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Depression and anxiety in glioma patients

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Abstract

Glioma patients carry the burden of having both a progressive neurological disease and cancer, and may face a variety of symptoms, including depression and anxiety. These symptoms are highly prevalent in glioma patients (median point prevalence ranging from 16–41% for depression and 24–48% for anxiety when assessed by self-report questionnaires) and have a major impact on health-related quality of life and even overall survival time. A worse overall survival time for glioma patients with depressive symptoms might be due to tumor progression and/or its supportive treatment causing depressive symptoms, an increased risk of suicide or other (unknown) factors. Much is still unclear about the etiology of depressive and anxiety symptoms in glioma. These psychiatric symptoms often find their cause in a combination of neurophysiological and psychological factors, such as the tumor and/or its treatment. Although these patients have a particular idiosyncrasy, standard treatment guidelines for depressive and anxiety disorders apply, generally recommending psychological and pharmacological treatment. Only a few nonpharmacological trials have been conducted evaluating the efficacy of psychological treatments (eg, a reminiscence therapy-based care program) in this population, which significantly reduced depressive and anxiety symptoms. No pharmacological trials have been conducted in glioma patients specifically. More well-designed trials evaluating the efficacy of nonpharmacological treatments for depressive and anxiety disorders in glioma are urgently needed to successfully treat psychiatric symptoms in brain tumor patients and to improve (health-related) quality of life.

Keywords:

anxiety | brain tumor | depression | glioma

Glioma is the most common primary malignant brain tumor with about 100.000 people diagnosed annually worldwide.[1] The 2021 World Health Organization (WHO) classification of tumors of the central nervous system differentiates three different types of adult-type diffuse gliomas, including astrocytoma isocitrate dehydrogenase (IDH)-mutant, oligodendroglioma IDH-mutant and 1p/19q-codeleted, and glioblastoma IDH-wildtype.[2] Median overall survival time differs greatly between the different diffuse gliomas, ranging from 15 months for glioblastoma to 13 years for WHO grade 2 astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted after antitumor treatment.[3,4] Usually antitumor treatment consists of a combination of surgical resection, radiotherapy, and chemotherapy.[5] Glioma patients may face different symptoms during their disease trajectory, including motor dysfunction, fatigue, seizures, neurocognitive dysfunction, and psychiatric symptoms.[6–8] Psychiatric symptoms are common in the general population, but seem to occur even more frequently in brain tumor patients. Especially depressive and anxiety symptoms,[9] which have a debilitating effect on the patient, their families, and caregivers, and have been associated with decreased aspects of health-related quality of life and worse overall survival time.[10–12] Effective management of these symptoms is of paramount importance to maintain optimal health-related quality of life.[13] However, the underlying mechanisms as well as medical treatment of depressive and anxiety symptoms in glioma are understudied in the scientific literature. High-quality studies describing prevalence, etiology, and treatment are scarce. In this review, we present the current evidence on (treatment of) depressive and anxiety symptoms in glioma patients, which may inform physicians and glioma patients on how to best treat symptoms of depression and anxiety. Electronic databases were searched (ie, PubMed and Web of Science) for recent findings on the epidemiology, etiology, treatment, and overall survival time of depression and anxiety in glioma.

Depression

Definition and epidemiology

Depression is one of the most commonly diagnosed psychiatric disorders in adults.[14] The term depression is an umbrella term for different types of depressive disorders, but generally used to describe a *Major Depressive Disorder* (MDD) diagnosis as defined in the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5) is meant. The 12-month and lifetime prevalence of MDD in the general population of the United States of America is 10% and 21%, respectively.[15] Key symptoms of MDD, which must be present for the diagnosis, include a depressed mood and/or anhedonia (ie, a loss of interest or pleasure). A minimum of five out of nine symptoms, which includes depressed mood and/or anhedonia, have to be present during a 2-week period and need to reflect a change from previous functioning (Table 1).[16] Given the diagnosis is solely based on the presence/absence of these symptoms, no etiology is implied in the diagnosis. The severity of depressive disorders such as MDD is often assessed with scales based on cutoff values that inform on the course of the depressive symptoms. Many different assessment instruments exist, which are either self- or clinician-reported. These instruments include the Hospital Anxiety and Depression subscale for Depression (HAD-D), the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), the Beck Depression Inventory (BDI), and the Hamilton Rating Scale for Depression (HRSD).[17] These instruments are frequently used in research due to low cost and practicability and sometimes as a screening tool in clinical practice. However, for clinical diagnosis a diagnostic interview (eg, Structured Clinical Interview for DSM-5 Disorders [SCID]) by a trained professional is essential.

In patients suffering from glioma, the estimated frequency of depressive symptoms varies widely depending on the methods used for assessment. The median point prevalence of depressive symptoms with the BDI was 39% (cut-off score ≥ 10), the point prevalence with the PHQ-9 was 41% (only one study used this instrument, cut-off score ≥ 6), while this was only 16% (cut-off score ≥ 11) with the HAD-D.[18] In long-term survivors diagnosed with low-grade glioma 23% had depressive symptoms (mean of 26 years [standard deviation of four years] since diagnosis).[19] A study utilizing a structured clinical interview to diagnose MDD in newly diagnosed cerebral glioma patients resulted in 14% (21/155) of patients having MDD, of whom 24% (5/21) were prescribed antidepressant medication. During the six months follow-up of these patients, eventually, a total of 21% (32/155) were diagnosed with MDD.[20] The BDI and PHQ-9 questionnaires appeared to overestimate the prevalence of depressive symptoms in comparison to a structured clinical interview,[18,21] meaning the validated HAD-D questionnaire seems to be a more suitable questionnaire in this patient population.[22] The optimal cut-off for the HAD-D for the presence of MDD is ≥7 in glioma patients. The instrument had at baseline assessment (during primary radiotherapy) in the study by Rooney et al. (2013) evaluating different instruments, a sensitivity of 0.93, a specificity of 0.91, and a positive predictive value of 0.56. The latter means that when screened as having depressive symptoms with the HAD-D (ie, a score of ≥7), the probability of having MDD as diagnosed with a structured clinical interview was 56%.[22]

Etiology

An obvious hypothesis for the etiology of depressive symptoms in glioma is that it might be due to (neuro)physiological factors, such as the pathological effect of tumor growth and its treatment (eg, surgical resection and radiotherapy) on emotional pathways in the brain. However, a systematic review of observational studies in glioma patients by Rooney et al. (2011) did not find clear associations between depressive symptoms and tumor- or treatment-related variables, including WHO tumor grade, tumor location,

Table 1. Diagnostic criteria major depressive disorder.

A	≥5 of the following symptoms during a 2-week period with a change from the previous functioning
1.	Depressed mood most of the day, almost every day
2.	Loss of interest or pleasure in all or almost all activities most of the day, almost every day
3.	Significant weight loss or weight gain, or significant decrease or increase in appetite almost every day
4.	Insomnia or hypersomnia almost every day
5.	Psychomotor agitation or retardation almost every day
6.	Fatigue almost every day
7.	Feelings of worthlessness or guilt almost every day
8.	Impaired concentration or indecisiveness almost every day
9.	Suicidal thoughts
B	The symptoms cause impairment in functioning (social, occupational or other important areas)
C	The episode should not be attributable to the effects of a substance or another medical condition
D	Major depressive disorder is not better explained by other disorders (eg, schizoaffective disorder)
E	During the lifetime never a manic or hypomanic episode has occurred

size of the tumor, the extent of tumor resection, radio- or chemo-therapy, or antiseizure medications (ASMs).[18] A possible explanation for not identifying clear associations between depressive symptoms and tumor location is that lesions causing depressive symptoms may localize to a common brain network rather than to individual brain regions,[23] in brain tumors this common brain network was defined by the left striatum.[24] Recently, a cross-sectional study was conducted to evaluate the association between ASM use and self-reported depressive symptoms (assessed with the HAD-D, cut-off score ≥ 7) in *n* = 272 glioma patients, but ASM was not independently associated with concurrent depressive symptoms. Alternative factors (ie, a low Karnofsky Performance Score and other prescription medications with >1% risk of depressive adverse effects such as dexamethasone) seemed to have a greater contribution to the risk of developing depressive symptoms in this publication,[9] and interestingly, both a low Karnofsky Performance Score and dexamethasone were associated with MDD as well in a study utilizing a structured clinical interview to diagnose MDD.[20] However, the cross-sectional study had insufficient power to adequately detect differences between ASM types,[9] despite some ASMs being well-known for mood-modulating side effects. Especially the ASM levetiracetam is known for causing psychiatric adverse effects, including depressive and anxiety symptoms.[25] In a retrospective observational study in *n* = 429 glioma patients using levetiracetam, *n* = 69 discontinued their ASM due to adverse effects during 36 months of follow-up and in *n* = 7 patients due to depressive symptoms.[26] In a follow-up study evaluating ASM dual therapy, *n* = 236 patients were prescribed levetiracetam combined with valproic acid (widely used as a mood stabilizer as well), which resulted in ASM discontinuation due to adverse effects in *n* = 35 patients and in *n* = 2 patients due to depressive symptoms. When levetiracetam was combined with valproic acid, only 17% of intolerable adverse effects were psychiatric-related,[27] in comparison to 46% with monotherapy levetiracetam.[26]This result suggests a possible antagonism for psychiatric adverse effects of the dual therapy levetiracetam and valproic acid.[27] If levetiracetam is discontinued due to depressive symptoms or glioma patients with epilepsy also have depressive symptoms, ASMs with mood-stabilizing properties such as lamotrigine could be considered. Although studies in glioma patients may not have found clear links between tumor- or treatment-related variables and depressive symptoms on a group level, on an individual patient level a clinician might assess a situation differently. If a depressive disorder is thought to be directly related to the physiological effects of a substance/medication or medical condition (eg, glioma) the diagnosis should be *substance/medication-induced depressive disorder* or *depressive disorder due to another medical condition*, respectively.[16] Others believe the etiology of depressive symptoms in glioma is (partly) due to psychological factors, such as the patient's emotional responses to the tumor diagnosis, symptoms, and associated treatments.[17] A clinician should be aware of an *adjustment disorder with depressed mood* in the differential diagnosis, which occurs as a response to a psychosocial stressor, but can be distinguished from MDD as the full criteria for MDD are not fully met.[16] In such network approaches a psychiatric disorder is the result of the causal interplay between symptoms.[28] Fatigue and drowsiness have the greatest impact on the severity of other symptoms in glioma patients and might lead to the onset or exacerbation of depressive symptoms.[29] Greater family supports with the patient was associated with higher depressive symptoms, which could be explained by patients needing more support and subsequently responding in ways to increase that support.[30]

Treatment

The next important question is how to effectively treat depressive symptoms/MDD in glioma patients.[17] In principle, the same guidelines (eg, National Institute for Health and Care Excellence [NICE] guidelines) for the treatment of depressive disorders apply to patients with or without a comorbid medical condition (eg, glioma).The main treatment strategies consist of psychotherapy, pharmacotherapy, self-management, and treatment of the underlying medical condition.[31] Recommended first-line treatments differ between patients with less severe and more severe MDD. In less severe MDD guided self-help is recommended as first choice first-line treatment (based on clinical and cost-effectiveness), while in more severe MDD combined individual cognitive behavioral therapy with antidepressant medication is recommended. Generally, selective serotonin reuptake inhibitors (SSRIs, eg, sertraline and escitalopram) are prescribed as first-line antidepressant medication. If ineffective in reducing depressive symptoms, a serotonin and norepinephrine reuptake inhibitor (SNRI, eg, duloxetine and venlafaxine) could be prescribed.The next step in case of inefficacy could be a tricyclic antidepressant (TCA, eg, imipramine). Monoamine oxidase inhibitors (MAOIs, eg, tranylcypromine) are in most cases reserved for severe treatment-resistant depression.[32,33] If a patient has a clear preference and/or experience from previous treatment in most cases the patient's choice should be supported if there are no concerns about the suitability of the treatment for the current depressive episode.[34] In addition, there is much experience in treating depressive symptoms/MDD in neurological populations more generally which can be drawn upon clinically and empirically.[31,35]

Psychotherapeutic approaches in glioma patients with MDD can differ in important aspects from psychiatric patients with MDD. Due to the often aggressive nature of the disease, rapid deterioration in physical and/or mental health and time-consuming treatments such as chemotherapy and radiotherapy, the time frame for psychotherapy is often limited. This can have implications for the therapeutic relationship between patient and clinician, which is thought to play a crucial role in the therapeutic process.[34] In addition, long waiting lists for psychotherapy are no exception and glioma patients are often burdened by additional neurological symptoms, such as neurocognitive impairments, that may complicate psychotherapeutic interventions.[6] Ownsworth et al. (2015) conducted a randomized controlled trial (RCT) in which *n* = 50 brain tumor patients (>50% glioma) were randomly assigned to either the "making sense of brain tumor program" (ie, a home-based psychosocial intervention) or a waitlist control group. After 10 weeks, depressive symptoms were

significantly lower in the intervention group compared to the waitlist group (effect size 0.17).[36] RCTs evaluating a reminiscence therapy-based care program versus control care (n = 150 glioma patients) and a comprehensive nursing program based on cognitive behavioral therapy versus routine nursing (n = 108 glioma patients) resulted in the reduction of depressive symptoms.[37,38] An online problem-solving therapy versus a waitlist control group (n = 115 glioma patients) did not result in the reduction of depressive symptoms.[39] Problematic with most psychotherapy trials, including trials conducted in glioma patients, is the choice of the control groups. The choice of a waitlist control group or treatment as usual control group likely results in treatment effects being overestimated. Expectancy, a key contributor to the placebo effect, of patients in the psychotherapeutic intervention being more effective than the control group leads to improvement in outcomes, while symptoms may worsen in patients receiving the control intervention due to conscious disappointment or a nocebo effect, thus leading to enhancement of treatment effects in the intervention group.[40] Diagnosis of a depressive disorder was not an inclusion criterium in these trials, but glioma patients were included regardless of having depressive symptoms in most of these trials.[36–38] As a result of this, it is still unclear how effective these interventions are in glioma patients with MDD and/or depressive symptoms.

Choice of an antidepressant drug is generally based on efficacy, adverse effects, and patient factors such as the comorbid medical condition and its treatment, age, presence of comorbid pain, polypharmacy (ie, drug–drug interactions), the severity of the depressive episode, previously prescribed antidepressant drugs, and patients' preference.[31] A Cochrane systematic review, with an updated search up to 2019, evaluating pharmacological treatment of MDD in patients with a primary brain tumor did not find any high-quality comparative efficacy studies of pharmacological agents for MDD in patients with a primary brain tumor.[41] However, since then Zhou et al. (2021) conducted a placebo-controlled, double-blind RCT in a mixed sample of brain tumor patients (30% included had glioma) with depressive symptoms undergoing surgical resection evaluating the effect of ketamine on depressive symptoms. Ketamine led to a ≥50% reduction from baseline depression score (clinician assessed with the Montgomery–Asberg Depression Rating Scale [MADRS]) at postoperative day 3 in 41% (17/41) of patients compared to 16% (7/43) in placebo (relative risk [RR] = 2.51, 95%CI = 1.18–5.50). At discharge, there was no longer a significant difference in ≥50% reduction from baseline depression score between patients receiving ketamine compared to placebo (39% [16/41] versus 21% [9/43], RR = 1.86, 95%CI = 0.93–3.74), but one could argue the difference was still clinically relevant.[42] Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is especially interesting given the neurotransmitter glutamate seems to play a key role in promoting both tumor progression and epileptogenesis in glioma patients. Pharmacologically intervening glutamatergic mechanisms are promising strategies in addressing glioma-associated epilepsy and progression, in addition to depressive symptoms.[43] Therefore, with the exception of this one study utilizing ketamine, no specific evidence-based recommendation can be made regarding pharmacological treatment of depressive symptoms/MDD in glioma patients and patient-specific factors such as comorbidities and efficacy of previous treatments are important to consider when initiating treatment. Any decision to treat should be supported by a careful examination and documentation of any discussion of potential risks and benefits with the patient. Finally, ElectroconvulsiveTherapy (ECT) is the oldest and most effective treatment available for (treatment-resistant) MDD,[44] but its use in brain tumor patients is controversial.[45] The presence of a brain tumor is a relative contraindication for the use of ECT, but a review of n = 33 case reports of n = 75 patients by Buday et al. (2020) suggests that ECT may be feasible and has been safe to apply in isolated brain tumor patients with a benign or clinically insignificant lesion. In 90% of patients, ECT showed a "beneficial effect" on symptoms, which was not further defined by the authors.[46]

Overall survival time

Beyond the burden of depressive symptoms/MDD in itself, newer studies even point towards an effect on overall survival time. A systematic review and meta-analysis by Shi et al. (2018) reported a standardized mean difference in survival outcomes of –0.56 months (95%CI = –1.13 to –0.02) for high-grade and –1.69 months (95%CI = –3.26 to –0.13) for low-grade glioma patients with depressive symptoms/MDD, indicating depressive symptoms/MDD might be associated with significantly worse overall survival times.[12] While no definitive conclusions can be drawn based on this meta-analysis with regard to the causality of having depressive symptoms/MDD on overall survival time, future studies evaluating the treatment of depressive symptoms/MDD on overall survival time are warranted. A potential contributing factor decreasing overall survival in glioma patients with depressive symptoms/MDD might be the increased risk of suicide (observed to expected event ratio was three) found in glioma patients. Especially, male sex, patients ≥ 45 years, and glioblastoma patients were at increased risk of committing suicide.[47] The increased risk of suicide in the brain and other nervous system cancer patients is mainly during the first two years of diagnosis.[48] Frequency of suicidal ideation ranges from 12% to 21% in glioma patients, which was significantly associated with female sex, older age, history of psychiatric medication, history of a depressive disorder, epileptic seizures, no antitumor treatment at all or only surgical resection.[49,50] Another hypothesis, which could (partly) explain the decreased overall survival time in glioma patients with depressive symptoms/MDD, is that the depressive symptoms/MDD might occur due to tumor progression and/or the use of dexamethasone in prognostically less favorable tumors. SSRIs do not seem to have an impact on overall survival time,[51,52] but the TCA imipramine and MAOI tranylcypromine reduced the cytotoxic efficacy of temozolomide in glioblastoma cells in a preclinical study.[52] Clinical studies would need to assess whether these antidepressant drugs are associated with a worse overall survival time in glioma patients with depressive symptoms/MDD. Literature is scarce in this field, and more research

is urgently needed focusing on treatment strategies for depressive symptoms/MDD as well as suicidal ideation/behavior in glioma patients and the burden of suicidal ideation/behavior by patients on their caregivers.

Anxiety

Definition and epidemiology

Anxiety disorders, including disorders such as phobias, are prevalent psychiatric disorders with high comorbidity to other psychiatric disorders.[53] The DSM-5 diagnosis of *Generalized Anxiety Disorder* (GAD) may apply to (clinically troublesome) anxiety in oncological patients. Key symptoms of GAD are excessive anxiety and worry about events or activities, which have been present for ≥6 months (Table 2).The 12-month and lifetime prevalence of GAD in the general population in the United States of America is 2% and 9%, respectively.[54] The pooled period global prevalence and lifetime prevalence for anxiety disorders, in general, are 7% and 13%, respectively.[55] Frequently used self-report questionnaires to measure the presence and severity of anxiety symptoms in research studies include the Hospital Anxiety and Depression subscale for Anxiety (HAD-A), the GAD Screener (GAD-7), and the Beck Anxiety Inventory (BAI).[56]

Less is known about the prevalence of anxiety symptoms and anxiety disorders in glioma than depressive symptoms and depressive disorders, but estimates similarly depend on the diagnostic method used. GAD was diagnosed in 6% and *adjustment disorder* in 9% of brain tumor patients (39% included glioma) when a structured clinical interview was conducted.[57] A substantially higher point prevalence of anxiety symptoms was found in glioma patients when using a self-report questionnaire (48% with the GAD-7, cutoff score ≥ 4; 24% and 35% with the HAD-A, cutoff score ≥ 8 and ≥11, respectively).[9,58]The GAD-7 likely overestimates the prevalence of anxiety symptoms (similar to the findings in depressive symptoms). The HAD-A questionnaire might be more suitable in this patient population to assess anxiety symptoms.

Etiology

Little is known about the etiology of anxiety symptoms and anxiety disorders in glioma. Similar to depressive symptoms and depressive disorders, genetic/physiological factors and environmental factors (eg, childhood adversities) have been associated with anxiety disorders, but to what extent these factors contribute to anxiety symptoms and anxiety disorders in glioma is not clear.[16] Presumably a mix of both factors as well as psychological factors are responsible for anxiety symptoms and anxiety disorders in glioma. Patients undergoing interval MRI (ie, periodically preplanned imaging to assess tumor status) might experience anxiety symptoms due to the procedure itself of undergoing MRI, and awaiting the results of the MRI, so-called "scanxiety."[59] Mainio et al. (2003) found that before surgical resection patients with a right hemisphere tumor had significantly higher anxiety symptom scores (assessed with the Crown–Crisp Experiential Index [CCEI]) compared to patients with a left hemisphere tumor (39% included had glioma),[60] but others did not find an association between anxiety symptoms and tumor laterality in brain tumor patients.[61,62] No clear association exists for other tumor- or treatment-related variables with anxiety symptoms.[9,61,62] Comparable to anxiety disorders in psychiatric patients, consistent associations with anxiety symptoms in glioma seem to exist for the female sex and a prior history of mood disorder treatment.[9,16,57,62,63] In rare cases anxiety disorders seem to be directly caused by the brain tumor, such as a mass effect of the tumor on the amygdala, with anxiety symptoms completely going into remission after surgical removal of the tumor.[64,65] In these rare cases, the diagnosis of *anxiety disorder due to another medical condition* should be used, but in most glioma cases the etiology of anxiety is much less clear. Glioma patients displaying signs of anxiety should always undergo a comprehensive medical workup. Endocrine diseases such as hyperthyroidism and pheochromocytoma are known to potentially cause anxiety and therefore should be ruled out.[16] However, in most glioma patients the etiology of anxiety is much less clear. Other reasons include medication adverse effects (eg, dexamethasone or levetiracetam)

Table 2. Diagnostic criteria generalized anxiety disorder.

A	Excessive anxiety and worry about several events or activities (eg, work or school), more days than not for ≥6 months
B	Difficulty controlling the worry
C	The excessive anxiety and worry are associated with ≥3 of the following symptoms (at least some symptoms present more days than not for ≥6 months)
1.	Restlessness
2.	Fatigue
3.	Impaired concentration
4.	Irritability
5.	Muscle tension
6.	Sleep disturbance
D	The symptoms cause impairment in functioning (social, occupational or other important areas)
E	The disturbance should not be attributable to the effects of a substance or another medical condition (eg, hyperthyroidism)
F	Generalized anxiety disorder is not better explained by another disorder (eg, negative evaluation in social anxiety disorder)

and the diagnosis of *substance/medication-induced anxiety disorder* should be used.[16,26,66] Knudsen-Baas et al. (2018) identified risk factors for pharmacotherapy-treated anxiety in glioma patients in a nationwide cohort study of *n* = 1828 patients. Systemic steroid use was a risk factor for pharmacotherapy-treated anxiety in glioma, grade 2 or 3 (hazard ratio [HR] = 3.58, 95%CI = 2.19–5.84) and glioma, grade 4 (HR = 1.52, 95%CI = 1.13–2.03).[67] Temozolomide chemotherapy was also a risk factor for pharmacotherapy-treated anxiety in glioma, grade 2 or 3 (HR = 3.15, 95%CI = 1.79–5.56) and glioma, grade 4 (HR = 1.81, 95%CI = 1.20–2.75). In 1% (3/429) of diffuse glioma patients with epilepsy treated with levetiracetam, levetiracetam was discontinued due to intolerable anxiety symptoms.[26]

Treatment

Standard treatment guidelines for anxiety disorders apply to patients with glioma as well, including psychotherapy, pharmacotherapy, or a combination of both. A stepped-care approach is recommended in which the least intrusive, most effective intervention is offered first and if no improvement in anxiety symptoms, interventions from the next step are offered. Step 1 involves educating the patient and his/her family members about GAD with the use of self-help websites, education about lifestyle changes (eg, encouragement of regular exercise such as yoga), and monitoring the patient's lifestyle changes. Step 2 involves low-intensity psychotherapeutic interventions (eg, guided self-help); step 3 involves high-intensity psychotherapeutic interventions (eg, individual-based cognitive behavioral therapy) or pharmacotherapy; and step 4 involves referral to specialized care for different pharmacological agents, different high-intensity psychotherapeutic interventions, or both.[68]

Cognitive behavioral therapy is considered an effective first-line psychological treatment for anxiety disorders in the general population.[69,70]Traditional cognitive behavioral therapy techniques are based on the premise that patients with anxiety disorders unrealistically overestimate negative outcomes. This subsequently leads to nonbeneficial coping behaviors (eg, avoidance or substance abuse). Therapy is focused on restructuring dysfunctional thinking patterns, sometimes combined with exposure-based therapies. The goal is to facilitate more adaptive thinking and beneficial coping behaviors, aimed at reducing anxiety symptoms.[70,71] However, glioma, with its related symptoms and treatment-related adverse effects, is a disease-causing pain, drowsiness, seizures, neurocognitive impairment, functional impairment, and eventually death. Classic cognitive behavioral therapy techniques may therefore be hindered in patients with glioma, for instance, due to neurocognitive impairment and aphasia. On that account an adapted cognitive behavioral therapy protocol for glioma patients and the brief semi-structured psychotherapeutic intervention *Managing Cancer and Living Meaningfully* have been developed,[70,72] but widespread clinical evidence is missing. However, two RCTs in glioma patients, evaluating a reminiscence therapy-based care program versus control care and a comprehensive nursing program based on cognitive behavioral therapy versus routine nursing, resulted not only in a reduction of depressive symptoms, but also in a reduction of anxiety symptoms. However, as described earlier, glioma patients were included regardless of having depressive or anxiety symptoms in these two trials and the efficacy of these interventions in reducing anxiety symptoms in glioma patients with anxiety symptoms and anxiety disorders has yet to be investigated.[37,38] Other studies (RCTs and studies with a different design) did not report the benefit of nonpharmacological interventions on anxiety symptoms.[73] Of interest are the findings of a recent systematic review evaluating the use of virtual reality as a treatment for anxiety symptoms in cancer patients, which showed a beneficial effect of virtual reality on anxiety symptoms. Virtual reality might be a suitable intervention for patients experiencing "scanxiety".[74] Interim results of an ongoing clinical trial evaluating a virtual reality intervention targeting anxiety symptoms in glioma reported only mild adverse effects and supported the feasibility and acceptability of the intervention.[75]

Favored first-line pharmacological agents with both good efficacy and tolerability in GAD include SSRIs, SNRIs, and pregabalin (ASM).[76] However, special treatment considerations not only apply to anxiety disorders, but also to depressive disorders, in glioma.[77] Caution should be exercised with regard to SSRIs and SNRIs in glioma to avoid serotonin syndrome. Procarbazine (a monoamine oxidase inhibitor), opioids (eg, tramadol) or ondansetron (a 5-HT3 antagonist), all medications regularly prescribed in glioma patients, increase the risk of serotonin syndrome when taken together with SSRIs or SNRIs.[77] In addition, SSRIs and SNRIs may induce nausea, which glioma patients are already at high risk of due to systemic treatment, and which may compromise the health-related quality of life scales (eg, symptom scale nausea and vomiting).[78] However, Caudill et al. (2011) did not find a difference in overall survival time or toxicity in glioblastoma patients using and not using SSRIs, suggesting SSRIs are safe to prescribe in this patient population.[51] Given the increased risk for seizures in glioma patients, pregabalin (approved for GAD [European Medicines Agency] and as an add-on for focal epilepsy [European Medicines Agency and Food and Drug Administration]) might be an especially appealing pharmacological agent for treating anxiety in glioma.[79,80] Unfortunately, no RCTs or (high-quality) comparative effectiveness observational studies evaluating pharmacological agents for anxiety disorders or anxiety symptoms in glioma have been conducted. Recently, phase II RCTs have been conducted evaluating the efficacy and safety of psilocybin and lysergic acid diethylamide (LSD)-25 in patients with an anxiety disorder and life-threatening cancer and found a beneficial effect on anxiety symptoms. However, as is often the case in cancer trials, brain tumor patients were either excluded beforehand or not included.[81–83]

Overall survival time

To our knowledge, no systematic review and meta-analysis have been conducted investigating the effect of anxiety on overall survival time in brain tumor patients. Hao et al.

(2021) reported a worse overall survival time for glioma patients with anxiety symptoms,[63] while Bunevicius et al. (2017) did not find a difference in overall survival time between glioma and meningioma patients with and without an anxiety disorder.[84] Therefore, no clear conclusion can be drawn whether anxiety is negatively associated with overall survival time in brain tumor patients.

Conclusion

Both depressive and anxiety symptoms occur frequently in glioma patients, which may impact health-related quality of life and even overall survival time. The etiology of these conditions in glioma patients is still unclear and involves a combination of neurophysiological and psychological factors, such as the tumor and its associated treatment. Several risk factors of potential interest have been associated with these symptoms, including a low Karnofsky Performance Score, the use of prescription medications with >1% risk of depressive adverse effects, and a prior history of mood disorder treatment. While not all factors can be avoided or modulated, it might be helpful to consider them in the context of early screening and prevention. Despite their distinct profile, standard clinical treatment guidelines apply for both depressive and anxiety disorders. A few trials have been conducted evaluating the efficacy of psychological therapies, which showed a reduction in depressive and anxiety symptoms. To date, no pharmacological trials have been conducted in glioma patients specifically and only one pharmacological trial assessing the efficacy of ketamine in a mixed sample of brain tumor patients. Considering that glioma patients suffer not only from cancer, but also from a neurological disease, specific trials in this population are warranted. Future research should focus on the underlying mechanism of mental health issues in neuro-oncology and future clinical trials need to be adequately designed to evaluate the efficacy of nonpharmacological treatments for depressive and anxiety symptoms and disorders, and ideally include family caregiver data as well.

Supplementary material

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