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SNI: Neuro-Oncology

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Case Report

Long-term survival in glioblastoma patients treated with dopamine agonists: A report of two cases and implications for drug repurposing

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Received: 23 February 2026
Accepted: 25 April 2026
Published: 05 June 2026

DOI
10.25259/SNI_243_2026

Quick Response Code:

ABSTRACT

Background: Glioblastoma (GBM) remains the most lethal primary brain tumor, with a median survival of 15 months and a 10-year survival rate of <1%. While current research into the dopaminergic system has largely focused on dopamine receptor antagonists, we aimed to investigate the potential therapeutic benefit of dopamine agonists (dopamine receptor D2) through the observation of incidental "super-survivors."

Case Description: We report two cases of adult GBM patients who received concurrent treatment with dopamine agonists for unrelated comorbidities. The first patient, treated with the ergot derivative bromocriptine for a prolactinoma, presented with multifocal disease and underwent subtotal resection. Despite developing a recurrence, he remains alive and progression-free for >11 years after diagnosis. The second patient, a 70-year-old male with Parkinson's disease treated with the non-ergot dopamine agonist pramipexole and with Sinemet, which increases the amount of available dopamine. He had a low Karnofsky Performance Score and received minimal adjuvant therapy. Despite these poor prognostic factors, he achieved a progression-free survival of 15 months and did not succumb to tumor progression.

Conclusion: These observational cases suggest a hypothetical association between dopamine agonist therapy and improved survival outcomes in GBM, challenging the current paradigm that favors receptor antagonism. Given the safety, low cost, and blood–brain barrier penetrance of these Food and Drug Administration-approved drugs, we propose that dopamine agonists warrant further investigation as repurposed adjuvant agents in GBM treatment.

Keywords: Agonists, Bromocriptine, Dopamine, Glioblastoma, Repurposing

INTRODUCTION

Glioblastoma (GBM) is the deadliest adult brain cancer. The current standard-of-care is maximal safe resection followed by radiotherapy and temozolomide, which results in a median survival time of only 21 months.[43] The efficacy of chemotherapies and targeted therapies in GBM is very limited because most of these drugs do not pass the blood–brain barrier (BBB), and due to the remarkable plasticity exhibited by GBM cells, which allows them to effectively adapt to changes in the microenvironment induced by conventional radiation and chemotherapy.[33] Thus, new drugs that can cross the BBB and can either inhibit the tumor's plasticity or act as second or third lines of therapy once adaptability has occurred are of absolute necessity. Since

the development of new drugs is an extremely long, complex, and expensive process, scientists and clinicians are strongly motivated to consider drug repurposing as a valid alternative due to the benefits of safety, cost, and ability to reach the bedside faster.[36] In recent years, some established Food and Drug Administration (FDA)-approved antipsychotic drugs were considered candidates for drug repurposing for GBM treatment and were studied as such, mainly through their mechanism as dopamine receptor D2 (DRD2) antagonists. It was found that GBM tumors in patients express DRD2 in levels that are often elevated compared with the healthy brain,[29] and are specifically elevated in the glioma-initiating cell population. He *et al*. revealed that combined treatment with the DRD2 antagonist ONC201 and radiation improves the efficacy of radiation against GBM *in vitro* and *in vivo* through suppression of glioma-initiating cell.[11] Indeed, accumulating data support the role of the neurotransmitter dopamine and its receptors in gliomagenesis. GBM cells synthesize and secrete dopamine themselves, suggesting even a potential autocrine mechanism.[12] Nevertheless, great controversy exists whether dopamine possesses pro-tumoral or anti-tumoral effects in GBM, and hence, should DRD2 antagonists or agonists be potentially used against GBM.[5] DRD2 agonists have been in extensive use for many decades for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia, and galactorrhea, and more recently have been repurposed to treat diabetes mellitus. They are also active against pituitary hormone-dependent tumors such as prolactinomas and growth-hormone-producing adenomas. Bromocriptine, a DRD2 agonist, has very limited systemic side effects, and its over 40 years of use in the field of medicine has made it an attractive candidate for repurposing, especially in oncology.[41] Bromocriptine has been suggested as a potential therapy against different systemic tumors,[16,17,37] including multi-drug-resistant tumors.[41]

We present two GBM cases in which patients were treated with DRD2 agonists - one for prolactinoma and one for Parkinson's disease. The prolactinoma patient had a remarkable overall survival (OS) of >11 years (still alive with no evidence of recurrence), and the Parkinson's disease patient has shown extended progression-free survival (PFS) before succumbing to his Parkinson's disease. We also discuss thoroughly the current evidence regarding the effects of dopamine on GBM and its potential therapeutic implications.

CASE 1

In 2014, a 55-year-old male presented to the neurosurgical department with a sudden onset of blurry vision while driving. His past medical history included prolactinoma (diagnosed at age 50) for which he was under treatment with a dopamine agonist (bromocriptine, 2.5 mg/day), started 5 years before his current admission. His neurological and vision examinations on admission were consistent with left homonymous hemianopsia. Brain magnetic resonance imaging (MRI) has shown the known pituitary microadenoma. In addition, a new, intra-axial multifocal lesion in the right occipital lobe was discovered [Figure 1a-f]. The patient underwent an uneventful right occipital craniotomy for resection of the lesion. The surgery was assisted with an intraoperative ultrasound. Post-operative MRI shows gross total resection of the major lesion with residual of the smaller, multifocal lesions [Figure 1g and h]. The patient was discharged home after 3 days in good condition. Pathology was consistent with the diagnosis of GBM, WHO grade 4, isocitrate dehydrogenase (IDH) wildtype (KI67 20%, P53 = 50%; Figure 1i). On molecular analysis, O6-Methylguanine-DNA Methyltransferase (MGMT) methylation was discovered. No other significant molecular testing was done. The patient received the standard adjuvant chemo-radiation "Stupp" protocol, started 4 weeks post-surgery. Karnofsky performance score (KPS) was 90 before therapy. Prolactin level at that time was still high at 666 mIU/L (normal range 45–375 mIU/L). He went on to receive 12 cycles of temozolomide (200 mg/m^2) without any major side effects. During all this time, he was kept on the same dose of bromocriptine. Prolactin levels were decreased gradually, reaching normal values 12 months post-surgery. In May 2018, 41 months following his first craniotomy, a progression on imaging was noted [Figure 1j and k]. The patient had no new neurological signs or symptoms. KPS was still 90. Following a multidisciplinary tumor board meeting, the patient underwent an uneventful right occipital re-craniotomy with gross total resection of the recurrent lesion [Figure 1l and m]. Pathology was again consistent with GBM. An active tumor was noted with mitotic activation (KI67 40%), necrosis, and microvascular proliferation [Figure 1n]. Following surgery, the patient was treated with stereotactic radiosurgery linear accelerator (LINAC), (20 Gy to the 80% isodose line of the lesion) and 6 more cycles of temozolomide (300 mg × 5 days/month). Prolactin levels at the time of recurrence were 34 mIU/L, under the same dose of bromocriptine (2.5 mg/day). The patient is now 140 months following his initial diagnosis of GBM. He is doing extremely well. He has persistent left homonymous hemianopsia, but other than that, he is neurologically intact. Following endocrinology consultation, bromocriptine was stopped 9 years after the GBM diagnosis, so he is now 2 years without any dopamine agonist therapy. He is not receiving any oncological treatment. The most recent prolactin level is normal at 275 mIU/L. His most recent MRI (November 2025) shows no recurrence of both the prolactinoma and the GBM [Figure 1o and p]. Figure 2 summarizes the patient's clinical course illustratively.

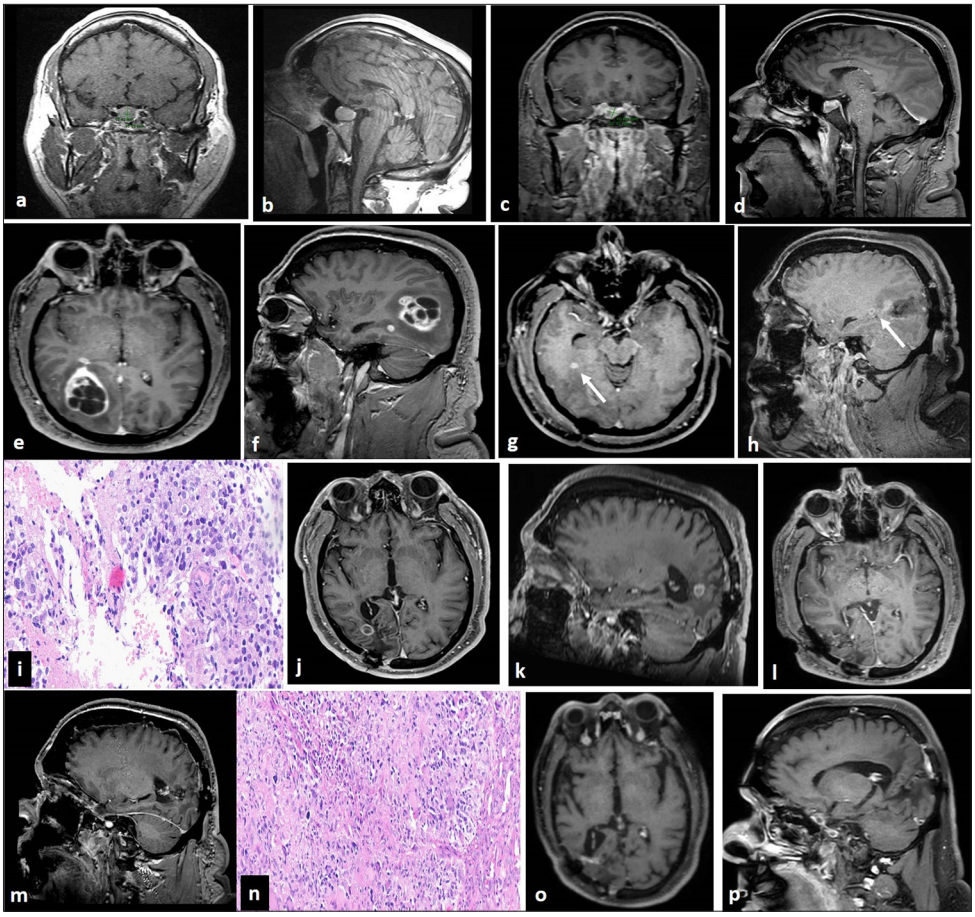

Figure 1: Case 1. All MR images are T1-weighted with gadolinium. In 2009 the patient was diagnosed with prolactinoma measuring 15*10mm: a) axial and b) sagittal views. In 2014 an MRI demonstrated reduction in size of the prolactinoma, measuring 12*10mm (c, axial view; d, sagittal view); However, a new, large, multifocal, necrotic, right occipital lesion was detected (e, axial view; f, sagittal view). The patient underwent resection of the occipital lesion with residual of a small lesion (arrow in g and h): g) axial and h) sagittal views. i) Pathology, H&E staining shows areas of pseudopalisading necrosis, microvascular proliferation, significant hypercellularity and nuclear atypia, confirming the diagnosis of a WHO Grade 4 GBM. In 2018 a small, asymptomatic recurrence was noted: j) axial and k) sagittal views. The patient underwent re-craniotomy with gross total resection of the tumor: l) axial and m) sagittal views. n) Pathology, H&E staining was again consistent with GBM, showing the typical features as in the original tumor. On his most recent MRI, done on November 2025, there are no radiologic signs of recurrence: o) axial and p) sagittal views. H&E= Hematoxylin and eosin; MRI= magnetic resonance imaging.

CASE 2

In March 2018, a 70-year-old male presented with a general functional deterioration over the past 4 weeks. His past medical history included Parkinson's disease, which was diagnosed in 1999. He was initially treated with selegiline only. Since 2004, he was treated with Sinemet (50/200; 5 tabs/day) and either PK-merz (200 mg/day) or pramipexole (Sifrol; 0.75 mg/day), depending on the severity of extrapyramidal symptoms. 19 years following his initial diagnosis of Parkinson's disease, he became less mobile, more confused, had recurrent falls, speech difficulties, and headaches. On neurological examination, he was partially oriented. He had severe rigidity in the 4 limbs. An MRI revealed a large (53 × 7 mm), left parietal intra-axial lesion, with heterogeneous enhancement, necrotic center, mild edema, and some infiltration of the splenium. The lesion was most consistent with high-grade glioma [Figure 3a-c]. He underwent an uneventful left, fluorescence-guided (using 5-aminolevulinic acid) craniotomy with the aid of intraoperative electrophysiology monitoring and had near total resection of the lesion (incomplete resection due to reaching functional boundaries of corticospinal tracts [Figure 3d and e]). Due to his general condition, he was

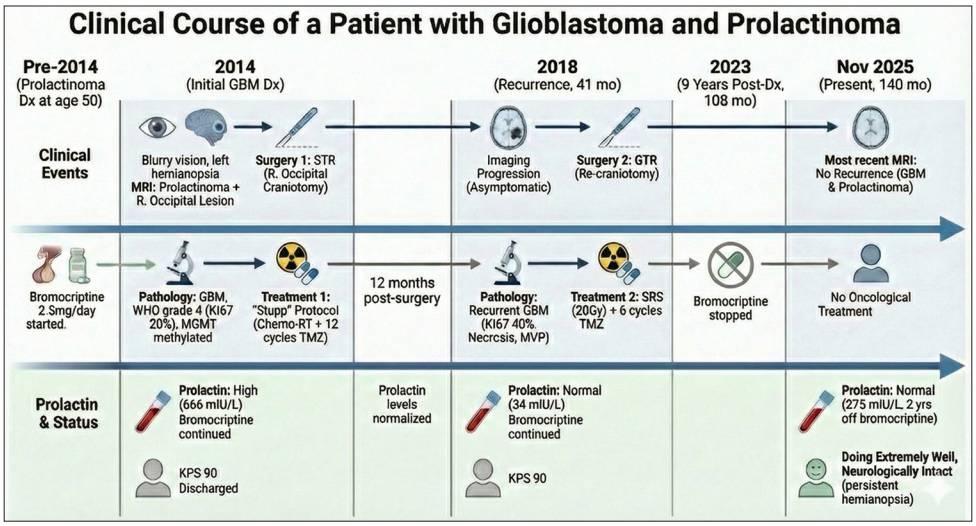

Figure 2: Case 1. Graphical illustration of major events in the clinical course along the timeline. See text for details. Chemo-RT: Chemoradiation therapy, Dx: Diagnosis, KPS: Karnofsky performance score, mo: Months, R: Right, SRS: Stereotactic radiosurgery, STR: Subtotal resection, TMZ: Temozolomide.

discharged 7 days post-surgery to a rehabilitation center. Pathology confirmed the diagnosis of GBM, grade 4 (IDH wildtype, MGMT-unmethylated; [Figure 3f]). Four weeks after surgery, he was given adjuvant chemoradiation therapy (the short "Stupp protocol") which he tolerated relatively well. Pre-treatment KPS was 50. Due to severe weakness, he only got 1 cycle of temozolomide (300 mg × 5 days/month). The patient has not received any more oncology treatments and continues with radiological and clinical follow-ups. During this period, he continued his treatment for Parkinson's disease. The initial MRI scan (July 2018) was consistent with pseudo-progression. Further MRIs have shown continuous improvement, with no radiologic signs of true progression for 15 months post-surgery [Figure 3g-i]. Nevertheless, the patient's condition continued to deteriorate, mainly due to progression of his Parkinson's disease, and he passed away in September 2019 (OS of 18 months). Figure 4 summarizes the patient's clinical course illustratively.

DISCUSSION

The definition of "long-term survival" varies by study but is often used to refer to GBM patients who have survived more than 3 years after diagnosis. In GBM, the OS rate is 6.8% at 5 years and 0.71% at 10 years[35] and the median PFS is only 7.4 months.[22] Over the past few decades, different therapeutic approaches such as angiogenesis inhibitors, immunotherapies, targeted therapies, and vaccines have been evaluated in clinical trials for patients with newly diagnosed or recurrent GBM with a modest improvement in OS and PFS. In fact, tumor treating fields are the only new therapy that has shown meaningful improvement in OS over the past decades[43] despite extensive worldwide research. Finding new treatments is crucial to improve the grim prognosis associated with this malignancy. In this regard, the field of drug repurposing is particularly attractive.

We presented two cases in which GBM adult patients who were treated with DRD2 agonists showed an unexpected improvement in survival. Our prolactinoma patient was treated with bromocriptine, an ergot alkaloid DRD2 agonist. On one hand, he was MGMT-methylated, a favorable prognostic factor. On the other hand, this important epigenetic profile is associated with a median OS of only 21.7 months.[14] In addition, he was IDH-wildtype, underwent subtotal resection, and had a recurrence, three unfavorable prognostic factors.[15,21] Yet, he is now >11 years since diagnosis without evidence of progression. Our Parkinson's disease patient was treated with pramipexole, a non-ergot dopamine agonist that binds with high selectivity and specificity to the dopamine D2 subfamily receptors, and with Sinemet, which increases the amount of available dopamine, which then activates DRD2. He was 70-years-old at diagnosis, had a subtotal resection, had a low KPS at the beginning of adjuvant treatment, and received minimal adjuvant therapy, all known unfavorable prognostic factors.[30,45] Based on established nomograms,[10] his predicted OS was merely 9 months. Yet, he had a PFS of 15 months and an OS of 18 months, twice as predicted. In fact, he was never diagnosed with true progression. A direct correlation between prolonged PFS and significantly longer median OS in GBM patients has been shown repeatedly.[15,46] It is possible that if he had not suffered from an end-stage Parkinson's disease, he might have been reaching a long-term OS. We realize that an OS of 18 months is not considered a long-term survival in GBM and that it falls within the known variability of GBM outcomes. Nevertheless, we are speculating that being treated

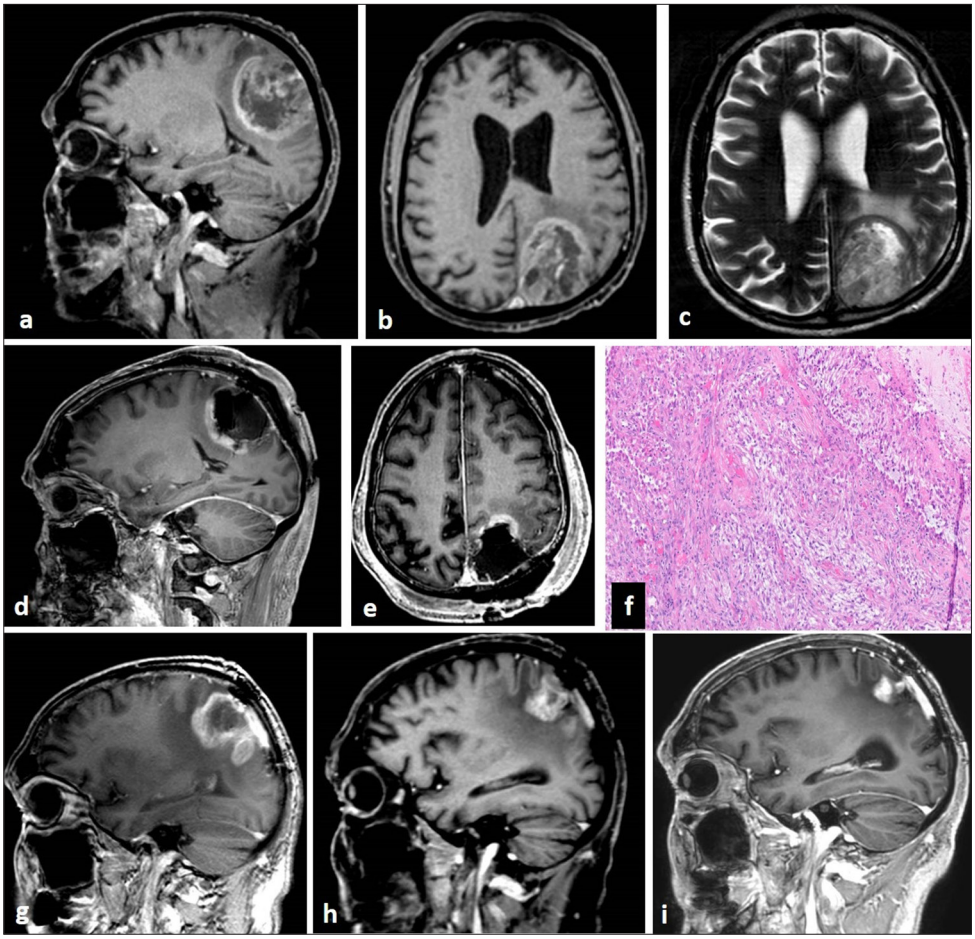

Figure 3: Case 2. On march 2018 an MRI scan showed a contrast enhancing, large, left parietal, intraaxial lesion with necrosis and surrounding edema: a) sagittal and b) axial views, T1-weighted with gadolinium; c) axial view, T2-weighted. The patient underwent subtotal resection of the lesion due to eloquence limitations: d) sagittal and e) axial views, post-operative, T1-weighted MR images with gadolinium. f) Pathology, H&E staining shows areas of pseudopalisading necrosis, microvascular proliferation, significant hypercellularity and nuclear atypia, confirming the diagnosis of a WHO Grade 4 GBM. A suspected progression was first noticed on July 2018 (g, T1-weighted with gadolinium, sagittal view), but follow up scans have shown significant shrinkage of the lesion, supporting the diagnosis of pseudo-progression (h - November 2018 and i – May 2019, T1-weighted with gadolinium, sagittal views).H&E= Hematoxylin and eosin

with dopamine agonists might have been associated with the described survival in both patients. In their thorough review on monoamines in GBM,[5] Caragher *et al.*[6] have remarked on the dual, yet contradictive, effect of dopamine in GBM: The pro-proliferative effect on one hand, advocating the use of DRD2 antagonists, and the anti-angiogenic effect on the other hand, advocating the use of DRD2 agonists. We will further discuss these important effects.

DRD2 antagonists in GBM

In a study by Caragher *et al.*,[6] DRD2 expression was increased in response to temozolomide treatment, promoted self-renewal of tumor cells, and augmented their growth, leading the authors to conclude that specific inactivation of DRD2 is required to provide therapeutic benefit in GBM. Other groups have shown that DRD2 inhibition is important for reducing GBM proliferation, whether as a single agent[18] or in conjunction with epithelial growth factor receptor (EGFR) antagonists.[29,32] Antipsychotic medications with DRD2 antagonist activity were also studied as potential treatment for GBM. For example, trifluoperazine was found to enhance the efficacy of radiotherapy in GBM.[4] Trifluoperazine was also found to inhibit GBM invasion.[19] Olanzapine was found to inhibit proliferation and migration in human GBM cell lines and to enhance temozolomide's

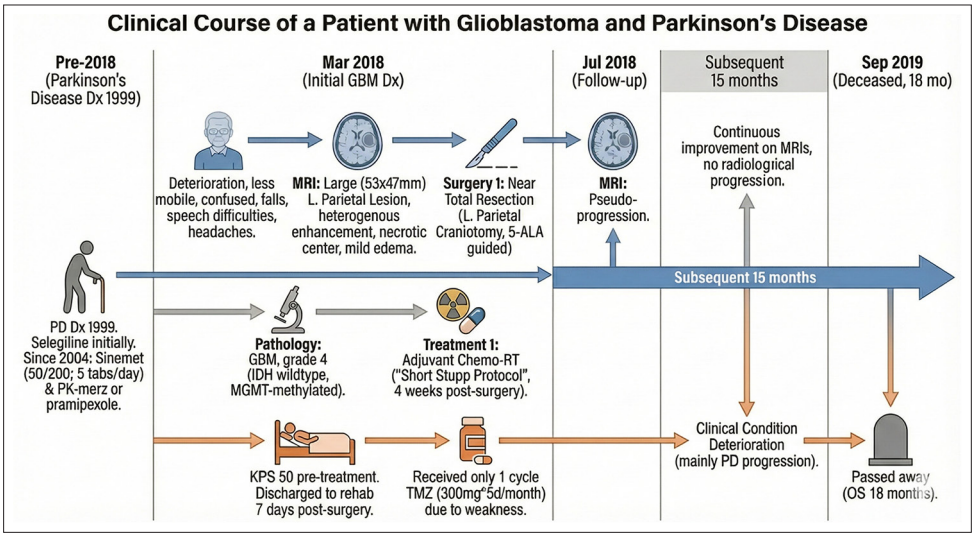

Figure 4: Case 2. Graphical illustration of major events in the clinical course along the timeline. See text for details. 5-ALA: 5- aminolevulinic acid, Chemo-RT: Chemoradiation therapy, Dx: Diagnosis, IDH: Isocitrate dehydrogenase, KPS: Karnofsky performance score, L: Left, mo: Months, PD: Parkinson's disease, TMZ: Temozolomide.

antiproliferative effect.[20] Haloperidol, through its anti-DRD2 activity, was suggested as an effective adjunct therapy to inhibit adaptive temozolomide resistance and to enhance the efficacy of chemoradiation therapy in GBM.[42] It was suggested that high EGFR expression is a determinant of poor GBM response to DRD2 antagonists. Accordingly, a phase 2 clinical trial is studying the safety and efficacy of ONC201 in adults with EGFR-low GBM (NCT04629209), emphasizing the possible need for a tailored therapy based on specific molecular characteristics of the tumor.

DRD2 agonists in GBM

ONC201 (dordaviprone), a DRD2 antagonist, has been recently approved by the FDA for recurrent diffuse midline glioma, and a phase 3 study for its use in newly diagnosed H3K27M-mutant diffuse midline glioma is currently ongoing.[2] Nevertheless, we are not aware of any clinical evidence in humans suggesting a survival benefit of a DRD2 antagonist in GBM, excluding a single case report.[9] ONC201 has been investigated in phase 2 clinical trials for recurrent GBM; however, this trial was administratively terminated. Furthermore, *in vitro* and *in vivo* studies have shown opposite results regarding the role of DRD2 in gliomagenesis.[26] Two studies have demonstrated that treatment with haloperidol, a DRD2 antagonist, in fact increases cell proliferation and neurogenesis in rodent brains.[13,24] Aripiprazole is a third-generation antipsychotic that has also been studied for repurposing against cancer.[31] Interestingly, unlike many other psychiatric drugs, aripiprazole is a partial DRD2 agonist, and some of its anti-tumor effects are attributed to activation of DRD2-related pathways,[28,31] including in glioma cell lines.[23,48] Apomorphine is another potent DRD2 agonist largely used for the treatment of Parkinson's disease. Its potential in anti-proliferative activity against different tumors, including GBM, has been described.[27,38] Parkinson's disease is characterized by the loss of dopaminergic neurons. A meaningful reduction in GBM prevalence was found in Parkinson's disease patients relative to controls in epidemiological studies,[8,25] suggesting that lack of dopamine protects from GBM development. However, another epidemiological study found that Parkinson's disease patients are at higher risk of glioma in the 1st year following diagnosis but are protected against glioma 5 or more years from diagnosis.[34] Dopamine deprivation may be associated with increased risk for GBM, but following treatment with dopamine agonists, the risk is substantially reduced. Together, these studies indicate that dopamine agonists may actually have potential as a novel therapy against human malignant glioma, especially through activation of DRD2. This potential is even greater when considering the anti-angiogenic effect of DRD2 activation, as further discussed

DRD2 and angiogenesis

Remarkably, dopamine has been shown to interact with the vascular endothelial growth factor (VEGF) pathway and induce multiple anti-angiogenic mechanisms, both in non-glioma[16,39,44] as well as glioma models.[3] More specifically, activating DRD2 signaling blocks the VEGF pathway.[1,3,40] VEGF primarily exerts its effects through VEGF receptor 2 (VEGFR2).[47] Using the cBioPortal and the Cancer Genome Atlas database on GBM samples (n = 2746),[7] we have found that the prevalence of genetic alteration in the genes

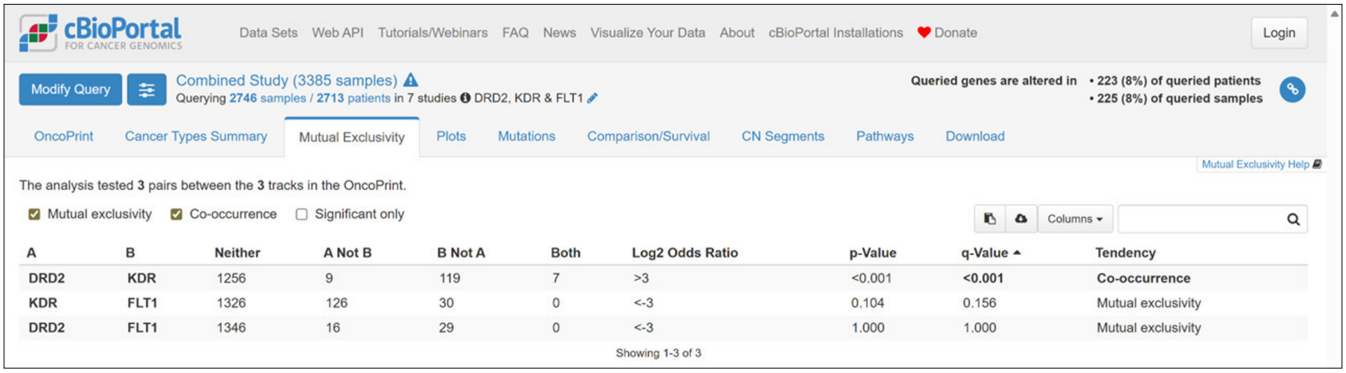

Figure 5: Screenshot taken from the cBioPortal website, showing a mutual exclusivity analysis in a cohort of 2746 glioblastoma samples. The analysis was performed on 3 genes: Dopamine receptor D2 (DRD2), vascular endothelial growth factor receptor 1 (Fms-like tyrosine kinase 1 [FLT1]) and vascular endothelial growth factor receptor 2 (Kinase insert domain receptor [KDR]). Statistically significant co-occurrence was observed between DRD2 and KDR. See text for further interpretation.

VEGFR1 (Fms-like tyrosine kinase 1), VEGFR2 (Kinase insert domain receptor), and DRD2 were 1%, 7% and <1% of cases, respectively; with gene amplification being the major alteration. Interestingly, alterations in VEGFR2 and DRD2 showed statistically significant co-occurrence ($P < 0.001$) [Figure 5]. This finding further supports a possible biological interaction or pathway relationship between DRD2 and VEGF in GBM pathogenesis.

Due to the availability of many FDA-approved drugs that affect dopamine-related pathways, it is critical for more research to unravel the precise mechanisms by which dopamine signaling influences both proliferation and angiogenesis in GBM.[5] It is possible that the use of a DRD2 agonist versus. The antagonist will be determined individually, taking into consideration the variable expression of dopamine receptors, and will be based on a detailed molecular profile of each tumor.

CONCLUSION

No significant improvement in GBM survival was reached despite decades of extensive research. Long-term survival in GBM has remained an extremely rare event. We described two GBM patients with improved survival parameters, one with significantly long OS. Both patients were treated with DRD2 agonists parallel to the course of their GBM. The therapeutic potential of DRD2 agonists in GBM is supported by accumulating data, especially through their effects on angiogenesis, a hallmark of GBM pathogenesis. Although our experience is limited and our conclusion is merely theoretical, we offer to consider including FDA-approved DRD2 agonists for the treatment of GBM in future clinical trials.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for their images and other clinical information to be reported in the journal. The patient understands that the patient's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was use of artificial intelligence (AI)-assisted technology for creating Figures 2 and 4 using Gemini 3. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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How to cite this article: Oxman L, Laviv Y. Long-term survival in glioblastoma patients treated with dopamine agonists: A report of two cases and implications for drug repurposing. Surg Neurol Int. 2026;17:340. doi: 10.25259/SNI_243_2026