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## REVIEW

# 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Population studies in Westernised countries suggest a point prevalence of clinical depression of between 2% and 5%.<sup>4 5</sup> 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.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8</sup> The hypothesis underlying its identification as a syndrome (that co-varying symptoms reflect a unifying pathophysiology) is currently unproven. Even the research criterion standard diagnosis of Major Depressive Disorder (MDD)<sup>9</sup> (box 1: Symptoms of MDD) amounts to a convention, and despite a certain cachet is not necessarily equivalent to a disease in the traditional sense.<sup>10</sup>

Depression may be defined more loosely still, particularly in research, as scoring highly on a rating scale designed to measure the presence and severity of depressive symptoms. Many such scales exist and can be completed either by patients (eg, the depression subscale of the Hospital Anxiety and Depression Scale (HAD-D) or the Patient Health Questionnaire-9 (PHQ-9))<sup>11 12</sup> 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.

The limitations of a purely descriptive approach to diagnosis, combined with multiple methods of case ascertainment, can lead to heterogeneous patient groups between and within studies of depression. These characteristics probably restrict, to some extent, the reliability of generalising from research to depressed individuals in clinical practice. However, it is important to make this effort because depression is a potentially treatable complication of medical illness.<sup>13</sup>

There is a relative lack of guidance for clinicians assessing or treating depression occurring in patients with glioma. In this narrative review, we summarise current knowledge about depression in glioma, the main unanswered questions and the types of studies that should be prioritised in order to answer them.

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**Box 1 Symptoms of MDD**

- ▶ Low mood
  - ▶ Anhedonia
  - ▶ Fatigue
  - ▶ Insomnia or hypersomnia
  - ▶ Reduced appetite or increased appetite
  - ▶ Psychomotor slowing or agitation
  - ▶ Poor concentration
  - ▶ Guilt
  - ▶ Suicidal thoughts
- MDD, Major Depressive Disorder.

**CURRENT KNOWLEDGE****How often do patients with glioma suffer from depression?**

We previously reviewed 42 observational studies of depression in glioma.<sup>14</sup> Most were cross-sectional, of small sample size ( $n < 100$ ) and tended to enrol younger and better functioning

**Box 2 Tips for diagnosing depression in glioma**

- ▶ Allow at least 1 month from the diagnosis of glioma before diagnosing depression, unless symptoms are very severe.
- ▶ Each symptom should be severe enough to impact on lifestyle, persistent (present most of the day for most days in the last few weeks) and be a change from normal for the patient.
- ▶ Sadness is very common. Sadness that comes in waves alternating with normal mood suggests adaptive grief or emotionality secondary to frontal disinhibition. The sadness of depression has a more pervasive quality.
- ▶ Apparent loss of interest in normal activities (including hobbies) is sometimes attributable to functional impairments. Loss of interest for family interactions is more likely to be due to depression.
- ▶ Many glioma patients feel intermittent guilt about functional impairment limiting their previous domestic roles. Persistent rumination is more suggestive of depression.
- ▶ Appetite change, sleep change, fatigue, poor concentration and psychomotor slowing may all be caused by depression or by glioma and its treatment. Disentangling causes is difficult. Weigh symptoms in the overall clinical context.
- ▶ Suicidal thoughts appear to be rare in glioma, at least in the early stages of treatment—if present they should trigger a more detailed risk assessment.
- ▶ Take a collateral history wherever possible. Some patients may lack insight into their presentation over the previous month.
- ▶ The differential diagnosis may include adjustment disorder, hypoactive delirium, cognitive impairment secondary to glioma and organic personality change. There is little evidence to aid in distinguishing between these conditions in glioma. Local liaison or neuropsychiatry services may be able to give useful advice or a second opinion on what is essentially a difficult clinical judgement.
- ▶ Explain to the patient and carer the uncertainties of diagnosis, and the possible risks versus benefits of treatment. Document the discussion and outcome.

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.<sup>15</sup>

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.<sup>16</sup> So-called criterion contamination presents a considerable problem for clinicians attempting to diagnose depression in glioma.<sup>17</sup> 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),<sup>18</sup> Exclusive (exclude from diagnostic criteria any symptoms frequently caused by cancer),<sup>19</sup> Substitutive (use different diagnostic criteria)<sup>20</sup> and Etiologic (only count symptoms if clearly caused by depression).<sup>21</sup> None of these different approaches to diagnosing depression in cancer are clearly superior to the others.<sup>22</sup>

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.<sup>23–25</sup> 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 suffering that doctors should identify and treat.

Similarly to taking a history of epilepsy, the best way to clinically 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.<sup>26</sup>

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).<sup>27</sup> 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 colloquial and medical meanings of 'depressed': while nearly every glioma patient will feel understandably sad, the evidence suggests 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 occurring after loss as an evolutionary mechanism designed to ease the process of adaptation.<sup>28</sup> Others respond that the evolutionary biology of sadness remains largely a theoretical field.<sup>10</sup> Despite differences in 'where to draw the line', both sides of the debate affirm that clinical depression can develop following a decline in health.<sup>29,30</sup>

It matters in practice because (often unspoken) attitudinal differences between treating clinicians may lead to differences in care. We previously conducted a survey of 105 Scottish consultant 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 influenced choice of management: only 2/41 consultants diagnosing an 'understandable reaction' prescribed antidepressants compared to 38/64 diagnosing MDD ( $p < 0.001$ ).<sup>31</sup>

The question is unlikely to be resolved without further study on the normal response to multiple losses. We support a pragmatic approach. Depression severe and persistent enough to justify a clinical diagnosis is invariably associated with considerable, potentially treatable suffering. The WHO defines health as "a state of complete physical, mental and social well-being".<sup>32</sup> 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-oncology researchers explain depression in primarily biological terms.<sup>33–35</sup> Aetiological hypotheses include neurochemical imbalance and the direct destructive effect of glioma or surgery on critical emotional pathways. Others view depression more in terms of an abnormal psychological reaction to overwhelming stress and loss.<sup>30,36</sup> Others favour a combination of biological and psychological causes.<sup>37–39</sup>

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,<sup>14</sup> although this relationship could be mediated by other factors (eg, psychological distress 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 tumour, looking for associations between depressive symptoms and variables classified a priori either as 'neurological' (tumour type, location, size, extent of resection and cognitive impairment) or 'psychological' (extent of denial, use of psychological defences, hypochondriasis, hysteria and fatigue). Results suggested a mixture of neurological and psychological causes, but the study was not adequately powered.<sup>40</sup>

Well-designed case–control studies could shed light on this question, but teasing out the many confounding variables would need large sample sizes. In some ways, the question of cause is less important than the question of whether depression in glioma can be effectively treated.

### 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.<sup>41</sup>

In physically ill people, antidepressants are effective in treating depression in the absence of underlying structural brain disease.<sup>42</sup> Antidepressants are also considered first-line treatment in depressed patients with functional neurological disorders for example, epilepsy.<sup>43</sup> It is, however, completely unclear whether antidepressants are effective in the presence of a tumour progressively 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 treatment studies are few and have either treated depression as a secondary outcome or studied mixed populations of patients with different types of cancer.<sup>44</sup>

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.<sup>45–47</sup> 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.<sup>48 49</sup>

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.<sup>50</sup>

### 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.<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup> 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.<sup>54</sup> Nearly all glioma patients have some cognitive impairment that ranges in severity from subclinical to profound.<sup>55</sup> 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.<sup>56 57</sup> 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.<sup>58</sup> Fatigue is also listed as a side effect

of all antidepressants.<sup>59</sup> It is therefore unclear whether antidepressants may improve or worsen fatigue in glioma.<sup>60</sup> 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.<sup>61</sup> 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.<sup>62 63</sup> 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.<sup>64</sup> These and other retrospective studies are reassuring,<sup>52 65</sup> but the potential risks of prescribing antidepressants in glioma justify prospective studies.<sup>66</sup>

### Could antidepressants improve survival in glioma?

Untreated depression is an established risk factor for mortality in cancer and neurological disease.<sup>67 68</sup> 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.<sup>35</sup> Depression has also associated with reduced survival in prospective cohort studies of patients with high-grade and low-grade glioma,<sup>69 70</sup> although analyses in these studies did not control for all potentially relevant confounding variables.

SSRIs are associated with improvements in disability and neurological impairment after stroke.<sup>71</sup> Might the successful antidepressant treatment of depression therefore improve survival and functioning in glioma? Existing clinical research is sparse and retrospective. Walker *et al* conducted a case-control study from the UK General Practice Research Database and found an association between historical TCA prescription and a lower frequency of subsequent diagnosis of glioma. The effect was strongest for higher doses and longer prescription duration, suggesting a preventative dose-response element.<sup>72</sup> However, a subsequent case-control retrospective study by the same group found no association between tricyclic antidepressant (TCA) prescription and all-cause mortality following glioma diagnosis.<sup>73</sup> A retrospective case-note review suggested, by contrast, that GBM patients who received an SSRI had a reduced risk of death in the first 2 years postoperatively.<sup>64</sup> Prospective case-control studies are warranted to explore these interesting but contradictory findings.

There is a growing preclinical literature to suggest that antidepressants may have a direct chemotherapeutic effect in glioma. The SSRIs Paroxetine and Fluoxetine,<sup>74</sup> and the TCAs Imipramine,<sup>75</sup> Desipramine<sup>76</sup> and Clomipramine,<sup>77 78</sup> 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.<sup>79</sup> 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.<sup>80</sup> 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

drug has, however, been associated with an increased risk of causing epileptic seizures in humans.<sup>53</sup> 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.<sup>15</sup> 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.<sup>81</sup>

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.<sup>82</sup> 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 the neuro-oncology clinic, using either HAD-D (threshold 8+) or PHQ-9 (threshold 10+). High screening scores should trigger a clinical assessment with collateral history from an informant where possible.

In the absence of conclusive evidence, we support fully informing depressed glioma patients about the potential risks and benefits of available treatments, documenting the discussion and working with the patient and their family in a collaborative manner. Within this framework, an SSRI may be tried cautiously as a first-line antidepressant, with regular clinical review, or else advice sought from the local psychiatry service.

In terms of future research, there is a pressing need for intervention studies aimed at finding safe and effective treatments for depression in glioma. A Phase II RCT could provide a platform to design and safely conduct a large multicentre study.

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