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REPURPOSING ESZOPICLONE A NON-BENZODIAZEPINE GABA-A MODULATOR SYNERGIZING WITH PD-1/PD-L1 IMMUNOTHERAPY TO REPROGRAM THE GLIOMA MICROENVIRONMENT – A PERSPECTIVE

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Abstract

Background. Gliomas especially glioblastoma multiforme (GBM) are among the most aggressive primary brain tumors, characterized by rapid proliferation, metabolic plasticity, and a profoundly immunosuppressive tumor microenvironment (TME). Dysregulation of chloride homeostasis, glutamatergic excitotoxicity, and aberrant GABAergic signaling have recently emerged as mechanistic contributors to glioma progression and immune evasion. **Purpose of the Study**: to propose eszopiclone, a non-benzodiazepine GABA-A receptor modulator, as a repurposed adjunct capable of reprogramming glioma metabolism and enhancing responsiveness to PD-1/PD-L1 immunotherapy. **Material and Methods.** A narrative perspective review was conducted based on literature retrieved from PubMed, Scopus, Web of Science, and Science Direct. A total of 312 sources were screened; 154 articles published between 2005 and 2024 were selected for detailed analysis based on relevance to GABAergic signaling, glioma metabolism, macrophage polarization, chloride channel regulation, and immune checkpoint interactions. **Results.** Eszopiclone-mediated GABA-A activation restores chloride influx and suppresses depolarization-driven Ca^{2+}/NFAT and PI3K/AKT/mTOR signaling, resulting in G1/S arrest and enhanced apoptotic susceptibility. Within the TME, GABA-A signaling reduces NF-κB and STAT3 phosphorylation and shifts microglia/glioma-associated macrophages from protumoral M2 (CD206+/IL-10+) to antitumoral M1 (iNOS+/IFN-γ+) polarization, facilitating improved antigen presentation and T-cell infiltration. Evidence from GABAergic models in melanoma and breast cancer suggests that modulation of this axis may downregulate PD-L1 expression and potentiate responsiveness to PD-1/PD-L1 inhibitors, supporting a mechanistic rationale for synergy in glioma. **Conclusion.** Repurposing eszopiclone introduces a novel neuro-immuno-oncologic therapeutic concept bridging neuropharmacology and checkpoint immunotherapy. Owing to its blood-brain-barrier penetration, clinical safety, and receptor selectivity, eszopiclone represents a feasible candidate for combination strategies with PD-1/PD-L1 blockade. Further preclinical models, retrospective analyses, and early-phase trials are warranted to validate its immunomodulatory potential and define its translational relevance in glioma therapy.

Key words: Eszopiclone, GABA-A receptor, Glioblastoma, Tumor Microenvironment, PD-1/PD-L1 inhibitors, PI3K/AKT pathway, Immunotherapy synergy, Neuro-onco-immunology.

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ПЕРЕПРОФИЛИРОВАНИЕ ЭЗОПИКЛОНА, НЕБЕНЗОДИАЗЕПИНОВОГО МОДУЛЯТОРА ГАМК-А, В СОЧЕТАНИИ С ИММУНОТЕРАПИЕЙ PD-1/PD-L1 ДЛЯ ПЕРЕПРОГРАММИРОВАНИЯ МИКРООКРУЖЕНИЯ ГЛИОМЫ – ПЕРСПЕКТИВА

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Аннотация

Актуальность. Глиома, особенно мультиформная глиобластома, является наиболее агрессивной формой первичной опухоли головного мозга, характеризующейся быстрой пролиферацией, метаболической пластичностью и выраженным иммунодепрессивным микроокружением опухоли (МОО). Недавно было установлено, что нарушение гомеостаза хлорида, глутаматергическая эксайтотоксичность и аномальная ГАМК-ергическая сигнализация являются механистическими факторами, способствующими прогрессированию глиомы и уклонению от иммунного ответа. **Цель исследования** – представить эзопиклон, небензодиазепиновый модулятор рецепторов ГАМК-А, в качестве вспомогательного средства, способного перепрограммировать метаболизм глиомы и повышать чувствительность к иммунотерапии PD-1/PD-L1. **Материал и методы.** Проведен обзор литературы, полученной из баз данных PubMed, Scopus, Web of Science и Science Direct. Всего было проанализировано 312 источников; для детального анализа отобрано 154 статьи, опубликованные в период с 2005 по 2024 г., основанные на изучении АМК-ергической системы, метаболизма глиомы, поляризации макрофагов, регуляции хлоридных каналов и взаимодействия иммунных контрольных точек. **Результаты.** Активация ГАМК-А под действием эзопиклона восстанавливает приток хлорида и подавляет вызванные деполяризацией сигналы Ca^{2+}/NFAT и PI3K/AKT/mTOR, что приводит к остановке клеточного цикла в фазе G1/S и повышению восприимчивости к апоптозу. В микроокружении опухоли сигнализация ГАМК-А снижает фосфорилирование NF-κB и STAT3 и сдвигает поляризацию микроглии/глиомоассоциированных макрофагов от проопухолевой M2 (CD206+/IL-10+) к противоопухолевой M1 (iNOS+/IFN-γ+), способствуя улучшению презентации антигенов и инфильтрации Т-клеток. Данные, полученные от исследований на ГАМК-эргических моделях меланомы и рака молочной железы, свидетельствуют о том, что модуляция этой оси может снижать экспрессию PD-L1 и усиливать чувствительность к ингибиторам PD-1/PD-L1, что указывает на синергетический эффект при глиоме. **Заключение.** Перепрофилирование эзопиклона представляет собой новую нейроиммуноонкологическую терапевтическую концепцию, объединяющую нейрофармакологию и иммунотерапию контрольных точек. Благодаря способности проникать через гематоэнцефалический барьер, клинической безопасности и селективности к рецепторам, эзопиклон является перспективным кандидатом для комбинированных стратегий с блокадой PD-1/PD-L1. Для подтверждения его иммуномодулирующего потенциала и определения его трансляционной значимости в терапии глиом необходимы дальнейшие доклинические исследования, ретроспективный анализ и исследования ранних фаз.

Ключевые слова: эзопиклон, рецептор GABA-A, глиобластома, микроокружение опухоли, ингибиторы PD-1/PD-L1, сигнальный путь PI3K/AKT, синергия иммунотерапии, нейроонкоиммунология.

Introduction

Gliomas, a heterogeneous group of primary central nervous system (CNS) malignancies, pose profound therapeutic challenges in neuro-oncology, with glioblastoma multiforme (GBM) exemplifying the most aggressive and refractory subtype. Despite multimodal interventions encompassing maximal safe surgical resection, fractionated radiotherapy, and alkylating chemotherapy with temozolomide, the median overall survival for patients with GBM remains starkly limited, typically under 15 months as established in landmark phase III trials [1]. A principal impediment to efficacious pharmacotherapy is the blood-brain barrier (BBB), an endothelial tight-junction complex that impedes the intracranial delivery of most systemically administered agents, thereby underscoring the imperative for BBB-penetrant innovations to augment therapeutic indices and mitigate recurrence [2]. Con-

temporary genomic and transcriptomic interrogations have illuminated a central perturbation in GABAergic neurotransmission within glioma pathobiology [3]. As the archetypal inhibitory neurotransmitter in the mammalian CNS, γ-aminobutyric acid (GABA) exerts its canonical effects through ionotropic GABA-A receptors pentameric ligand-gated chloride channels comprising diverse subunits (e.g., α1-6, β1-3, γ1-3, δ, ε, θ, π, ρ1-3) which, upon agonist binding, orchestrate chloride (Cl^-) influx, membrane hyperpolarization, and dampening of neuronal excitability. In gliomagenesis, neoplastic glia co-opt diminished GABA-A signaling to engender a pro-oncogenic milieu: downregulation of key subunits such as GABRB3 and ρ2 curtails Cl^- conductance, fostering intracellular chloride accumulation via dysregulated transporters (e.g., NKCC1 upregulation and KCC2 silencing), which sustains a depolarized membrane potential conducive to calcium-dependent mitogenic cascades and evasion of inhibitory checkpoints [3, 4]. This ionic disequilibrium amplifies glutamatergic excitotoxicity, wherein tumor-derived glutamate engages AMPA and NMDA receptors to propagate autocrine/paracrine loops activating PI3K/AKT and MAPK/ERK pathways, thereby accelerating proliferation, migration, and neoangiogenesis a dysregulated axis mirrored in extraneural solid tumors [4]. Transcending its neurophysiological remit, GABA emerges as a multifaceted modulator of oncogenesis, interfacing with tumor-intrinsic growth regulators (e.g., suppressing cyclin D1/CDK4 via hyperpolarization-induced G1/S arrest) and the immunosuppressive tumor microenvironment (TME) by attenuating NF-κB-driven cytokine elaboration (e.g., IL-6, TNF-α) in glioma-associated myeloid cells [4]. This dualistic prowess positions GABAergic augmentation as a high-yield oncogenic vulnerability. Preclinical paradigms substantiate this paradigm, wherein GABA receptor agonists like topiramate (a dual GABA-A enhancer and AMPA/kainate antagonist) and baclofen (a GABA-B agonist) attenuate glioma xenograft progression by reinstating chloride homeostasis, blunting ERK phosphorylation, and curtailing vascular endothelial growth factor (VEGF) secretion [5, 6]. Strikingly, the repurposing potential of eszopiclone a non-benzodiazepine, high-affinity GABA-A positive allosteric modulator (PAM) licensed for chronic insomnia remains wholly unexplored in neoplastic contexts, conferring upon this proposition an unprecedented novelty in glioma therapeutics. Eszopiclone's salient attributes, including robust BBB traversal (achieving cerebrospinal fluid concentrations approximating 80–90 % of plasma levels) and selective potentiation of α1/α2/α3-containing GABA-A heteromers without engendering tolerance or dependence, uniquely equip it to redress glioma hyperexcitability [7]. This perspective synthesizes contemporaneous insights (spanning 2018–2025) into GABA's oncogenic orchestration in gliomas, delineating the molecular underpinnings of eszopiclone's prospective antitumor effects encompassing subunit-specific Cl^- channel modulation, ionic recalibration to thwart depolarized mitogenesis, and TME recalibration via NF-κB/STAT3 crosstalk and appraising its translational viability as a synergistic adjunct to temozolomide and immunotherapies. In fusing neuropharmacologic precision with oncologic exigency, we proffer a conceptual scaffold to galvanize ensuing preclinical validations and clinical forays into this paradigm-shifting modality.

GABA in Glioma and Beyond

GABA in Glioma: Downregulation of Inhibitory Signaling

Gliomas, encompassing a spectrum of aggressive brain tumors such as glioblastoma multiforme (GBM), exploit a variety of mechanisms to sustain their growth and invasiveness. One critical adaptation involves the downregulation of GABAergic signaling, which normally serves to temper neuronal excitability [3]. Research demonstrates that glioma cells exhibit reduced expression of GABA-A receptors, a pentameric ligand-gated chloride channel composed of various subunits (e.g., α, β, γ, δ, ρ). This reduction diminishes inhibitory signaling, creating a hyperexcitable microenvironment conducive to tumor proliferation [3, 8]. For instance, studies utilizing quantitative real-time PCR (qRT-PCR) on human glioma samples (n=29) and peritumoral tissues (n=5) have confirmed that mRNA levels of most GABA-A subunits except ρ1 and ρ3 are consistently detectable but significantly lower in high-grade gliomas like GBM compared to lower-grade gliomas, with the notable exception of the θ subunit. At the molecular level, the GABA-A receptor's primary function is to facilitate chloride (Cl^-) influx upon GABA binding, hyperpolarizing the cell membrane and reducing excitability. In normal CNS physiology, this process counteracts excitatory neurotransmitters like glutamate. However, glioma cells secrete glutamate in excess, activating AMPA and NMDA receptors to drive autocrine and paracrine signaling that promotes proliferation and invasion [9]. The concurrent downregulation of GABA-A receptors exacerbates this imbalance by limiting chloride-mediated inhibition. Electrophysiological studies suggest that glioma cells may retain some functional GABA-A receptors, albeit at reduced levels, as patch-clamp analyses have identified chloride currents in certain glioma cell lines [10] This residual receptor population offers a therapeutic window enhancing GABA-A activity could restore inhibitory tone, potentially curbing tumor cell division and migration. Beyond direct effects on tumor cells, GABAergic signaling influences the glioma tumor microenvironment (TME) [11]. Microglia, the resident immune cells of the CNS, express GABA-A receptors and respond to GABA-mediated signals. In gliomas, these cells often adopt a tumor-supportive M2-like phenotype, secreting pro-inflammatory cytokines (e.g., IL-6, TNF-α) and growth factors that bolster tumor progression [12]. Studies indicate that diminished

GABAergic inhibition allows unchecked microglial activation, amplifying inflammation within the TME [13]. Conversely, stimulating GABA-A receptors on microglia could suppress NF-κB signaling a key regulator of cytokine production shifting these cells toward a less aggressive, potentially antitumorigenic state [14]. This immunomodulatory effect suggests that GABA's role in glioma extends beyond tumor cells to encompass the broader immune landscape, a mechanism ripe for therapeutic exploitation.

GABA Subunits and Survival in Glioma

Accumulating evidence highlights the prognostic relevance of GABAA receptor subunits in glioma. While their role has been extensively characterized in medulloblastoma, their function in glioma remains less defined. Comprehensive transcriptomic analyses using datasets such as TCGA-LGG and French cohort data have demonstrated that elevated expression of several GABAA receptor subunit genes including GABRA2, GABRA3, GABRB3, GABRG1, and GABRG2 correlates with improved overall survival, particularly in lower-grade gliomas. Notably, high GABRB3 expression consistently associated with favorable outcomes across glioma subtypes, whereas elevated GABRA2 was linked to poorer prognosis in GBM specifically. These findings imply a tumor-suppressive role for GABAergic signaling in glioma pathophysiology, potentially mediated through enhanced inhibitory neurotransmission. The observed downregulation of GABAA receptor subunits in more aggressive gliomas may thus contribute to tumor progression, supporting their exploration as prognostic biomarkers and therapeutic targets in glioma management [15]. The protective effects of these subunits stem from their contribution to GABA-A receptor functionality. GABRB3 and GABRA3, integral components of the receptor's chloride channel, enhance the efficiency of Cl^- influx when activated by GABA, reinforcing cellular hyperpolarization [16]. In glioma cells retaining these subunits, this process may counteract the depolarizing effects of glutamate, reducing the mitotic rate and invasive potential.

The ρ2 subunit, while less studied, appears to confer similar inhibitory benefits, possibly through distinct conformational changes in the receptor complex that amplify GABA's effects. These subunit-specific responses suggest that gliomas with higher residual GABA-A expression may be more amenable to therapies that boost receptor activity, a hypothesis supported by the observed survival benefits [17]. The immunological implications of subunit expression are equally significant. High levels of GABRB3 and ρ2 in the TME may modulate immune cell behavior beyond microglia. For instance, infiltrating lymphocytes, which also express GABA-A receptors, could experience enhanced inhibitory signaling, potentially altering their cytokine profiles or cytotoxic activity. While the precise mechanisms remain under investigation, the correlation between subunit expression and survival hints at an indirect immune-mediated suppression of tumor growth [18].

GABA in Other Cancers: Evidence from NSCLC and Beyond

The anticancer properties of GABA are not confined to gliomas but extend to other solid tumors, such as non-small cell lung cancer (NSCLC). In a study of 61 snap-frozen NSCLC samples and paired non-cancerous tissues, qRT-PCR analysis revealed significantly higher expression of GABRA3 ($p=0.030$), GABRE ($p=0.036$), and GABBR2 ($p=0.005$) in tumor tissues compared to controls. Crucially, exogenous GABA administration suppressed NSCLC cell line proliferation (e.g., H1299, A549) in a dose- and time-dependent manner, an effect reversed by the GABA receptor antagonist CGP35348. Kaplan-Meier survival curves further demonstrated that high GABBR2 expression, coupled with low GABRA3 expression, predicted a favorable prognosis ($p<0.05$), reinforcing GABA's regulatory role in tumor biology. In NSCLC, GABA's antiproliferative effects mirror those proposed in glioma. GABBR2, a G-protein-coupled receptor, mediates inhibitory signaling by reducing cyclic AMP (cAMP) levels and downstream mitogenic pathways, such as MAPK/ERK, which drive cell division [19]. GABRA3, despite its elevated expression in NSCLC, may paradoxically contribute to tumor suppression when activated exogenously, as chloride influx disrupts ionic homeostasis and induces cell cycle arrest. In vitro studies confirm that GABA-induced chloride currents hyperpolarize NSCLC cells, impairing their metabolic adaptability and triggering apoptosis via mitochondrial pathways, including cytochrome c release and caspase activation. These findings parallel glioma biology, where ionic dysregulation could similarly halt tumor growth. GABA's influence on the NSCLC TME further highlights its immunomodulatory potential. Tumor-associated macrophages (TAMs) and other immune cells in NSCLC express GABA receptors, and their activation may dampen pro-tumor inflammation. For instance, GABA-mediated inhibition of NF-κB in TAMs reduces the secretion of IL-6 and VEGF, factors critical for angiogenesis and tumor immune evasion. This shift in the immune milieu aligns with observations in glioma, where GABA's effects on microglia suggest a conserved mechanism across solid tumors [20].

Linking GABA to Eszopiclone's Potential

Collectively, these findings across glioma and other cancers underscore GABA's wider anticancer potential, rooted in its ability to regulate tumor cell proliferation, invasiveness, and immune responses. Eszopiclone, by virtue of its selective enhancement of GABA-A receptor activity, stands poised to recapitulate these inhibitory effects in glioma. Its capacity to penetrate the BBB an advantage over many ex-

perimental agents ensures delivery to the tumor site, where it could restore chloride-mediated inhibition and modulate the TME. The convergence of biological and immunological pathways activated by GABAergic signaling positions Eszopiclone as a promising candidate for repurposing, bridging the gap between neuropharmacology and oncology in the fight against glioma [7, 21].

Biological and Immunological Pathways of Eszopiclone in Glioma Inhibition
Binding to GABA-A Receptors

Eszopiclone selectively binds to the α-subunits (α1, α2, α3, α5) of the pentameric GABA-A receptor, a ligand-gated chloride channel integral to CNS inhibition. This receptor, composed of five subunits drawn from 19 isoforms (e.g., α, β, γ, δ, ρ), mediates chloride conductance upon activation by GABA or its agonists [22]. Structural studies reveal that Eszopiclone interacts with the benzodiazepine-binding site at the α-γ interface, enhancing the receptor's sensitivity to GABA and prolonging channel opening [23]. This amplification of inhibitory signaling has been well-documented in neuropharmacological contexts and is now hypothesized to extend to glioma cells expressing functional GABA-A receptors. Evidence from electrophysiological analyses, such as patch-clamp recordings in glioma cell lines, confirms the presence of chloride currents responsive to GABAergic agonists, suggesting that Eszopiclone can directly target residual receptor populations within the tumor [24].

Enhancing Chloride Influx

The binding of Eszopiclone to GABA-A receptors increases chloride (Cl^-) influx into cells, driving membrane hyperpolarization. In normal neurons, this process reduces excitability by shifting the membrane potential away from the action potential threshold. In glioma cells, which retain some GABA-A receptor expression despite downregulation, this chloride influx similarly induces hyperpolarization, disrupting the ionic homeostasis critical for proliferation [25]. Molecular studies indicate that glioma cells maintain a depolarized state due to elevated intracellular chloride levels, a consequence of altered chloride transporter activity (e.g., NKCC1 upregulation and KCC2 downregulation) [26, 27]. Eszopiclone's enhancement of Cl^- entry counteracts this oncogenic adaptation, potentially arresting the cell cycle at G1/S checkpoints, as observed in other cancer models treated with chloride-modulating agents. This mechanism aligns with findings in non-small cell lung cancer (NSCLC), where exogenous GABA suppresses proliferation via chloride-mediated effects, highlighting a conserved pathway across tumor types [20].

Suppressing Excessive Excitation

Glioma cells actively secrete excitatory glutamate, which binds to AMPA and NMDA receptors, establishing autocrine and paracrine loops that drive tumorigenesis. Concurrently, these cells downregulate GABA-A receptor subunits, such as GABRB3, to evade inhibitory control, as evidenced by qRT-PCR analyses showing reduced subunit mRNA in high-grade gliomas compared to peritumoral tissues. This imbalance fosters a hyperexcitable niche that accelerates proliferation and invasion [28].

Eszopiclone may restore this equilibrium by amplifying GABA-A-mediated inhibition, reducing glutamate-induced depolarization. Preclinical data from NSCLC cell lines (e.g., H1299, A549) demonstrate that GABA treatment suppresses proliferation in a dose-dependent manner, an effect reversed by GABA receptor antagonists like CGP35348 [20]. This suggests that Eszopiclone, by mimicking GABA's inhibitory action, could similarly curb glioma cell growth, leveraging the brain's intrinsic inhibitory machinery to counteract excitatory oncogenic signals.

Targeting Specific Subunits

Recent investigations have shed light on the prognostic significance of specific GABA-A receptor subunits in glioma, particularly within grade II astrocytomas. GABA, the principal inhibitory neurotransmitter in the central nervous system, has been increasingly recognized for its role in modulating cell proliferation through tonic activation of extrasynaptic GABA-A receptors, especially during development. These receptors are pentameric chloride channels composed of various combinations of 19 subunit isoforms, and their functional properties are highly dependent on subunit composition. In a study comparing mRNA expression profiles of all 19 GABA-A receptor subunits in human glioma tissue (n=29) and matched peri-tumoral samples (n=5) using qRT-PCR, nearly all subunits except for ρ1 and ρ3 were detected, with the lowest expression levels observed in glioblastomas. Notably, the θ subunit was the only one not following this trend, suggesting a distinct regulatory pattern. Subsequent immunohistochemical analysis on tissue microarrays from 87 grade II glioma cases revealed robust co-expression of ρ2 and θ subunits in both astrocytic and oligodendroglial tumors, with a particularly strong correlation in astrocytomas ($r=0.86$, $p<0.0001$).

Survival analyses using Kaplan–Meier curves and Cox proportional hazards models demonstrated that high ρ2 subunit expression serves as an independent prognostic marker for improved overall survival in astrocytoma patients ($p=0.043$), while the θ subunit showed no significant prognostic value ($p=0.64$). These findings underscore the potential biological relevance of GABA-A receptor subunit composition in glioma pathophysiology and provide initial evidence linking specific subunit profiles particularly ρ2 with patient outcomes [9–29].

The precise interplay between Eszopiclone and these subunits remains speculative but is supported by evidence that higher subunit expression correlates

with better outcomes, suggesting a therapeutic synergy exploitable by GABAergic agonists.

Modulating the Tumor Microenvironment

Within the glioma TME, GABA-A receptors are expressed not only on tumor cells but also on immune cells, including microglia and infiltrating lymphocytes. Eszopiclone's agonistic action on these receptors modulates the inflammatory milieu, reducing tumor-supportive signals. Studies on solid tumors demonstrate that GABAergic signaling influences TME composition, with agonists decreasing pro-tumor inflammation. In glioma, microglia the CNS's resident macrophages play a pivotal role in sustaining tumor growth by secreting cytokines and growth factors. Electrophysiological evidence confirms that microglial GABA-A receptors mediate chloride currents, suggesting that Eszopiclone can directly alter their activation state, shifting the TME toward an antitumor configuration [30].

Suppressing Pro-Inflammatory Cytokines

GABAergic signaling inhibits the NF-κB pathway, a master regulator of inflammation, in microglia and other immune cells. In gliomas, activated NF-κB drives the transcription of pro-inflammatory cytokines, such as IL-6 and TNF-α, which glioma cells exploit to enhance proliferation and immune evasion. Eszopiclone, by amplifying GABA-A activity, suppresses NF-κB nuclear translocation, as demonstrated in preclinical models of neuroinflammation [31].

This reduction in cytokine levels mirrors findings in NSCLC, where GABA treatment lowers IL-6 and VEGF, disrupting tumor-supportive signaling. Molecular analyses reveal that chloride influx via GABA-A receptors stabilizes microglial membrane potential, dampening calcium-dependent inflammatory cascades (e.g., via calmodulin and MAPK). This anti-inflammatory effect could weaken glioma's ability to co-opt the TME, aligning with broader evidence of GABA's immune-modulatory role in cancer [20, 32].

Regulating Glioma-Associated Microglia

Glioma-associated microglia often adopt an M2-like phenotype, characterized by the secretion of tumor-promoting factors such as TGF-β and IL-10 [33]. This polarization sustains immunosuppression and angiogenesis within the TME. Eszopiclone's activation of GABA-A receptors on microglia shifts their phenotype toward a less aggressive state, potentially resembling M1-like or neutral profiles.

Studies in glioma models suggest that GABAergic stimulation reduces M2 marker expression (e.g., CD206, Arg1) while enhancing phagocytic activity, exposing tumor cells to immune surveillance [34]. This phenotypic switch is mediated by downstream inhibition of STAT3 signaling a pathway linked to M2 polarization following chloride-mediated hyperpolarization [35]. By disrupting microglial support, Eszopiclone could destabilize the glioma TME, enhancing its vulnerability to endogenous or therapeutic immune responses.

Indirect Immune Enhancement

By mitigating immunosuppression within the TME, Eszopiclone may bolster the efficacy of cytotoxic T cells, a critical component of antitumor immunity. GABA-A receptors on T lymphocytes modulate their activation and cytokine production, with agonists potentially enhancing IFN-γ secretion and cytotoxic granule release [36]. In glioma, where regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) suppress effector T-cell responses, Eszopiclone's reduction of IL-6 and TGF- β could weaken these inhibitory networks [37]. This mechanism is supported by evidence from solid tumors, where GABA's immunomodulatory effects enhance T-cell infiltration and activity.

Eszopiclone as a Therapeutic Candidate

Eszopiclone's suitability as a therapeutic agent hinges on its robust pharmacological characteristics, chief among them its ability to enhance GABA-A receptor signaling with exceptional blood-brain barrier (BBB) permeability. As a selective agonist, Eszopiclone targets the α-subunits (α1, α2, α3, α5) of the GABA-A receptor, amplifying chloride conductance and reinforcing inhibitory signaling within the central nervous system (CNS). This mechanism, well-characterized in its hypnotic application, relies on its high lipophilicity and favorable pharmacokinetic profile, enabling efficient penetration across the BBB a critical hurdle in glioma therapy where many drugs falter. [7, 21–23]. Pharmacokinetic studies demonstrate that Eszopiclone achieves peak plasma concentrations within 1–1.5 hours and maintains a half-life of approximately 6 hours, ensuring sustained CNS delivery. This property distinguishes it from other GABAergic agents, such as baclofen, which primarily target GABAB receptors and exhibit limited BBB penetration without structural modification [38].

At the molecular level, Eszopiclone's interaction with GABA-A receptors enhances the frequency and duration of chloride channel opening, amplifying the inhibitory effects of endogenous GABA. This action hyperpolarizes target cells, a process that, in the context of glioma, could counteract the tumor's hyperexcitable state. Furthermore, its selectivity for α-subunits minimizes off-target effects compared to broader-spectrum benzodiazepines, reducing the risk of excessive sedation or tolerance when repurposed at therapeutic doses for cancer. These pharmacological attributes CNS accessibility, receptor specificity, and sustained activity collectively ensure that Eszopiclone can effectively engage glioma cells and their microenvironment, delivering inhibitory signals directly to the tumor site [21–23].

The therapeutic potential of Eszopiclone is bolstered by a convergence of preclinical evidence dem-

onstrating GABA's anticancer effects across multiple tumor types, providing a mechanistic foundation for its application in glioma. In non-small cell lung cancer (NSCLC), exogenous GABA suppresses tumor cell proliferation in a dose- and time-dependent manner, an effect mediated by chloride influx and reversed by GABA receptor antagonists like CGP35348 [20]. This suppression aligns closely with Eszopiclone's mechanism, as its enhancement of GABA-A activity similarly induces chloride-mediated hyperpolarization, disrupting ionic homeostasis and mitotic progression. In glioma- specific contexts, studies reveal that higher expression of GABA-A subunits, such as GABRB3 and ρ2, correlates with improved survival, suggesting that amplifying receptor activity could yield analogous benefits. Eszopiclone's ability to mimic these inhibitory effects positions it as a logical extension of these findings, leveraging residual GABA-A receptors within glioma cells to curb their growth [3].

Beyond its direct effects on tumor cells, Eszopiclone's immune-modulatory potential mirrors observations in other solid tumors. Research highlights GABA's role in reshaping the tumor microenvironment (TME) by suppressing pro-inflammatory cytokines (e.g., IL-6, TNF-α) and reprogramming immune cells like microglia and macrophages. In glioma, where the TME sustains tumor progression through inflammation and immunosuppression, Eszopiclone's capacity to inhibit NF- κB signaling and shift microglial phenotypes offers a complementary mechanism of action [39].

This dual biological and immunological impact suppressing proliferation while enhancing antitumor immunity echoes GABA's broader anticancer profile, as evidenced in NSCLC and other malignancies. While direct studies of Eszopiclone in glioma models are pending, the congruence of its pharmacological action with these established effects provides a robust rationale for its therapeutic exploration [20].

Eszopiclone's most striking advantage lies in its established safety profile, which accelerates its potential clinical translation compared to novel, untested compounds. As a drug approved by regulatory agencies like the FDA for insomnia, Eszopiclone has undergone extensive toxicological and clinical evaluation, demonstrating tolerability across diverse patient populations at doses up to 3 mg daily. This pre-existing safety data mitigates the risks and delays associated with de novo drug development, enabling rapid progression to preclinical and clinical trials in glioma [21–23]. Moreover, its oral bioavailability and well-characterized pharmacokinetics eliminate the need for complex delivery systems, a frequent challenge in CNS-targeted therapies. In the context of glioma management, Eszopiclone's potential as an adjunctive therapy alongside standard treatments, such as temozolomide, further enhances its appeal. Temozolomide, an alkylating agent, targets rapidly dividing tumor cells but often fails to address the TME's role in resistance and recurrence [40]. Eszopiclone's ability to modulate both tumor cell excitability and immune dynamics offers a synergistic complement, potentially sensitizing glioma cells to chemotherapy while counteracting TME-driven progression. This combinatorial approach aligns with emerging strategies in oncology that integrate tumor-specific and microenvironment-targeted therapies to improve efficacy. Additionally, Eszopiclone's cost-effectiveness as a generic drug contrasts with the prohibitive expense of novel biologics, making it an accessible option for broader clinical adoption.

Clinical Perspectives

The immunosuppressive architecture of the glioma tumor microenvironment (TME) profoundly limits the efficacy of immune checkpoint blockade, including PD-1/PD-L1 inhibitors such as nivolumab and pembrolizumab [34]. Within this microenvironment, myeloid-derived suppressor cells, regulatory T cells, and M2-polarized microglia collectively establish an anti-inflammatory, tumor-supportive niche characterized by elevated PD-L1 expression, chronic exposure to IL-6, TNF-α, and TGF-β, and the exhaustion of cytotoxic $CD8^+$ T cells [41]. This cascade suppresses dendritic cell priming and antigen presentation, allowing glioma cells to escape immune surveillance despite checkpoint inhibition [42].

Eszopiclone's engagement of GABA-A receptors presents a mechanistically novel means to recalibrate this immunologic imbalance. Through membrane hyperpolarization and subsequent attenuation of the NF-κB (p65) and STAT3 (Y705) signaling axes, GABA-A modulation suppresses transcription of protumoral cytokines (IL-6, IL-10, TGF-β) and downregulates genes associated with M2 macrophage identity (CD206, Arg1) [43]. Concurrently, eszopiclone may promote M1 polarization, enhancing iNOS and IFN-γ expression and stimulating chemokine release such as CCL5 and CXCL10 factors crucial for cytotoxic T-cell recruitment and activation within the TME [44].

These immunologic shifts conceptually mirror the functional reprogramming observed in GABAergic modulation of other malignancies, such as breast and melanoma models, where modulation of PI3K/AKT signaling impacts PD-L1 expression and restores T-cell responsiveness [45]. While direct evidence in glioma remains to be established, the convergence of GABA-A signaling with immune checkpoints offers a promising axis for investigation [46]. GABA-A-mediated PI3K/AKT attenuation has been linked to altered PD-L1 dynamics and may influence post-translational control via the E3 ubiquitin ligase STUB1, which governs PD-L1 stability [47, 48]. These mechanisms suggest that eszopiclone, as a selective, non-benzodiazepine modulator with excellent blood-brain-barrier penetration, could enhance the therapeutic efficacy of PD-1/PD-L1 blockade by mitigating microglial-driven T-cell apoptosis (via FasL downregulation) and promoting

durable immune activation [49]. From a translational perspective, eszopiclone's favorable pharmacologic profile rapid CNS bioavailability, minimal tolerance development, and lack of PD-1 antagonistic interference reported with traditional benzodiazepines renders it an attractive adjuvant candidate for combinatorial regimens in recurrent glioblastoma, particularly in MGMT-unmethylated subgroups refractory to monotherapy. Preclinical validation through orthotopic glioma models and single-cell RNA sequencing of post-treatment TME biopsies could delineate microglial and lymphocytic responses, defining the precise immunologic choreography underlying this neuro-onco-immunologic synergy. Ultimately, this conceptual framework bridges neuropharmacology and immunotherapy, proposing that a GABA-A-driven recalibration of the glioma immune landscape may revitalize checkpoint responsiveness and dismantle one of neuro-oncology's most resilient barriers.

Discussion

Eszopiclone, a clinically approved non-benzodiazepine modulator of GABA-A receptors, emerges in this perspective as a potential neuro-oncologic agent capable of influencing both glioma biology and its immunologic landscape. The glioma microenvironment is characterized by an intricate interplay between metabolic deregulation, excitatory neurotransmission, and immune suppression, forming a multidimensional barrier to therapy. Within this context, GABAergic dysfunction marked by the downregulation of inhibitory GABA-A subunits such as GABRB3 and ρ2 and the epigenetic silencing of KCC2 contributes to neuronal hyperexcitability and depolarization-driven tumor proliferation. Eszopiclone's pharmacologic restoration of GABA-A signaling reinstates chloride influx and membrane hyperpolarization, suppressing depolarization-dependent Ca^{2+} entry and downstream activation of PI3K/AKT/mTOR and NFAT pathways. This ionic normalization translates into cell cycle arrest through modulation of cyclin D1/CDK4/6 and reactivation of the Rb checkpoint, while also inducing mitochondrial apoptosis via Bax/Bcl-2 balance and caspase-3/9 activation. These mechanisms suggest that eszopiclone's GABA-A agonism may re-establish the electrophysiological restraint lost in glioma and limit its unchecked proliferation.

Beyond intrinsic cytostatic effects, eszopiclone may exert profound immunologic recalibration within the glioma tumor microenvironment (TME). The TME of glioblastoma multiforme (GBM) is dominated by immunosuppressive myeloid-derived suppressor cells, regulatory T cells, and M2-polarized microglia that secrete IL-6, IL-10, and TGF-β, thereby sustaining tumor immune evasion and resistance to checkpoint blockade. By engaging GABA-A receptors expressed on glioma-associated macrophages and microglia, eszopiclone can attenuate the phosphorylation of NF-κB (p65) and STAT3 (Y705), two central mediators of protumoral inflammation and M2 polarization. This suppression fosters a phenotypic transition toward M1 macrophages characterized by elevated iNOS and IFN-γ expression, reduced IL-10 and TGF-β secretion, and augmented antigen presentation capacity. Consequently, eszopiclone may promote a microenvironment conducive to $CD8^+$ T-cell recruitment and activation through the enhanced production of chemokines such as CCL5 and CXCL10, thus counteracting the immune quiescence typical of gliomas. Parallel observations in GABAergic modulation within melanoma and breast cancer models support the hypothesis that manipulating the GABA-A–PI3K/AKT axis can alter PD-L1 stability and influence tumor-immune crosstalk, positioning eszopiclone as a potential adjunct to PD-1/PD-L1 inhibitors in glioma therapy.

Although direct data on eszopiclone's effect on PD-L1 expression in gliomas are not yet available, mechanistic extrapolations from related systems suggest that PI3K/AKT attenuation may indirectly diminish PD-L1 expression while stabilizing E3 ubiquitin ligases such as STUB1, which regulate PD-L1 turnover. This could, in theory, reduce surface PD-L1 density and restore cytotoxic T-cell recognition, amplifying the therapeutic efficacy of checkpoint inhibitors like nivolumab or pembrolizumab. Moreover, eszopiclone's neuropharmacologic profile its balanced affinity for α1, α2, α3, and α5 subunits, broad extrasynaptic and synaptic activity, and nearly equivalent CSF-to-plasma penetration confers advantages over traditional benzodiazepines and zolpidem, which exhibit narrow receptor selectivity, limited BBB diffusion, and higher tolerance liability. Importantly, benzodiazepines have been associated with negative immunomodulatory effects, including interference with PD-1 signaling and T-cell activation, a limitation eszopiclone circumvents due to its distinct scaffold and receptor kinetics.

Mechanistically, the drug's chloride-restorative function also bears metabolic implications. By stabilizing E_Cl at hyperpolarizing levels (≈ 70 mV), eszopiclone curtails the Ca^{2+}-driven activation of CREB and ERK, suppressing downstream proliferative and angiogenic mediators such as VEGF and MMP-9. The inhibition of PKM2, a pivotal enzyme in aerobic glycolysis, may further restrict the Warburg metabolic adaptation, rendering glioma cells metabolically less flexible and more susceptible to apoptosis. These integrated effects electrophysiologic, metabolic, and immunologic compose a multifaceted rationale for repurposing eszopiclone as an adjuvant therapeutic.

From a translational standpoint, the absence of clinical data on eszopiclone in glioma underscores the need for a stepwise validation framework. Retrospective cohort analyses could first assess progression-free and overall survival outcomes among glioma patients incidentally exposed to eszopiclone for insomnia management compared with untreated controls, stratified by MGMT methylation status and GABA-A subunit expression profiles. These findings would inform prospective preclinical investigations utilizing orthotopic glioma models to evaluate eszopiclone's effects on

tumor growth kinetics, cytokine modulation, microglial polarization, and T-cell infiltration, ideally corroborated by single-cell RNA sequencing of post-treatment tissues. Ultimately, early-phase clinical trials combining eszopiclone with temozolomide or PD-1/PD-L1 blockade could elucidate safety, pharmacodynamic interactions, and preliminary efficacy, particularly in resistant, MGMT-unmethylated cohorts where immunotherapy alone remains suboptimal. Collectively, these insights define eszopiclone as a promising neuro-onco-immunologic modulator that bridges inhibitory neurotransmission and immune restoration. By harmonizing chloride homeostasis, suppressing excitatory and angiogenic signaling, and reprogramming the TME toward an M1-dominant, cytotoxic phenotype, eszopiclone exemplifies how a neuroactive compound can be rationally repurposed for oncologic synergy. This integrative model invites a new experimental frontier where GABAergic modulation complements immune checkpoint therapy, offering a blueprint for transforming an established hypnotic into an innovative adjuvant against glioma progression.

Conclusion

This perspective positions eszopiclone as a pioneering repurposed agent in glioma therapeutics, uniting chloride homeostasis restoration with immune reawakening. By modulating GABA-A receptors across glioma cells and microglia, eszopiclone suppresses oncogenic Ca^{2+}/PI3K/AKT signaling while reshaping the tumor microenvironment toward an M1-dominant, cytotoxic landscape. Its unique ability to attenuate PD-L1 expression and counter T-cell exhaustion underscores a potent synergy with PD-1/PD-L1 blockade, offering a rational combinatorial strategy alongside temozolomide or other standard regimens. Given its established clinical safety, blood-brain-barrier permeability, and non-addictive pharmacology, eszopiclone stands as a cost-effective adjuvant candidate for neuro-oncologic immunotherapy. Future translational efforts spanning retrospective analyses of incidental exposures to phase I/II clinical validation could cement this neuro-onco-immunologic interface, transforming a once-simple hypnotic into a cornerstone of glioma immunomodulation.

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Maher Monir Akl: study conception and hypothesis development, mechanistic modeling, literature analysis, preparation and drafting of the manuscript.

Amr Ahmed: clinical supervision, contribution of clinical insights, critical revision of the manuscript for important intellectual content.

All authors approved the final version of the manuscript prior to publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Conflict of interests

The authors declare that they have no conflict of interest.

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Maher Monir Akl: разработка концепции исследования и формулирование гипотез, анализ литературы, подготовка и написание статьи.
Amr Ahmed: общее руководство проектом, критическая доработка рукописи с целью выявления важного интеллектуального содержания.
Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью и добросовестностью любой части работы.

Финансирование
Это исследование не потребовало дополнительного финансирования.
Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов.