruiting to an RCT of an internet-based self-help intervention for depressive symptoms in glioma. To date, however, the few published studies of psychological interventions in glioma have focussed on cognitive rehabilitation. Among patients with systemic cancers, psychosocial interventions such as cognitive behavioural therapy (CBT) and supportive psychotherapy may have a small but beneficial impact on depressive symptoms, both shortly after diagnosis and in the palliative phase.

The feasibility of psychological treatments for depressed glioma patients depends partly on the ease of access to local services. If waiting times for treatment are long, some patients referred to psychology—especially those with Glioblastoma multiforme (GBM) may deteriorate clinically before being treated. In this situation, psychotherapy may be a more practical option for low-grade glioma patients, who have a more slowly progressive course. Looking to the future, a compelling case can be made for a model of integrated psychosocial care, involving the systematic identification of need, integrated delivery of care by care managers, appropriate specialist supervision and the stepping of care based on systematic measurement of outcomes.

Could antidepressants cause harm in glioma?
Antidepressants have a broad range of potential neurological and general side effects that, conceivably, could cause harm to patients at increased risk of epilepsy, cognitive dysfunction and fatigue.

Studies of patients from the general population presenting to A&E suggest that antidepressant overdose is associated with an increased risk of epileptic seizures. Epilepsy affects approximately 50% of patients with glioma as an integral part of the illness, and practically all patients are at a generally increased risk of epilepsy throughout. The question therefore arises as to whether, in such a high-risk population, antidepressants could cause seizures in therapeutic doses. Alper et al conducted a large meta-analysis of seizure risk in over 30,000 participants in the US Food and Drug Administration (FDA) antidepressant licensing trials. They found evidence suggesting an increased risk of new-onset seizures for the antidepressants Bupropion and Clomipramine. Most antidepressants included in this study, however, showed no association with increased seizure risk in therapeutic doses, and some were associated with a reduced risk. The difficulty here is that very few (if any) glioma patients will have been eligible to participate in drug company licensing trials. To our knowledge, no prospective data pertain specifically to the high-risk group of patients with glioma. Another risk of harm lies in their potential effects on cognitive function. Nearly all glioma patients have some cognitive impairment that ranges in severity from subclinical to profound. In turn, nearly all antidepressants have some degree of anticholinergic action. It is well known that medicines with anticholinergic activity can worsen cognitive function in vulnerable individuals. The impact of antidepressants on cognitive functioning in glioma is currently unknown.

A similar situation holds for fatigue. In symptom surveys, fatigue is consistently reported by a clear majority of glioma patients and is usually the single most frequently reported problem of daily living. Causes are likely to be multifactorial and may include the effects of brain cancer, radiotherapy, chemotherapy and reduced levels of physical activity secondary to functional impairment. Fatigue is also listed as a side effect of all antidepressants. It is therefore unclear whether antidepressants may improve or worsen fatigue in glioma. A meta-analysis of two RCTs (n=643 participants) comparing paroxetine against placebo in patients with systemic cancers found no statistically significant difference in fatigue outcomes. There are currently no prospective data on their effect in a group as prone to fatigue as glioma patients. Yet it is possible that the successful treatment of depression could improve each of these outcomes. Untreated depression is itself a risk factor for epilepsy. Cognitive dysfunction and fatigue are part of the depressive syndrome. Retrospective data further suggest that selective serotonin reuptake inhibitor (SSRI) antidepressants may be safe in glioma. In one large case notes review (n=160), there was no evidence of increased toxicity among patients with glioblastoma multiforme taking an SSRI. These and other retrospective studies are reassuring, but the potential risks of prescribing antidepressants in glioma justify prospective studies.

Could antidepressants improve survival in glioma?
Untreated depression is an established risk factor for mortality in cancer and neurological disease. Whether it predicts mortality in such a naturally aggressive disease as glioma remains to be firmly established, although some studies suggest a relationship. One retrospective study found depression to independently predict mortality in HGG. The SSRIs Paroxetine and Fluoxetine, and the TCAs Imipramine, Desipramine and Clomipramine, have been shown to induce glioma cell death by apoptosis in cell cultures. Among these potential therapeutic candidates, Clomipramine is currently attracting particular attention within neuro-oncology, with one study suggesting increased cytotoxicity when combined with Imatinib. Such has been the publicity surrounding Clomipramine that The Brain Tumour Charity, the largest of its kind in the UK, recently published a Patient Information Leaflet summarising the evidence for its chemotherapeutic effect. While recognising the tantalising nature of these developments to patients and families often desperate for a cure, we suggest caution. The evidence that Clomipramine has a chemotherapeutic effect is entirely preclinical. This particular
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drug has, however, been associated with an increased risk of causing epileptic seizures in humans.\textsuperscript{82} It has more anticholinergic activity than SSRIs and could therefore affect cognitive function to a greater degree. Currently there is, unfortunately, no high-quality trial evidence to inform clinicians deciding whether to prescribe Clomipramine to glioma patients. RCTs are needed to quantify the risk/benefit of this particular antidepressant and of antidepressants in general in glioma.

Are treatment trials of depression in glioma feasible?

Glioma is a progressive disease, and depressed patients generally are at higher risk of dropping out of research studies. Longitudinal study of depression in glioma is therefore a particularly challenging prospect. One prospective study of 155 patients retained 70\% of patients at 3 months and 57\% at 6 months after glioma diagnosis; by far the most frequent reason for dropout was death or clinical deterioration.\textsuperscript{11} Future treatment trials need to be adequately powered in anticipation of high attrition. A possible strategy may be to study patients intensively over a relatively short time-frame (eg, 8 weeks), at points in the illness where distress is known to peak. These points include diagnosis, end of primary treatment, recurrence and the palliative phase.\textsuperscript{81}

Glioma patients can be difficult to interview timeously: in one prospective study, only 75/92 eligible patients could be interviewed within 3 months of glioma diagnosis.\textsuperscript{82} The relatively low population frequency of glioma and a high number of potential confounding variables are additional hurdles suggesting a need for multicentre studies. Treatment studies must therefore be well planned and realistically funded with adequate support for recruitment and interview.

Given the difficulties, what we believe is initially required is a pilot RCT, to test the feasibility of recruitment and retention of patients. A prospective Phase II study of antidepressants in depressed glioma patients would aid the development of tested methodologies for a multicentre randomised controlled trial and provide vital safety data.

SUMMARY

Depression is a frequent complication of glioma, with considerable morbidity and an adverse effect on quality of life. It is likely that many depressed patients pass unrecognised, either because clinicians may assume sadness is normal and not enquire about it, or patients may not volunteer these symptoms.

We suggest that, following 1 month from the initial diagnosis to allow initial sadness to subside, mood is routinely screened in glioma patients. A prospective Phase II RCT could provide a platform to design and safely conduct a large multicentre study.

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REFERENCES
