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Recognizing the Psychological Impact of a Glioma Diagnosis on Mental and Behavioral Health: What Neurosurgeons Need to Know

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Abstract

A cancer diagnosis is life altering and frequently associated with both acute and long-lasting psychosocial and behavioral distress for patients. The impact of a diffuse glioma diagnosis on mental health is an important aspect of the patient experience with their disease. This needs to be understood by neurosurgeons so these concerns can be appropriately addressed in a timely fashion and integrated into the multidisciplinary care of neuro-oncology patients. The relatively grave prognosis associated with diffuse gliomas, the morbidity associated with treatment, and the constant threat of developing a new neurological deficit all can negatively affect a patient's mental ability to cope and ultimately manifest in mental health disorders like anxiety and depression. The objective of this review was to describe the variety of behavioral health disorders patients may experience following of a glioma diagnosis and discuss possible treatment options. Given the strong correlation between quality of life and patient mental well being, there is a considerable need for early recognition and treatment of these behavioral health disorders to optimize everyday functioning for patients.

Keywords

Glioma; Primary Brain Tumor; Mental Health; Psychosocial; Quality of Life; Neurobehavioral

Introduction

Diffuse gliomas represent the most common intrinsic brain tumor in adults and, despite treatment advances, patients must navigate life with the knowledge of this somber diagnosis and the constant threat of tumor recurrence. The treatment of these tumors relies on a multidisciplinary care team comprising neurosurgeons, neuro-oncologists, and radiation

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oncologists and prioritizes prolonging a high quality of life (QOL) and minimizing neurological deficits. Although the presence of this serious diagnosis frequently has a severe behavioral and psychological impact on the patient, professional psychological services may not be offered. During surgery, adjuvant therapy, disease surveillance, or times of disease progression, patients may experience psychiatric or behavioral symptoms that impact their social interactions, QOL, mood, and even their clinical decision-making. These changes in personality, mood, and behavior can be challenging to recognize and treat, as well as substantially impact both the patient and their loved ones who become their informal caregivers. In addition, their QOL can be negatively impacted by commonly utilized medications such as, corticosteroids and anti-epileptics, that often have behavioral side-effects. Additionally, the stress and emotional toll from the diagnosis can lead to feelings of sadness and interfere with everyday functioning.[1] In this systematic review, we describe the relevance of mental health disorders in patients with intra-axial brain tumors, the role for interventions that address both long-standing and new mental health conditions, and the importance of recognizing this aspect of patient care for neurosurgeons.

Methods

A literature search, guided by the Preferred Reporting Items for Systematic Reviews (PRISMA) (Figure 1), was performed of the following electronic databases through July 1st, 2022: PubMed, Web of Science, Embase, and PsycINFO. Search terms included MeSH terms and relevant word combinations (Online Appendix 1). Covidence systematic review software was used for duplicate detection and screening. Two reviewers conducted the title and abstract screening, full-text review, and extraction. Conflicts were handled through discussion or, if necessary, by consulting another author. Following full-text review, studies were categorized qualitatively according to the following subtopics: generic discussion, anxiety, depression, distress, stress, pharmacology, interventions, and caregivers.

Studies reported in English were included if the population included those with a Glioma diagnosis and the primary aim was the assessment of mental health related outcomes (i.e., depression, anxiety, mood, etc.). Exclusion criteria included animal studies, studies with a heterogenous patient population without specifically reporting outcomes for Glioma patients, and those that indirectly reported mental health related outcomes.

Results

A total of 5,208 studies were identified and uploaded to Covidence. After the removal of duplicates (n = 3167), 2,041 title and abstracts were screened. Of the 227 studies sought for full-text review, 220 full-texts were available for review. A total of 145 additional studies were excluded due to incorrect outcomes (n = 120), incorrect design (n = 20), ongoing study (n = 3), or the study was redacted (n = 2). Our literature search culminated in 75 articles which continued to extraction.

Domains of Emotional and Social Dysfunction in Brain Tumor Patients

Patients with diffuse gliomas may experience dysfunction in multiple mental health domains that neurosurgeons should be familiar with (see Table 1 for summary). In fact, although physical deficits dominate health-related QOL scores for patients early in their disease course, psychological, emotional, and cognitive dysfunction become the most common complaints reported by longer-term survivors.[2] As such, for patients with low-grade gliomas (LGGs) specifically, with longer life expectancies than high-grade gliomas (HGGs), it is even more imperative for neurosurgeons and neuro-oncologists to recognize the presence of mental health disorders (MHDs) that could negatively impact quality-of-life. In fact, a recent report utilized the IBM Watson Health MarketScan Database explored the incidence, prevalence, and risk factors of MHDs for LGG patients. Overall, 60.9% of patients had at least MHD before or after their diagnosis. In patients without a pre-existing MHD, nearly 17% received a first time diagnosis within one year of their LGG diagnosis.[3] Importantly for surgeons, they reported biopsy or surgical resection, compared to no surgical treatment, female gender, seizures, and age, between 34 and 45 years, as unadjusted risk factors for MHDs. Perhaps more applicable to the clinician, variability may exist according to treatment stage, tumor grade, and assessment timing. Studies have reported a greater prevalence of MHDs in HGG patients but only at 6 months following surgery.[4] In LGG patients, 3 months post-operative, MHDs were more prevalent in those receiving radiation compared to no therapy at all.[4] On the other hand, in a multivariate regression analysis of mood disturbances (MDs) in a cohort of 186 glioma patients, risk factors depended on whether they were new or recurrent patients. In the former, steroids and marital status were protective factors while anticonvulsant and steroid use in low-income patients with recurrent tumors were significant risk factors for MDs.[5] From these two studies alone, it is evident that there is variability in factors associated with MHDs overall, and a large interplay between socioeconomic and clinical factors likely exist.

Anxiety

Anxiety, which is already common amongst the general population, is nearly universal amongst patients scheduled for neurosurgery, with reported preoperative rates of anxiety and severe anxiety in over 80% and 55% of patients, respectively.[6,7] Given the potential risks of surgical intervention for diffuse glioma, this high prevalence is not particularly surprising.[8] However, many do not receive psychological or pharmacological treatment for their anxiety. For example, one study reported that while 48% of neuro-oncology patients had generalized anxiety disorder (GAD), only 31% were receiving medical treatment for their GAD, suggesting anxiety symptoms in this population may be undertreated.[9] Importantly, although there was no association with survival, preoperative anxiety was associated with longer hospitalizations, a higher need for information from health care providers, increased depressive symptoms, more physical disability, worse QOL [6], and post-operative pain[10]. As such, there remains a large potential value of treating these patients for anxiety, alone.[6] Other important risk factors for anxiety may be time and grade dependent. Studies reporting risk factors at certain time points are scarce and lack clinical applicability however, they implore an important take away such that, the risks associated with Temozolomide (TMZ) and steroid use is stable across all patient groups and time intervals, which may be more important for the clinician.[11] Although relatively few studies have investigated if awake craniotomies induce more anxiety than asleep procedures, two studies found no difference in pre-operative rates.[12,13] Following surgery, glioma patients frequently continue to experience fear and anxiety that contributes to an overall lower QOL and may warrant either behavioral counseling or medical management.[14,15]

Additionally, many brain tumor patients may suffer from ‘scanxiety,’ a phenomenon that occurs when patients undergo a routine scan and follow-up with their care team. Surveillance scans are a critical aspect of patient management but there is varied guidance on the utility of regular scans when juxtaposed with the potential for anxiety with each scan. This phenomenon is not unique to brain tumor patients, as over 80% of lung cancer patients have anxiety regarding scans.[16] While patient anxiety decreases with a stable scan result, there is a significant positive relationship between the scan-to-discussion interval and severity of symptoms and long-lasting distress. These findings underscore the need for long-term and consistent assessment and treatment for anxiety related symptoms.

Depression

The prevalence of depressive symptoms in primary brain tumor(PBT) patients during the course of their disease varies widely between studies, ranging from 5% to 44%[17–19], and is may be time-dependent (Figure 2)[20]. Given the relatively high rates of depression in glioma patients, some authors suggest screening one month after diagnosis to allow for a common and expected initial period of sadness.[21] Depression has been shown to predict worse survival outcomes in some studies even after controlling for functional status, tumor grade, and treatment[17,18,20,22]. While this relationship was true for both pre- and post-operative diagnosis, pre-operative depression appeared to be more significantly related to outcomes in a recent meta-analysis[22]. Data from the Glioma Outcomes Project found a significant gap between high-grade glioma patients’ self-reported rates and those recognized by physicians, with over 90% of patients reporting symptoms but only 15% of physician recognition. This study found an increase in depressive symptoms in the 6-month post-operative period and revealed an association with survival outcomes,[8,23] similar to other studies. Notably, depressive symptoms appear to be one of the most important predictors of a lower post-operative QOL[24,25] and are associated with higher rates of memory impairment, neurologic complications, and nonroutine discharges.[26,27]

In addition to recognizing the prevalence and effect of depression on outcomes in these patients, practitioners should be aware of some of the risk factors, as well. Intuitively, patients with anteriorly located[28] or higher-grade tumors[29] have increased levels of depression, which is similar to the increased anxiety seen in right-sided tumors[30]. Wellisch et al. reported that a frontal region tumor, sadness, lack of motivation, and a positive psychiatric family history were all risk factors for a Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis of major depressive disorder (MDD) on multivariate analysis.[31] Interestingly, compared to their counterparts, patients with frontal lobe tumors are more amenable to relief of these psychiatric symptoms following resection.[28] Regarding treatment, while increased rates of depression have been reported in patients undergoing a second operation[32], multivariate analyses have shown that only pre-operative functional status is associated with depression while controlling for employment status, coping strategies, insurance status, treatment stage, steroid use, surgical intervention, extra ventricular drain placement, number of admissions, number of operations, histology, recurrence, and structures involved.[33] Similar studies, in line with these analyses have widely reported the lack of association between treatment stage, timing of treatment, and various demographic datapoints, suggesting a largely global prevalence of depression in these patients.[13,34–36] On the other hand, a study evaluating hope found that patients with recurrent tumors experienced lower levels of interconnectedness and overall hope on the Herth Hope Index (HHI) as well as, significantly greater mood disturbances.[37]

Although depression is common in this population, treatment is inconsistent. Studies have reported that only 36% to 63% of patients, identified as having symptoms of depression, were prescribed an antidepressant or other psychotropic medication.[25] Similarly, in 788 patients evaluated in the Glioma Outcomes Project, only 6.7% received antidepressants in the perioperative period.[38] This possible under-prescription may be a result of poor physician recognition of patient-reported symptoms[39], or perhaps due to physicians ascribing these symptoms to tumor-related structural sequalae. Interestingly, type of and number of years in practice have a significant impact.[40] Accordingly, neurosurgeons at research institutions were less likely to prescribe antidepressants while, general and brain tumor neurosurgeons were more likely to do so.[40] In parallel with these prescribing rates, current trends for screening[41], despite resource availability, and referral to mental health services[42] are equally concerning. On a promising note, a recent nationwide matched LGG study reported increases in the use of antidepressants within recent years.[43] Nonetheless, given the significant impact of depression on survival and QOL, interventions to target these symptoms could provide substantial benefit.

Distress/Despair

Distress, defined by the National Comprehensive Cancer Network (NCCN) as “a multidetermined 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,” is extremely common and long-lasting[44] among PBT patients, with up to 74% reporting feelings of distress at some point in the course of their disease[45]. As suspected, very few of these patients go on to receive psychiatric care.[46] Distress and Despair are closely associated with depression and additional physical and emotional impairments. Fatigue, memory and concentration impairment, nervousness, and worry, are the most commonly reported symptoms contributing to feelings of distress.[47] PBT patients, in particular, have a high prevalence of death-related distress, especially death anxiety, which contributes significantly to overall distress.[14] Multiple studies have reported that newly diagnosed patients suffer from higher levels of distress when compared to patients greater than a year out from diagnosis, highlighting the importance of early recognition and intervention.[39,47] Not surprisingly, distress scores as measured on the NCCN-Distress Thermometer show a significant inverse relationship with QOL, including lower social and emotional well-being.[48] These findings, taken together, suggest that the early phase post-diagnosis is associated with a high risk of distress and possible depression for patients with a PBT. Consequently, early interventions to target MHDs could be beneficial in reducing levels of distress in such patients.

Stress

Greater than 60% of PBT patients, regardless of tumor grade, report elevated levels of stress, which is defined as the psychological or physical response that occurs when adapting to changing conditions.[49,50] While initial diagnosis can understandably invoke high levels of stress, they appear to persist in longer term survivors.[50,51] Of particular concern are the implications of stress severity, as rates of Post-Traumatic Stress Disorder (PTSD) have been reported to be as high as 16% in LGG patients only 3-months following surgery.[52] Overall however, PTSD is understudied in patients with PBTs[53] although, it is a well-documented phenomenon amongst other cancer patients. In one cross-sectional study of inpatients with both malignant and benign brain tumors, the former experienced higher levels of clinically relevant post-traumatic stress symptoms (PTSS), which could be explained by the provocation of fears of death due to the certainty of tumor progression and poor survival rates.[54] Additionally, stress from the diagnosis may also affect the caregiver. In one study of pediatric brain tumor survivors, roughly a third of both the survivors and their parents reported severe levels of PTSS.[55] In the patients, longer duration of hospitalization was associated with increased PTSS, while a higher number of tumor recurrences was associated with PTSS in their parents.[55] Future work studying the risk factors for the development of PTSD and the potential benefit of early incorporation of behavioral health counseling services in the management of brain tumor patients are urgently needed. While targeted treatments such as, Eye Movement Desensitizing Reprocessing (EMDR)[56] and reminiscence[57] therapy have shown promise as non-pharmacological options, additional evidence is needed regarding feasibility and safety.

Corticosteroids, Anti-Epileptics, and Behavioral Disturbances

Many of the medications used in the management of glioma patients can have behavioral side effects that are important for neurosurgeons to be aware of. For example, Corticosteroids, which are commonly prescribed to manage vasogenic cerebral edema, can induce symptoms of psychosis and insomnia.[58] As a result of an altered sleep-wake cycle and hyperarousal, corticosteroids may induce delirium and exacerbate other behavioral disorders.[51] One retrospective study of 340 recurrent glioma patients found the incidence of insomnia was 52% in patients taking corticosteroids, the severity of which appeared to correlate with dose.[59] As a result, interventions to mitigate the disturbance of sleep including sedative-hypnotics and other sleep aids including melatonin and reinforcement of sleep hygiene including avoidance of caffeine late in the day may help minimize these side effects and improve QOL while taking steroids. Neurosurgeons should be mindful of these side-effects and attempt to wean steroids as quickly as possible when appropriate.

Levetiracetam, which has become the first-line anti-epileptic medication (AED) for brain tumor patients, due to its limited interaction with other medications, has also been implicated in the development of behavioral side-effects[60], a risk that may be heightened in the presence of an anteriorly located tumor[61]. The most commonly reported side effects in retrospective studies include depression, fatigue, and irritability. Although the severity of these side-effects rarely warrant discontinuation[62], in rare instances, patients have developed psychosis or visual hallucinations indicating cessation[63]. Interestingly, in glioma patients, a recent meta-analysis found no association between AED use and concurrent depression, anxiety, or subjective cognitive impairment.[64] Nevertheless, neurosurgeons should be aware of these potential drugrelated side effects particularly in patients with a history of MHD and/or symptoms after starting this medication post-operatively.

Can Behavioral Health and Pharmacological Interventions Improve Mood and Patient Quality of Life?

Given the high prevalence of psychiatric, emotional, and neurobehavioral symptoms among patients with PBTs, coupled with their significant impact on QOL, there is a high level of interest in developing targeted interventions. Literature exploring this topic, particularly in PBT patients, is limited. A recent systematic review reported ten studies with promising results.[65] One randomized controlled trial reported that a home-based psychosocial intervention for brain tumor patients enhanced well-being and QOL.[66] In this study, patients who received 10 onehour weekly sessions on psychoeducation, cognitive rehabilitation, psychotherapy, and couple and family support had significantly lower levels of depression and higher levels of existential and functional well-being. These findings support a home-based intervention as a beneficial adjunct to their oncologic treatment regimen.[66] Another study of brain tumor patients undergoing post-operative radiotherapy found that for patients identified as being distressed at baseline, an intensive schedule of psychological therapy significantly improved their distress levels, mood, and overall QOL over time.[67] In a similar cohort, Eisenhut et al. studied the effects of different exercise programs in patients with HGGs and reported that endurance training was superior to strength training in improving psychiatric symptoms.[68] Interestingly, their active control group, which simply met twice weekly to share their experiences also outperformed the strength training group, which suggests that a connection with other cancer patients should be of priority, as well.

Given the success of these home-based interventions, there is considerable interest to develop interventions that can be delivered remotely to ease the burden of participation and improve access to care. This is especially relevant for brain tumor patients, whose neurological symptoms can make travelling to in-person services challenging. Studies have demonstrated that telephone-administered psychotherapy is effective in reducing depressive symptoms in non-tumor patients[69], and one small-scale study aimed at investigating the feasibility and utility of telephone-based psychotherapy for patients with a brain tumor also demonstrated promising results. The study enrolled four patients who received 10 telephone-based therapy sessions followed by a booster session four weeks after completing the initial sessions. Sessions covered topics such as mindfulness and relaxation techniques, couple and family support, and existential and end-of-life discussions. Although this study was small, all four participants reported improved QOL post-treatment as well as a strong therapeutic alliance with their providers. Compliance to behavioral care is often poor but all four participants successfully completed the telephone-based therapy.[70] Taken together, these studies suggest that behavioral health interventions, including those delivered remotely via telephone or Telehealth in the post COVID-19 era, can be effective in improving QOL for patients with a PBT.

Pharmacological management of anxiety and depression has been surprisingly understudied in cancer patients broadly and certainly in the glioma patients. In fact, there is no randomized trial investigating antidepressants in glioma patients and Cochrane reviews have reported no highquality studies[71]. Retrospective studies suggest that selective serotonin reuptake inhibitors (SSRIs) are safe to use and do not appear to negatively influence complications or survival[72] and, although widely used in the treatment of depression and anxiety, they do not appear to improve overall survival in glioblastoma multiforme (GBM) patients[73]. Nevertheless, in a recent meta-analysis investigating the treatment of depression in cancer patients, older than 65 years of age, of various etiologies, there was a general trend towards improved behavioral health and mood in patients treated with SSRIs and SNRIs.[74] On the other hand, in patients with advanced cancer and a high-risk of depression (The Hospital Anxiety/Depression Scale [HADS] score ≥ 15), Pu et al. reported rates of mood improvement exceeding 50% within less than 3 weeks as well as, improved treatment tolerance and associated side effects.[75] Taken together, these reports may suggest not only that these drugs may be of use in brain tumor patients but also, that future studies should tailor their inclusion criteria towards those with clinically significant symptoms for optimal applicability. Although outside the scope of this review, there is also some preclinical evidence that SSRIs have a direct anti-cancer effect by inhibiting a lipid metabolism enzyme, SMPD1, which has motivated a large investment by the National Brain Tumor Society (NBTS) to explore fluoxetine (Prozac) treatment for GBM[76].

Another active area of interest for the treatment of psychiatric and MHDs in brain tumor patients is the potential role of medicinal cannabinoids.[77,78] Although preclinical animal studies are promising, and there is evidence that cannabinoids can improve cancer-related pain and stimulate appetite, patients in early-phase trials have reported some side-effects associated with their use. [79] Additional studies are ongoing that evaluate whether medicinal cannabis, prescribed in conjunction with cognitive behavioral therapy and other psychopharmacological drugs, can aid in treating both MHDs and treatment-related insomnia in cancer patients.

Mental Health Struggles for Caregivers

A brain tumor diagnosis impacts more than just the patient’s life. Due to the nature of these tumors and the intensive treatments they require, patients frequently rely on loved ones and friends to serve as caregivers. The role is associated with complex feelings that can range from rewarding to stressful and mentally exhausting.[80,81] Caregivers even report feeling a sense of total responsibility for all aspects of patient care. As the patient is their primary focus, caregivers can find it difficult to obtain emotional support for themselves and face a lack of education and information on how to care for the patient leading to further feelings of anxiety.[81] And although caregivers face many challenges, ranging from the physical demands of caring for the patient to the financial burden of taking time away from their own employment, they often describe the neuropsychiatric symptoms the patient exhibits as the most challenging to deal with and as taking the largest toll on their own mental health.[81,82] Greater patient reported neuropsychiatric symptoms has been associated with a higher level of caregiver depression, whereas patient tumor grade, cognitive status and independent activities of daily living (IADL) status do not predict caregiver distress[80,82]. Some additional risk factors for distress in care givers of brain tumor patients are female gender and rural location.[83] Not surprisingly, caregivers of patients with brain tumors experience a decrease in QOL and higher levels of anxiety and depression symptoms compared to the general population[80]. Moreover, these symptoms are long lasting with studies reporting persistence over a 9-month period.[84] Longitudinal studies have demonstrated that these symptoms may necessitate treatment, as well. Compared to their counterparts, partners of glioma patients had a more than 4-fold risk of receiving a psychiatric prescription within the first year of diagnosis and that, within the first two years, nearly 30% of them had a first-time prescription.[85]

Incredibly, when surveyed, caregivers report a higher number of unmet care needs than patients. Two of the most reported unmet needs for caregivers were assistance in reducing stress in the life of patients with a brain tumor and help in managing difficult aspects in the behavior of these patients.[86] Given these findings, there is a need to provide psychological support not only to the patient but to the caregiver, as well. In fact, a combined treatment program involving dyadic yoga was not only feasible, but also effective at improving psychiatric symptoms in both the caregivers and the patients, who also experienced decreased cancersymptom severity.[87] Therefore, while a patient’s care team may struggle to provide medical treatment to their respective caregivers, alternative options that may be benefit both are needed.

Conclusion

Between half to three quarters of brain tumor patients suffer from a behavioral health disorder as a consequence of their diagnosis and corresponding treatment. Neurosurgeons should be aware of the impact a glioma diagnosis has on a patient’s mental well-being. With limited access to behavioral resources, providing services at home to the patient and caregiver through telehealth may be an important intervention in the management of brain tumor patients. By recognizing the stress and emotional toll patients experience as a part of their treatment journey following a glioma diagnosis, glioma surgeons can start the process of addressing these symptoms early in the patient’s treatment course. Principally, neurosurgeons must understand their role in the overall patient experience and be prepared to have an open discussion about these mental health conditions with patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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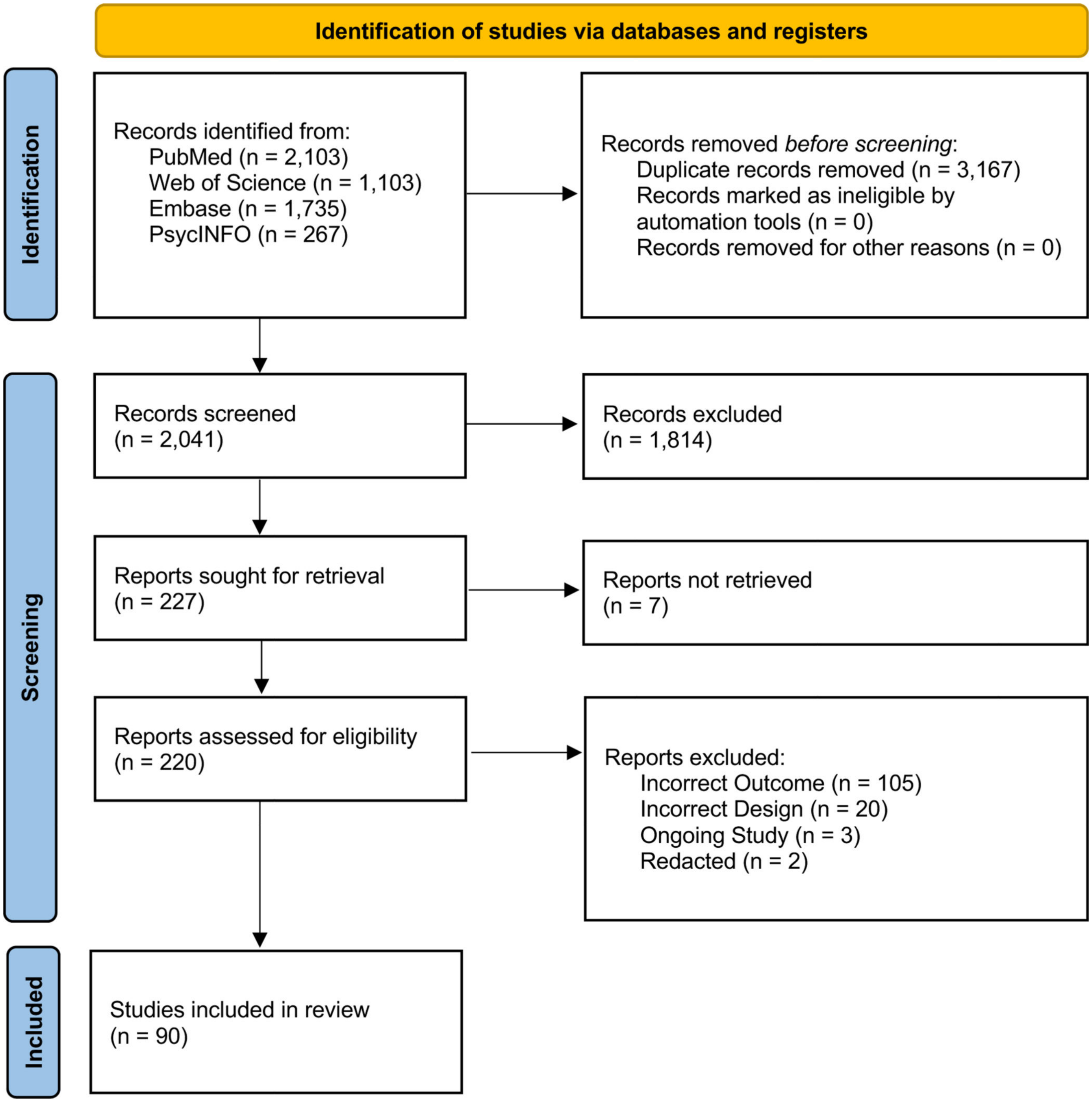

Figure 1.

Preferred Reporting Items for Systematic Reviews (PRISMA) Flow Diagram of Literature Search Performed.

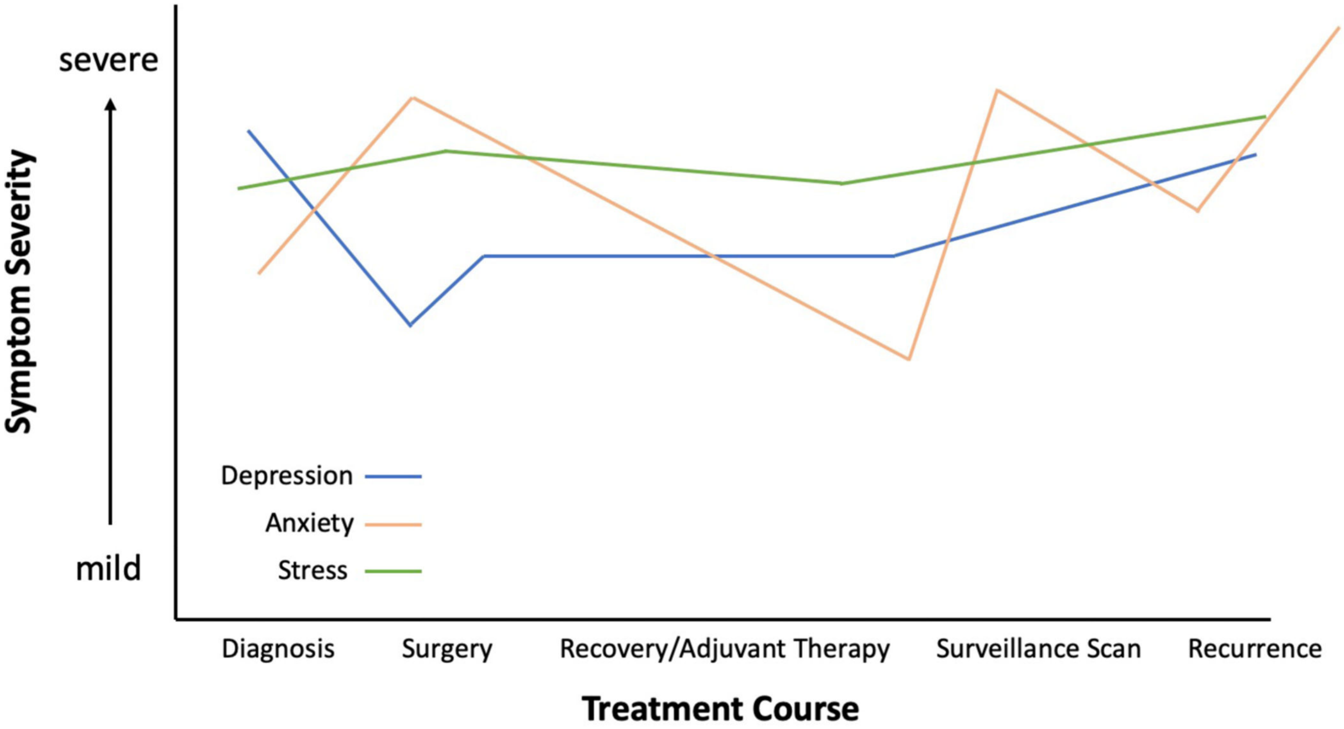

Figure 2. Schematic Demonstrating Variability in Symptom Severity Over Time in Brain Tumor Patients.

Certain times during the patient's treatment course, such as at the time of diagnosis, surgery, surveillance scanning, or tumor recurrence, maybe associated with elevated levels of anxiety or depression. Stress-levels have been reported to remain elevated throughout a patient's entire time with a disease.

Table 1.
Summary of Common Behavioral Health Disorders in Brain Tumor Patients.

Although there is a wide range of reported incidence for mental health disorders in glioma patients, and the evidence supporting treatment of these conditions in this patient population is limited, the table below highlights the impact these conditions have on patients and risk factors for their development.

Behavioral Health Disorder	Incidence	Risk Factors	Impact on Patient Care	Treatment Options	References
Anxiety	35–50%	• Prior anxiety disorder • Female gender • Prior psychiatric disorder • Lower WHO grade tumor	• Longer hospitalization • More health care utilization • Increased depressive symptoms • Worse QOL	• Pharmacotherapy • Psychotherapy	73, 74
Depression	15–27%	• Female gender • Marital status • Comorbid medical conditions • Higher WHO grade tumor	• Shorter survival • Impaired QOL • Memory impairment • Neurologic complications • Non-routine discharge	• Antidepressants • Psychotherapy	9, 20, 75
Distress/ Despair	74%	• Higher WHO grade tumor	• Impaired QOL	• Psychotherapy	37
Stress/PTSD	>60%	• Longer hospitalizations • Complications	• Development of post traumatic disorder	• Education on stress reduction techniques • Psychotherapy	45

Abbreviations: WHO, World Health Organization; WOL, Quality of Life

Table 1.

Anxiety [88,99]

Depression [9,21,90]

Distress/Despair [45]

Stress/PTSD [55]