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# Effect of Antidepressants on Glioblastoma Survival: A Systematic Review and Meta-analysis

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## ADMINISTRATIVE INFORMATION

**Support -** NA.

**Review Stage at time of this submission -** Formal screening of search results against eligibility criteria.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202470040

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 July 2024 and was last updated on 11 July 2024.

## INTRODUCTION

**Review question / Objective** Determine if Antidepressant therapy initiated before or during standard treatment (maximal resection followed by radiation and adjuvant chemotherapy) for adults with Glioblastoma (GBM) improves overall survival (OS) when compared to patients not on antidepressant therapy.
Patients:
- Adult patients (>18) with histologically/biospy confirmed GBM
Intervention:
- Antidepressant therapy in addition to standard of care
Comparator:
- Standard of care without antidepressant therapy
Outcomes
- Primary Outcome: Overall survival.

**Rationale** Despite advancements in the treatment of GBM, prognosis remains poor. Symptoms of depression are highly prevalent among patients with GBM and have been associated with poor outcomes. However, much of literature is inconclusive on whether the treatment of depression symptoms in GBM patients improves outcomes. Furthermore, there exist concerns that antidepressant may negatively GBM outcomes through downregulation of tumor inhibitor pathways.
In addition to managing depression symptoms, preclinical studies suggest that antidepressants may inhibit GBM progression and may be associated with improved outcomes. Several preclinical studies have identified Selective Serotonin Reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MOAIs), and tricyclic agents commonly used in the treatment of depression as having strong anti-GBM effects in both cell culture and mice models.3,5-8
Ultimately, depression rates are disproportionately high in patients with GBM. The treatment of depression in these patients may have improved survival. Preclinical studies also suggest that antidepressant therapy may improve survival via inhibition of growth receptors and other signaling pathways. However, the effect of antidepressants

on survival is unknown and results from existing studies are conflicting, with several recent retrospective studies reporting improved survival and others reporting either no effect or a detrimental effect on outcome. 9,10
We sought to perform a systematic review of the literature for any prospective, retrospective, or RCT studies that investigated the effect of antidepressant therapy on GBM survival and to perform a meta-analysis of these results. In doing so, we hope to better understand the true benefit of antidepressant therapy in the treatment of GBM.

**Condition being studied** Glioblastoma (GBM) is the most common primary malignant tumor of the brain, comprising nearly 50% of all central nervous system tumors. Despite improvements in care, it continues to carry a poor prognosis, with 5-year survival rates under 7% and an average survival time of 8 months post diagnosis. Depression is a common comorbidity of patients with GBM, with some studies suggesting rates ranging from 33% to 44%.11 Consequently, studies have shown that depression is associated with worsened outcomes in GBM. However, the effects of antidepressant therapy on GBM patient populations remains understudied and poorly understood.

## METHODS

**Search strategy** Concept1(Antidepressant Agents) AND Concept2(Glioblastoma) NOT ('animal'/exp NOT 'human'/exp)
(('antidepressant agent'/exp OR(anti-depress* OR antidepress* OR neurothymoleptic OR psychoenergizer OR thymoleptic OR thymolytic-agent):ti,ab,kw) OR ('serotonin uptake inhibitor'/de OR 'serotonin noradrenalin reuptake inhibitor'/de OR 'monoamine oxidase inhibitor'/exp OR (SSRI*OR SNRI*OR SSNRI* OR((serotonin OR'dual uptake' OR 'dual reuptake' OR noradrenalin OR monoamine OR dopamine OR norepinephrine OR MOA) NEAR/2 (inhibit*))):ti,ab,kw) OR('citalopram'/de OR (acelopam OR adeprenal OR apo-cital OR aurex OR ceform OR celexa OR cilopress OR cinavol OR ciprager OR cipram OR cipramil OR cipraned OR ciprotan OR ciral OR citabax OR citacip OR citagen OR cital* OR citalon* OR citalopram OR citalostad OR citalox OR citalvir OR citapram OR citaxin OR citesint OR citopam OR citrol OR citronil OR cytalopram OR dalsan OR elopram OR exenadil OR frimaind OR futuril OR galopran OR humorap OR kaidor OR kitapram OR linisan OR lopracil OR lopraxer OR loxopram OR lupram OR malicon OR nitalapram OR oropram OR percitale OR pralotam OR pramital OR prefucet OR pricital OR prisdal OR psiconor OR renevil OR ricap OR ropramin OR selon OR sepram OR seralgan OR seregra OR serital OR seropram OR seror OR sintopram OR sotovon OR talam OR talosin OR varom OR vesema OR xadorek OR zanipram OR zeclicid OR zentius OR zitolex OR zyloram):ti,ab,kw) OR ('escitalopram'/de OR (aciprex OR amasci OR anxila OR apoescitaxin OR betesda OR cipralex OR citafort OR citram OR clomentin OR depralin OR depresinal OR diprex OR ecytara OR elicea OR entact OR escidivule OR escipram OR esciprex OR escirdec OR escital* OR escitalopram OR escitalpro OR escitil OR esertia OR eslorex OR esoprex OR espoza OR estan OR etalopro OR giachela OR heipram OR itakem OR lenuxin OR lexapro OR mersinol OR miraklide OR mozarin OR nexpram OR oroes OR pralex OR pramatis OR prameffex OR pramulex OR premalex OR prilect OR raldon OR ratice OR scippa OR serodeps OR seroplex OR serpentil OR servenon OR sipralexa OR symescital OR tepram OR zecidec OR zocital):ti,ab,kw) OR ('fluoxetine'/de OR (Actan OR adofen OR afeksin OR andep* OR animex-on OR ansilan OR auroken OR auscap OR bioxetin OR captaton OR daforin OR dagrilan OR depren OR deprex-leciva OR deprexetin OR deprexin OR deprizac OR deproxin OR diesan OR digassim OR elizac OR eufor OR exostrept OR felicium OR fldiss OR flotinal OR floxet OR fluctin* OR fludac OR flufran OR fluketin OR flunil OR flunirin OR fluocim OR fluohexal OR fluoksetin OR fluoksetyna OR fluox OR fluoxac OR fluoxeren OR fluoxetin* OR fluoxifar OR fluoxil OR fluoxin OR fluoxone OR fluoxtab OR fluronin OR flusac OR flustad OR flutin OR flutine OR fluxemed OR fluxen OR fluxet* OR fluxil OR fluxomed OR fluzac OR fluzak OR fokeston OR fontex OR foxetin OR foxtin OR fropine OR fuloren OR gerozac OR ladose OR lanclic OR lorien OR lovan OR luramon OR magrilan OR margrilan OR meropan OR modipran OR mutan OR nopres OR nuzak OR olena OR oxactin OR oxedep OR plazeron OR plinzene OR pragmaten OR prizma OR proctin OR prodep OR prosac OR prozac OR prozamel OR prozamin OR prozep OR prozit OR psipax OR psiquial OR qualisac OR rapiflux OR reconcile OR reneuron OR rowexetina OR salipax OR sanzur OR sarafem OR sartuzin OR selfemra OR serelsa OR seromex OR seronil OR sinzac OR sofelin OR tuneluz OR veritina OR xeredien OR zactin OR zepax OR zinovat):ti,ab,kw) OR ('paroxetine'/de OR
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OR ainim OR altisben OR altruline OR aremis OR asentra OR aserin OR asertin OR atruline OR besitran OR certorun OR contulen OR depreger OR dominum OR doxime OR enidap OR enore OR epilyd OR ferbrain OR fridep OR gladem OR lesefer OR lustral OR luxeta OR miravil OR neurosedine OR nudep OR sastium OR seltra OR semonic OR sercerin OR serimel OR serlain OR serlan OR serlift OR serlin OR serolux OR seromeg OR sertabal OR sertadepi OR sertagen OR sertral OR sertralet OR sertraline OR sertralon OR sertranat OR sertranex OR sertranorm OR sertranquil OR sertrone OR serunato OR setaloft OR sonalia OR sosser OR stimuloton OR tatig OR tresleen OR zolof OR zoloft OR zolotrin OR zortal OR zosert OR zotral):ti,ab,kw) OR ('desvenlafaxine'/exp OR (desvenlafaxine OR desmethylvenlafaxine OR ellefore OR khedezla OR norvenlafaxine OR Pristiq OR pristiqs):ti,ab,kw) OR ('duloxetine'/exp OR (ariclaim OR cymbalta OR drizalma OR dulane OR duloxetine OR duzela OR irenka OR nodetrip OR xeristar OR yentreve):ti,ab,kw) OR ('milnacipran'/exp OR (dalcipran OR fetzima OR impulsor OR ixel OR joncia OR levomilnacipran OR midalcipran OR milnacipran OR milnaneurax OR savella OR toledomin):ti,ab,kw) OR ('venlafaxine'/exp OR (alventa OR amphero OR apclaven OR 'arafaxina retard' OR axyven OR bonilux OR depefex OR deprevix OR dobupal OR duofaxin OR efaxine OR efectin OR efexor OR effexor OR effexstad OR elafax OR elify OR faxigen OR faxiprol OR faxiven OR faxolet OR fobiless OR genexin OR hapixed OR ireven OR lafactin OR lanvexin OR majoven OR olwexya OR oriven OR pracet OR prefaxine OR serosmine OR sigven OR sivion OR sunveniz OR symfaxin OR tonpular OR trevilor OR trewilor OR vandral OR vaxor OR vedixal OR velafax OR velaxin OR velept OR venaxx OR vencarm OR venex OR venla OR venlablue OR venlabrain OR venladex OR venlafab OR venlafaxin OR venlafaxina OR venlafaxine OR venlafex OR venlagamma OR venlalic OR venlaneo OR venlasov OR venlatev OR venlax OR venlaxin OR venlaxor OR venlazid OR venlectine OR venlofex OR venlor OR venprimeven OR vensir OR vensuerteven OR venxin OR venzip OR vexarin OR viepax OR xenalven OR zacalen OR zaredrop OR zarelis OR zarelix OR venlafaxine):ti,ab,kw) OR('atypical antidepressant agent'/exp) OR('amfebutamone'/exp.

**Participant or population** Adult patients (>18) with histologically confirmed GBM including all IDH statuses and MGMT methylation status.

**Intervention** Antidepressant therapy in addition to standard of care.

**Comparator** Standard of care without antidepressant therapy.

**Study designs to be included** Randomized Clinical Trials, Observational Studies.

**Eligibility criteria** Study exclusion criteria: Case reports, pilot reports, opinion pieces, theses, conference proceedings, letters, editorials, meta-analysis, reviews, surgical technique papers, abstracts, presentations, and non-english language publications without translation.

**Information sources** PubMed, Embase, Scopus, PsycINFO, Web of Science.

**Main outcome(s)** Overall survival.

**Additional outcome(s)** Articles selected will be stored in Covidence for screening of studies and data extraction.
Selection process:
Two independent reviewers will assess remaining articles for relevance first based on titles and abstracts, and then will assess full-text articles for eligibility. Disagreements between reviewers will be resolved in both phases by either consensus or by a third reviewer.
Data Collection Process:
Each selected study will be distributed to two individuals for data extraction in duplicate using Covidence with preselected variables (see data items below). We anticipate no effort needed to contact authors of selected studies to obtain patient level data.
Data items for extraction:
- Study: (First author name followed by et al.)
- Year of publication
- Overall survival
- Effect size for antidepressant usage
- Odds ratio for antidepressant usage
- Hazard ratio for antidepressant usage
- Upper limit CI for each pre-defined outcome variable
- Lower limit CI for each pre-defined outcome variable
- Difference in survival
- Study size (number of patients in each treatment group)
- Standard Error (calculated)
- Demographic and patient enrollment characteristics
Metadata:
- Journal name where study was published.
- Year of publication
- Enrollment criteria
Analysis approach:
- Intention-to-treat vs per-protocol.

- Adherence to CONSORT or STROBE
- Potential sources of bias.

**Quality assessment / Risk of bias analysis** Risk of bias will be determined for each study via the ROBINS-I tool. Quality will also be addressed by assessing compliance to research reporting guidelines such as STROBE. Competing interests in each study will be noted if any author had ties to industry particularly those funded by an industry sponsor.

**Strategy of data synthesis** We expect variability in patient selection among the studies. Therefore, we plan on using a random-effects model with restricted maximum-likelihood estimation to perform. We plan on using an inconsistency index (I2) to assess for heterogeneity. We will also be calculating the mean difference in survival between treatment groups.

**Subgroup analysis** If available, separations based on antidepressant class and timing of therapy initiation will be made.

**Sensitivity analysis** We will perform a sensitivity analysis utilizing the copas selection model and the leave-one-out method.12 The magnitude of heterogeneity will be assessed with the I2 value. Publication bias will be assessed via Egger's method and assessed visually using funnel plots. All statistical analyses were performed using R (version 4.3.1).13 Packages utilized will include the meta package and its add-on, metasens.14,15 Alpha will be set at 0.05 and all test of significance will be 2-sided. Data and syntax used for the analysis will be made publicly available through GitHub.

**Language restriction** English.

**Country(ies) involved** United States.

**Keywords** Glioblastoma, GBM, Antidepressants, Survival.

**Contributions of each author**

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