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The investigation of the impact of Bipolar Manic Depression (BMD) on the progression of diseases in patients with glioblastoma

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Abstract

Bipolar manic depression (BMD) affects 0.8–1.2% of the global population and is associated with a lifelong burden of mood instability, pro-inflammatory immune profiles, and dysregulated stress-hormone axes. Glioblastoma (GBM) remains the most lethal primary brain tumour, with a median survival of 12–15 months despite maximal therapy. Emerging clinical observations and preclinical models suggest that a pre-existing or tumour-induced BMD may accelerate GBM progression. This review synthesises evidence from clinical, epidemiological, genetic, and mechanistic studies to examine whether BMD acts as a disease accelerator in GBM. We analyse three intersecting pathways: (i) neuroendocrine – chronic HPA-axis overactivity and glucocorticoid resistance, which impair anti-tumour immunity; (ii) immuno-inflammatory – elevated IL-6, TNF-α, and CCL3 suppression that fosters an immunosuppressive microenvironment; and (iii) genetic – shared susceptibility loci (e.g., *PDE4B*, *ANKRD55*) that simultaneously increase bipolar risk and predict worse glioma survival. Behavioural factors, including treatment non-adherence and delayed diagnosis, further compound the clinical picture. The review also critically examines the dual role of mood stabilisers and antidepressants, which may exert conflicting direct anti-tumour effects (e.g., lithium enhances temozolomide cytotoxicity *in vitro* and in animal models) while risking adverse drug–drug interactions and mood destabilisation. We conclude that bipolar manic depression is a plausible, multi-factorial accelerator of glioblastoma progression. Future prospective cohort studies and integrated psycho-oncology trials are urgently needed to establish causality and to develop personalised monitoring and treatment strategies for this exceptionally vulnerable patient population.

Keywords: Bipolar disorder, Glioblastoma, Disease progression, Neuro inflammation; HPA axis; Cancer survival; Psychiatric comorbidity; Drug repurposing

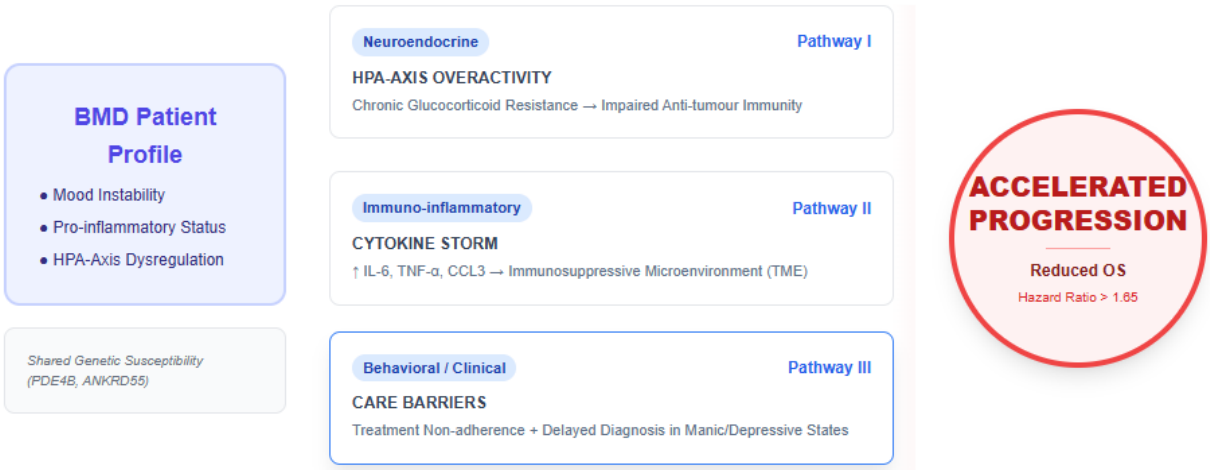
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Graphical abstract



Introduction

Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumour, with a dismal median overall survival of only 12–15 months even after maximal safe resection, radiotherapy, and temozolomide chemotherapy (1). In parallel, bipolar manic depression (BMD) affects approximately 40 million people worldwide, characterised by recurrent episodes of mania or hypomania and major depression (2, 3). The intersection of these two severe conditions has only recently begun to attract systematic research attention. Clinically, patients with severe mental illness, including bipolar disorder, confront an increased risk of cancer-related mortality, largely due to delayed diagnosis, poor adherence to oncology treatments, and complex biological interactions that remain poorly understood (4). The present review asks a focused question: does pre-existing or tumour-induced bipolar manic depression act as a disease accelerator in GBM? To answer this question, we examine evidence from clinical cohort studies, genetic linkage analyses, immune-endocrine investigations, and preclinical models. We highlight three major mechanistic pathways: (1) chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis with glucocorticoid resistance, (2) a systemic low-grade inflammatory state that fosters an immunosuppressive tumour microenvironment, and (3) shared genetic variants that predispose to both mood dysregulation and aggressive glioma behaviour. Behavioural factors such as treatment non-adherence and delayed oncological care are equally critical in shaping outcomes.

2. The clinical intersection: prevalence and diagnostic challenges

Estimates of concurrent depression in GBM range from 14% to nearly 50%, depending on the assessment tool and timing of evaluation. Among glioma patients, the prevalence of any mood disorder is strikingly high, and the severity of depressive symptoms correlates with lower quality of life and, in some studies, shorter survival (5). Bipolar disorder, although less common than unipolar depression in this population, poses distinct challenges: the alternation between manic and depressive states may be misinterpreted as personality change or tumour-related frontal lobe syndrome, leading to underdiagnosis. Moreover, patients with

bipolar disorder face significant barriers along the entire cancer care continuum. They are less likely to undergo routine cancer screening, more likely to present with advanced-stage disease, and frequently experience treatment interruptions or premature discontinuation of oncological therapy. The combination of a high-grade glioma and a pre-existing bipolar diagnosis, therefore, represents a "double burden" characterised by complex drug–drug interactions, heightened psychosocial distress, and vulnerable clinical trajectories.

3. Mechanistic pathways linking BMD to GBM acceleration

To understand whether and how bipolar disorder might accelerate glioblastoma progression, we must dissect the biological pathways that are pathologically activated in both conditions. Three such pathways have received the most empirical support: neuroendocrine dysregulation, systemic and local neuro-inflammation, and shared genetic architecture (6).

3.1. Neuroendocrine pathways: the HPA axis as a common driver

Bipolar disorder is associated with profound dysregulation of the HPA axis. During manic or mixed episodes, patients often exhibit elevated plasma cortisol and adrenocorticotropic hormone (ACTH) levels, whereas in the depressive phase, the axis may be relatively hypoactive or display blunted feedback sensitivity. Long-standing HPA activation leads to a state of glucocorticoid resistance, wherein immune cells become less sensitive to the anti-inflammatory signals of cortisol (7). In the context of glioblastoma, chronic stress and elevated glucocorticoids promote tumour growth through several mechanisms. Animal models of chronic stress show that increased corticosterone accelerates glioma progression, reduces recruitment of CD8+ T cells and M1-polarised tumour-associated macrophages (TAMs), and suppresses the secretion of the chemokine CCL3, a critical recruiter of anti-tumour immune cells (8). The net effect is an immunosuppressive tumour microenvironment (TME) that facilitates GBM invasion and resistance to therapy. Furthermore, the reciprocal loop between tumour-induced inflammation and HPA activation illustrated in classic stress–cancer models creates a vicious cycle: the glioma itself releases IL-1β and IL-6, which act on the brain to perpetuate HPA dysregulation, which in turn further impairs immune surveillance (9). Thus, for the patient with both bipolar disorder and GBM, the pre-existing HPA dysfunction is likely to be amplified by the tumour, leading to a supra-additive immunosuppressive state that accelerates disease progression.

Table 1. Frequency of common mental disorders in patients with high-grade glioma.

Diagnosis	Proportion (%)	95% Confidence Interval
Post-traumatic stress disorder	10%	8%–13%
Persistent depressive disorder	8%	6%–10%
Generalized anxiety disorder	7%	5%–9%
Major depressive episode	6%	4%–8%
Adjustment disorder	4%	3%–6%
Alcohol use disorder	1%	0%–2%
Bipolar disorder	1%	0%–2%
Total (≥1 disorder)	31%	28%–35%

3.2. Immuno-inflammatory pathways: from systemic cytokines to the TME

A low-grade, chronic inflammatory state is a hallmark of bipolar disorder, particularly during depressive and manic episodes. Meta-analyses have consistently reported elevated circulating levels of interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and C-reactive protein (CRP) in bipolar patients, even when they are euthymic on medication. This pro-inflammatory milieu is thought to arise from a combination of genetic predisposition, oxidative stress, and dysfunction of the compensatory immune response system. Glioblastoma, in turn, is notorious for its highly immunosuppressive TME. Myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarised TAMs dominate, while cytotoxic CD8+ T cells are scarce and dysfunctional (8). Recent evidence demonstrates that chronic psychological stress—comparable in magnitude to that experienced by bipolar patients—further skews the TME toward an immuno-cold state by inhibiting CCL3-dependent recruitment of M1-like TAMs and CD8+ T cells. Moreover, administration of CCL3 into the tumour bed was able to reverse this stress-induced progression in preclinical models, highlighting the mechanistic importance of chemokine signalling (10, 11). Direct evidence linking bipolar-type inflammation to GBM progression is still limited, but extrapolation from studies on major depressive disorder (MDD) in glioma patients is instructive. Zghaibeh et al. (2024) reported that GBM patients presenting with depression as their first symptom have a significantly worse outcome, particularly in the RTK2 molecular subclass, and that antidepressant treatment did not uniformly improve survival (12). Although that study focused on unipolar depression, the underlying inflammatory biology (elevated IL-6, dysregulated serotonin signalling) overlaps substantially with that of bipolar depression. Hence, it is plausible that the pro-inflammatory immune profile of BMD directly accelerates GBM by promoting angiogenesis, suppressing anti-tumour immunity, and enhancing tumour cell invasion.

3.3. Shared genetic architecture

Recent large-scale genetic analyses have begun to unravel pleiotropic loci that contribute both to mental disorders and to poor cancer prognosis. In a systematic bioinformatic study, 239 genes associated with psychiatric diseases were examined for their impact on cancer survival; 146 high-expression and 157 low-expression genes correlated with unfavourable prognosis across multiple cancer types, with particularly strong effects in low-grade glioma (3, 13). Among the overlapping genes were *PDE4B* (phosphodiesterase 4B), *ANKRD55*, and *RHEBL1*, all of which are implicated in immune signalling and neuronal plasticity. In bipolar disorder, *PDE4B* variants have been linked to mood regulation and response to antidepressants; in glioma, high *PDE4B* expression is associated with shorter patient survival, possibly through its role in modulating cAMP signalling and tumour cell proliferation. Such pleiotropic effects suggest that certain individuals are biologically predisposed both to the development of bipolar disorder and to a more aggressive glioma phenotype. This does not imply causality in either direction but does indicate shared molecular pathways that could be therapeutically targeted. For instance, drugs that modulate PDE4 activity (e.g., rolipram) are being investigated in both psychiatric and oncological settings, raising the possibility of a single agent addressing both the mood disorder and the tumour.

4. The double-edged sword: psychiatric medications in GBM patients

The pharmacological management of bipolar disorder in the context of glioblastoma is exceptionally challenging because many first-line mood stabilisers and antipsychotics have intrinsic effects on glioma biology—some beneficial, others potentially harmful.

4.1. Mood stabilisers

Lithium is the most extensively studied mood stabiliser in oncology. In human glioblastoma cell lines, low therapeutic concentrations (0.5–2 mmol/L) do not cause direct cytotoxicity but increase the expression of p21WAF/Cip1 and survivin, two proteins that can promote cell survival and contribute to treatment resistance (14, 15). At higher concentrations (20 mmol/L), lithium becomes cytostatic and arrests cells at the G2/M checkpoint. Encouragingly, combination of low-dose lithium with temozolomide (TMZ) has been shown to potentiate TMZ-induced cell death in TP53 wild-type GBM cells *in vitro* and to prolong survival in mouse xenografts through the NFAT1/FasL signalling pathway (16). This suggests that, when carefully monitored, lithium might actually enhance the efficacy of standard chemotherapy in a subset of patients.

Valproic acid (VPA), another common mood stabiliser, acts as a histone deacetylase (HDAC) inhibitor and has demonstrated anti-GBM activity in multiple preclinical studies, suppressing cell proliferation, inducing apoptosis, and sensitising tumour cells to TMZ and radiation (1, 17). However, VPA can interact with many antiepileptic and chemotherapeutic agents, and prolonged use carries risks of hepatotoxicity and thrombocytopenia, which are already common concerns in GBM patients receiving standard treatment.

4.2. Antipsychotics and antidepressants

Atypical antipsychotics such as aripiprazole and olanzapine are increasingly used as adjunctive therapy in bipolar disorder and have recently been found to possess direct anti-glioblastoma properties, including induction of autophagy and inhibition of cell migration. Conversely, selective serotonin reuptake inhibitors (SSRIs) have produced mixed results: some studies report reduced survival in GBM patients prescribed SSRIs, possibly due to effects on serotonin signalling that influence tumour cell proliferation, while others find no association or even a benefit (18). A meta-analysis is precluded by high heterogeneity among studies, indicating that the effect likely depends on molecular GBM subtype, concomitant medications, and the timing of exposure relative to diagnosis.

4.3. Clinical pharmacology considerations

The blood–brain barrier (BBB) is a major obstacle for many standard chemotherapeutics, but most psychotropic drugs cross the BBB efficiently, a property that underlies both their central effects and their potential for direct action on residual tumour cells (19, 20). However, this same property raises the risk of significant drug–drug interactions. For example, enzyme-inducing medications like carbamazepine (used as a mood stabiliser) can accelerate the metabolism of TMZ, reducing its therapeutic efficacy. Clinicians must therefore carefully evaluate the entire pharmacopeia when managing a patient with both bipolar disorder and GBM, avoiding harmful combinations while possibly exploiting synergistic ones (21, 22).

5. Behavioural and psychosocial mediators

Beyond direct biological mechanisms, bipolar disorder influences GBM progression through behavioural and social pathways. Patients with active bipolar illness frequently experience poor adherence to complex cancer treatment protocols, miss scheduled appointments, and have limited ability to report new neurological symptoms adequately (23, 24). Furthermore, bipolar disorder is associated with higher rates of substance use (especially alcohol and nicotine), both of which are independent risk factors for reduced cancer survival. The social determinants of health cannot be ignored. Many individuals with severe mental illness have reduced socioeconomic resources, unstable housing, and limited access to specialist oncology care. Stigma from healthcare providers may lead to delayed referrals and less aggressive treatment of the cancer. In the specific case of glioblastoma, where time from diagnosis to surgery and adjuvant therapy is measured in days, any delay can translate directly into a shorter overall survival.

6. Knowledge gaps and future research directions

Knowledge Gaps and Future Research Directions

This study leaves several critical gaps that need to be addressed by future research. Almost all of the available evidence comes from retrospective chart reviews or cross-sectional analyses. A large, prospective, multicenter cohort study including systematic psychiatric assessment at the time of GBM diagnosis and repeated follow-ups is necessary to establish the temporal order and disentangle the effects of preexisting BMD from tumor-induced mood symptoms. Also, while animal models have identified possible pathways (HPA dysregulation, CCL3 suppression, NFAT1/FasL signaling), human tissue studies linking mood status, circulating inflammatory markers, and tumor molecular features are scarce. Biobanking of blood and tumor samples with parallel detailed psychiatric phenotyping should become standard. In this regard, randomized controlled trials of psychiatric treatment algorithms in GBM patients with concomitant BMD are urgently needed. Do mood stabilizers that also have antitumor properties (e.g., lithium, VPA) confer a survival advantage over mood stabilizers that do not? Does coordinated psychiatric-oncology care improve adherence to treatment, mood control, and ultimately survival? Furthermore, given that many psychotropic drugs affect glioma biology in a molecular subtype-dependent manner (as observed with lithium in TP53 wild-type tumors), future strategies should integrate tumor genomic profiling with psychiatric drug selection. Machine learning models incorporating genomic and clinical data may help predict which bipolar GBM patients will benefit from which drug combination. Studies evaluating the effectiveness of integrated dual disorder clinics (neuronocology + psychiatry) on outcomes such as treatment completion and overall survival are also needed. Such clinics could serve as natural laboratories to test the hypotheses raised in this review.

7. Clinical implications and conclusions

Despite the current limitations in the evidence base, several actionable clinical recommendations can be derived from the available data. These recommendations are intended to reduce the presumed disease-precipitating effects of bipolar disorder in patients with glioblastoma.

First, a structured psychiatric assessment should be performed on each patient at the time of glioblastoma diagnosis and repeated at predetermined intervals throughout the course of treatment. Particular clinical

attention should be paid to bipolar spectrum symptoms—including episodes of elevated or irritable mood, psychomotor agitation, racing thoughts, decreased need for sleep, and impulsive behavior—as these symptoms may be mistakenly attributed to tumor-related frontal lobe dysfunction rather than to a primary mood disorder. Early identification of bipolar features is critical to avoid overdiagnosis and to allow for timely psychiatric intervention. Also, the choice of mood stabilizers or antipsychotics in this population with comorbid conditions should not be guided solely by psychiatric efficacy. Clinicians should also consider the known interactions of each drug with glioma biology and with temozolomide (TMZ), the standard chemotherapeutic agent. Enzyme-inducing psychotropic drugs (eg, carbamazepine), which may accelerate TMZ metabolism and reduce its antineoplastic effect, should be avoided whenever possible. Conversely, emerging preclinical evidence supports the potential synergy of lithium and valproic acid (VPA) with TMZ and suggests that these drugs may offer dual benefits—mood stabilization and increased sensitivity to chemotherapy—in appropriately selected patients (eg, those with TP53 wild-type tumors). In addition, optimal management of glioblastoma patients with co-morbid bipolar disorder requires a team approach that includes a neurologist, a psychiatrist, a clinical pharmacist, and a social worker. Such integration is essential to address the relevant medical, psychiatric, pharmacological, and psychosocial determinants of outcome. Dispersed care has been repeatedly identified as a risk factor for poor adherence, delayed treatment, and reduced survival in this vulnerable population. Therefore, the establishment of dedicated dual disorder clinics or formal communication models between neuro-oncology and psychiatry should be considered a quality improvement priority.In conclusion, this review has marshalled evidence from multiple levels of analysis—clinical, genetic, immunological, and preclinical to argue that bipolar manic depression acts as a significant disease accelerator in glioblastoma. The mechanisms are multifactorial, encompassing chronic HPA-axis overactivity, systemic and local immunosuppression, shared genetic susceptibility, and adverse behavioural patterns. However, the same pathways that accelerate progression may also offer therapeutic opportunities, as several mood-stabilising medications possess intrinsic anti-glioma activity and could be rationally repurposed. There is an urgent need for dedicated prospective studies integrating psychiatric and neuro-oncological phenotyping to move the field from circumstantial associations to causative mechanisms and, ultimately, to improved survival and quality of life for this exceptionally vulnerable group of patients.

Author contribution

S was involved in the investigation, methodology, and writing the primary draft of the manuscript. and also she was involved in different parts of this manuscript**.** **AAS** was involved in all sections of the manuscript, including writing the primary draft, supervision, reviewing, editing, conceptualization, and all other sections. All the authors studied the final edited version of the manuscript and confirmed this.

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