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Antidepressants and survival in glioma—A registry-based retrospective cohort study

Sonja Edström, Barbro Numan Hellquist, Maria Sandström, Sajna Anand Sadanandan, Benny Björkblom, Beatrice Melin†, and Rickard L. Sjöberg†,

All author affiliations are listed at the end of the article

Corresponding Author: Rickard L. Sjöberg, MD, PhD, Department of Clinical Sciences, Neurosciences, Umeå University, S901 85 Umeå, Sweden (rickard.sjoberg@umu.se).

†These authors contributed equally to the present paper.

Abstract

Background. Depression and treatment with antidepressant medication is common in patients with malignant glioma. However, the extent to which antidepressants may affect the disease is not fully understood. Therefore, the purpose of the present study was to investigate possible associations between treatment with antidepressant medication and survival in glioma patients.

Methods. We performed a registry-based cohort study including 1231 patients with malignant glioma (WHO grades 2, 3, and 4) having undergone surgery, and 6400 matched controls without glioma. All data were extracted from the RISK North database, which contains information from multiple national population-based registries in Sweden.

Results. Treatment with antidepressants is more common in patients with malignant glioma (27%), compared to controls (16%), $P < .001$. Treatment with antidepressants after surgery for glioma was significantly associated with poorer survival. These effects were observed both for selective serotonin reuptake inhibitors (SSRIs) and non-SSRIs. In grade 4 glioma, SSRI treatment was associated with a hazard ratio (HR) of 3.32 (95% CI 2.69–4.10, $P < .001$), and non-SSRI treatment a HR of 3.54 (95% CI 2.52–4.99, $P < .001$), compared to glioma patients without antidepressants. In grade 2-3 glioma, the HR for SSRI treatment was 3.26 (95% CI 2.19–4.85, $P < .001$), and for non-SSRI treatment was 7.71 (95% CI 4.22–14.12, $P < .001$).

Conclusions. Our results demonstrate a negative association between antidepressant medication and survival in glioma. Further research will be needed to clarify causation.

Keywords:
antidepressants | glioma | SSRI | survival

During the last decade, multiple studies have investigated how antidepressant medication affects survival in patients with malignant glioma. Despite this, no consensus has been reached.

Previous studies have hypothesized that selective serotonin reuptake inhibitors (SSRIs) could have beneficial effects on survival in glioma and have been able to show a positive association between SSRI use and survival in smaller cohorts.[1,2] Other studies have investigated the same association in slightly larger cohorts and found no clear association.[3,4] However, when Seliger et al. used a cohort of 1700 glioma patients, a significant association between reduced overall survival and use of antidepressants was found.[5]

Despite the lack of conclusive evidence regarding their effect on survival, use of antidepressants is common among patients with glioma.[6,7] Considering the already dismal prognosis of patients with malignant glioma as well as the frequent use of antidepressant medication, further evidence from large cohorts is needed. We therefore used Swedish national population-based registries to study associations between antidepressant use and survival in 1231 patients with malignant glioma (WHO grades 2, 3, and 4) treated in Sweden. We also compared survival outcomes in glioma patients treated with SSRI and non-SSRI antidepressants. Additionally, we determined the prevalence of treatment of depression with antidepressants in

our cohort and compared it to the prevalence among 6400 matched controls without a glioma diagnosis.

Materials and Methods

The RISK North Database

The data used in this study were extracted from the RISK North database, which contains data from several Swedish national registers, and has previously been described in detail.[8] The 1231 cases included in the cohort were diagnosed with glioma between 2009 and 2013 and were originally registered in the National Quality Register for Brain Tumors, with both ICD-code for the glioma diagnosis, and SNOMED-code for WHO-grading. For this study, ICD-codes 1930 (ICD7), 191 (ICD9), and C71 (ICD10) were used to identify a glioma diagnosis. SNOMED-code 94403 was used to distinguish high-grade from low-grade glioma. We decided to use date of surgery as a start of follow-up, in order to limit inclusion to histologically verified cases.

The completeness in registration of diagnoses in the National Quality Register for Brain Tumors varied between the 6 Swedish healthcare regions during the specified period.[9,10] Therefore, only regions with high coverage (≥97%) were included in this study. These regions were northern-, middle-, and south-eastern regions and the Stockholm-Gotland region. Coverage in this database was validated through comparison with data in the Swedish Cancer Registry to which all cancer cases are reported by legal mandate.

Through the RISK North database, each glioma case was matched with 5 controls without a glioma diagnosis from the Total Population Register. The 6400 controls were matched based on age and gender. Cases and controls that have been prescribed antidepressants were identified using data from the Swedish Prescribed Drug register, which has a 99% coverage of prescriptions.[11]

Inclusion and Antidepressant Use

In this study, cases with malignant gliomas (WHO grades 2, 3, or 4) were included. Cases were divided into 2 groups based on grade, with grade 4 (high grade) in one group and grade 2 and 3 (lower grade) in the other. The 1231 glioma cases were cross-referenced with the Prescribed drug register to identify prescriptions of antidepressant medications that occurred at any point after each patient's date of surgery (between 2009 and 2013) until death or end of follow-up. Cases who were currently taking antidepressants at the time of their diagnosis or had received antidepressants prior were excluded. We used the Patient register to identify depression diagnoses and identified four patients with a depression diagnosis but no antidepressant use in the Prescribed drug register. Due to the small number of patients, this group was not further investigated. The Patient register is not as reliable in terms of consistency and coverage as the Prescribed drug register. Therefore, antidepressant use was solely identified based on a history of prescriptions and not a diagnosis of depression. Antidepressant use among controls was identified using the same method.

Definitions of Antidepressants

Antidepressants were categorized into 2 groups: SSRI (ATC N06AB) and non-SSRI. In the non-SSRI group, N06A antidepressants other than N06AB SSRI were included (N06AA, selective monoamine reuptake inhibitors, N06AF monoamine oxidase inhibitors, nonselective, N06AG monoamine oxidase A inhibitors, and N06AX Other antidepressants). A detailed description of the drugs in each category is given in Supplementary Table 1.

Statistical Analyses

The Pearson's Chi-square test was used to test for differences in proportion, for example, proportion of cases and controls prescribed antidepressant medication after glioma diagnosis (or the corresponding date for controls). Hazard ratios (HRs) were estimated in uni- and multivariable Cox proportional hazards models, with prescription of antidepressants as time-dependent covariates, since exposure started after the start of follow-up. In addition, age, sex, and type of surgery were included in the analysis.

We used Kaplan-Meier curves to crudely illustrate the survival probability, they are, however, not adjusted for any covariates nor for the time-dependent nature of the antidepressant covariate. Survival time was calculated from the date of surgery to the date of death or last follow-up (2019-12-31). Type of surgery was divided into biopsy and resection. The Cox proportional hazards were performed with glioma cases without antidepressants as a reference for SSRI and non-SSRI-treated cases (Table 4), as well as an additional analysis with non-SSRI as a reference for SSRI-treated patients (Table 5). We also performed a Bonferroni-adjusted Chi-square test to assess possible geographical differences between the northern region of Sweden and the other Swedish regions included (middle-, south-eastern regions, and the Stockholm-Gotland region).

Results are presented for grade 4 and grade 2-3 separately. Some of the analyses additionally contain data on grades 2, 3, and 4 combined. All tests were two-sided, and $P < .05$ was considered statistically significant. Statistical analyses were performed using R version 4.0.3 (R Core Team, Vienna, Austria).

Ethics Statement

The current study falls within the aims of the RISK North database approved by the Regional Board of Ethics in Umeå (2014/278-31), and the Swedish Ethical Review Authority (2023-03199-01).

Results

Descriptive Data

A total of 1231 glioma patients having undergone surgery were included in the study, 59% males and 41% females (Table 1). Most patients were diagnosed with grade 4 glioma (61%). Resection was the most common surgical procedure (74%), which was consistent across high- and

low-grade gliomas. The mean age at time of diagnosis for the whole data set was 63 years, but those diagnosed with grade 4 glioma were slightly older than those with grade 2-3 (Table 1). The mean survival from time of diagnosis was 16 months in grade 4 glioma, and 27 months in grade 2-3 glioma.

A total of 346 patients (28%) were prescribed an antidepressant at any point after surgery (Table 1). There were no significant differences in prevalence of antidepressant medication between men and women (28% and 29%, respectively) or grade 4 compared to grade 2-3 (27% and 30%, respectively). The definition of non-SSRI, with medications included in this category is specified in the Methods section. Details on antidepressant drugs prescribed are given in Supplementary Table 1.

Descriptive statistics for antitumoral treatment are presented in Table 2, which shows the prevalence of antitumoral in patients receiving antidepressant treatment (SSRI or non-SSRI) and those who did not. In grade 4 glioma, 51% of SSRI-treated patients and 48% of patients treated with non-SSRI received antitumoral treatment, compared to 52% of patients who were not treated with antidepressants. For grade 2-3 glioma, 20% of SSRI-treated patients and 16% of non-SSRI-treated patients received antitumoral treatment, compared to 20% of patients who were not treated with antidepressants. Unfortunately, the reporting of antitumoral treatment in the database was limited, showing inconsistencies and large amounts of missing data.

Treatment With Antidepressants is Significantly More Common Among Glioma Patients

The prevalence of prescription of antidepressants was significantly higher in patients with glioma compared to matched controls without glioma (27% vs 16%, $P < .001$, Table 3). This was also true when looking at SSRI antidepressants (18% vs 10%, $P < .001$, Table 3), and non-SSRI antidepressants separately (13% vs 8%, $P < .001$, Table 3). We also analyzed possible differences in prevalence in prescription of antidepressants between northern and southern Sweden, but no differences were found (Supplementary Table 3).

Table 1. Descriptive Data

		All	Grade 4	Grade 2-3
Cases	Total, *n* (%)	1231	754 (61)	477 (39)
	Male/female, %	59/41	61/39	56/44
Surgery	Biopsy/resection, %	26/74	27/73	26/74
Prevalence of antidepressant medication[a]	Total, *n* (%)	346 (28)	205 (27)	141 (30)
	Male, *n* (%)	200 (28)	121 (26)	79 (30)
	Female, *n* (%)	146 (29)	84 (28)	62 (30)
Selective serotonin reuptake inhibitor (SSRI)/non-SSRI[b]	Total, %	58/42	60/40	57/43
Mean age[c]	Years	63	64	59
	Male/female, years	62/64	63/66	59/59
Mean survival[d]	Months	19	16	27

aPercentage of patients treated with antidepressants compared to group or subgroup total.
bDistribution of SSRI or non-SSRI treatment within groups.
cAt time of diagnosis.
dFrom time of surgery.

Table 2. Prevalence of Postoperative Antitumoral Treatment in Glioma Patients With and Without Antidepressant Medication

	Antidepressant Treatment	Concomitant Chemo- and Radiotherapy	Missing Data[a]
Grade 4	No antidepressants, %	52	46
	Selective serotonin reuptake inhibitor (SSRI), %	51	47
	Non-SSRI, %	48	51
Grade 2-3	No antidepressants, %	20	78
	SSRI, %	24	74
	Non-SSRI, %	16	84

aMissing data include all cases who were not registered as receiving concomitant antitumoral treatment. Therefore, it can include cases who received treatment but were not registered and cases who did not receive treatment due to poor registration.

Table 3. Chi-Square Test for Comparison of Prevalence of Treatment With Antidepressants in Glioma Cases and Matched Controls Without Glioma

Treatment	Cases, *n* (%)[a]	Controls, *n* (%)	*P* value
All antidepressants	340 (27)	965 (16)	< .001
Selective serotonin reuptake inhibitor (SSRI)	225 (18)	638 (10)	< .001
Non-SSRI	166 (13)	506 (8)	< .001

aPrevalence of antidepressant medication among total cases and controls.
Due to matching of glioma cases and controls without glioma based on time, the number of cases is 340 patients in this analysis compared to that of the whole cohort presented in Table 1 (*n* = 346).

Table 4. Uni- and Multivariable Cox Proportional Hazards Models Showing Hazard Ratio for Death in Glioma Patients Receiving Selective Serotonin Reuptake Inhibitor (SSRI) or Non-SSRI Treatment With Glioma Patients Without Antidepressants As a Reference

		Univariable			Multivariable		
Treatment	Grade	HR	CI	*P* value	HR	CI	*P* value
SSRI	Grade 4	3.45	2.79–4.26	< .001	3.32	2.69–4.10	< .001
	Grade 2-3	5.15	3.49–7.61	< .001	3.26	2.19–4.85	< .001
Non-SSRI	Grade 4	3.29	2.34–4.62	< .001	3.54	2.52–4.99	< .001
	Grade 2-3	4.41	2.42–8.03	< .001	7.71	4.22–14.12	< .001

Use of Antidepressants After Surgery is Associated With Poorer Survival Among Glioma Patients

Use of antidepressants, either SSRI or non-SSRI, after surgery for glioma was associated with a significant reduction in survival. The Kaplan-Meier plot (Figure 1) illustrates the crude survival difference between glioma patients treated with SSRI or non-SSRI compared to those who were not treated with any antidepressant. In both high-grade and low-grade gliomas, survival probability is reduced in SSRI-treated patients.

In the multivariable Cox regression, grade 4 glioma, SSRI use was associated with a HR for death of 3.32 (95% CI 2.69–4.10, $P < .001$, Table 4), and non-SSRI use was associated with a HR of 3.54 (95% CI 2.52–4.99, $P < .001$, Table 4), both compared to glioma patients without any antidepressant. The multivariable Cox regression analysis was adjusted for sex, age, and type of surgery, for which details are shown in Supplementary Table 2. When using patients treated with non-SSRI antidepressants as a reference for SSRI-treated patients, there was no significant difference in HR for death (HR = 0.94, 95% CI 0.64–1.37, $P = .737$, Table 5), which indicates that there is no difference in effect on survival between the 2 groups of antidepressants.

For grade 2-3 glioma, non-SSRI antidepressants were associated with the strongest negative effect on survival (HR = 7.71, 95% CI 4.22–14.12, $P < .001$, multivariable analysis Table 4). Selective serotonin reuptake inhibitor treated patients showed a HR for death of 3.26 (95% CI 2.19–4.85, $P < .001$, multivariable analysis Table 4). Glioma patients treated with SSRI showed a HR of 0.42 compared to patients treated with non-SSRI (95% CI 0.21–0.84, $P = .013$, Table 5), showing a significant difference in survival between the two groups of antidepressants in grade 2-3 glioma patients.

Discussion

The main findings of the present study were that the use of antidepressants was significantly more common in glioma patients compared to matched controls, but also that the use of antidepressants correlated with reduced survival. The negative effects were seen across tumor grades, and regardless of choice of antidepressant. The largest negative effect on survival was seen in patients with grade 2-3 glioma treated with non-SSRI, whereas no significant difference between SSRI and non-SSRI use and survival was found in grade 4 glioma. The direction of our results is largely consistent with the trends reported in the publication by Seliger et al., where antidepressant use was associated with reduced overall survival in a large cohort of glioma patients in clinical trials.[5] However, our study has some methodological differences, most importantly the fact that it was population-based, that both high- and low-grade gliomas were included, and that the prevalence of antidepressant use was higher.

The interest in antidepressants in treatment of glioma goes beyond their anti-depressive effect and is based on molecular hypotheses of interactions between glial cells and monoamines.[12–15] Earlier studies have shown that gliomas arise from a type of neural progenitor cell that are sensitive to dopamine and serotonin.[16,17] There is also evidence of in vitro sensitivity of glioma cell lines to perturbations in serotonin signaling,[18] and our group has previously showed that intratumoral serotonin metabolism appears to differ between different glioma subgroup.[19] In

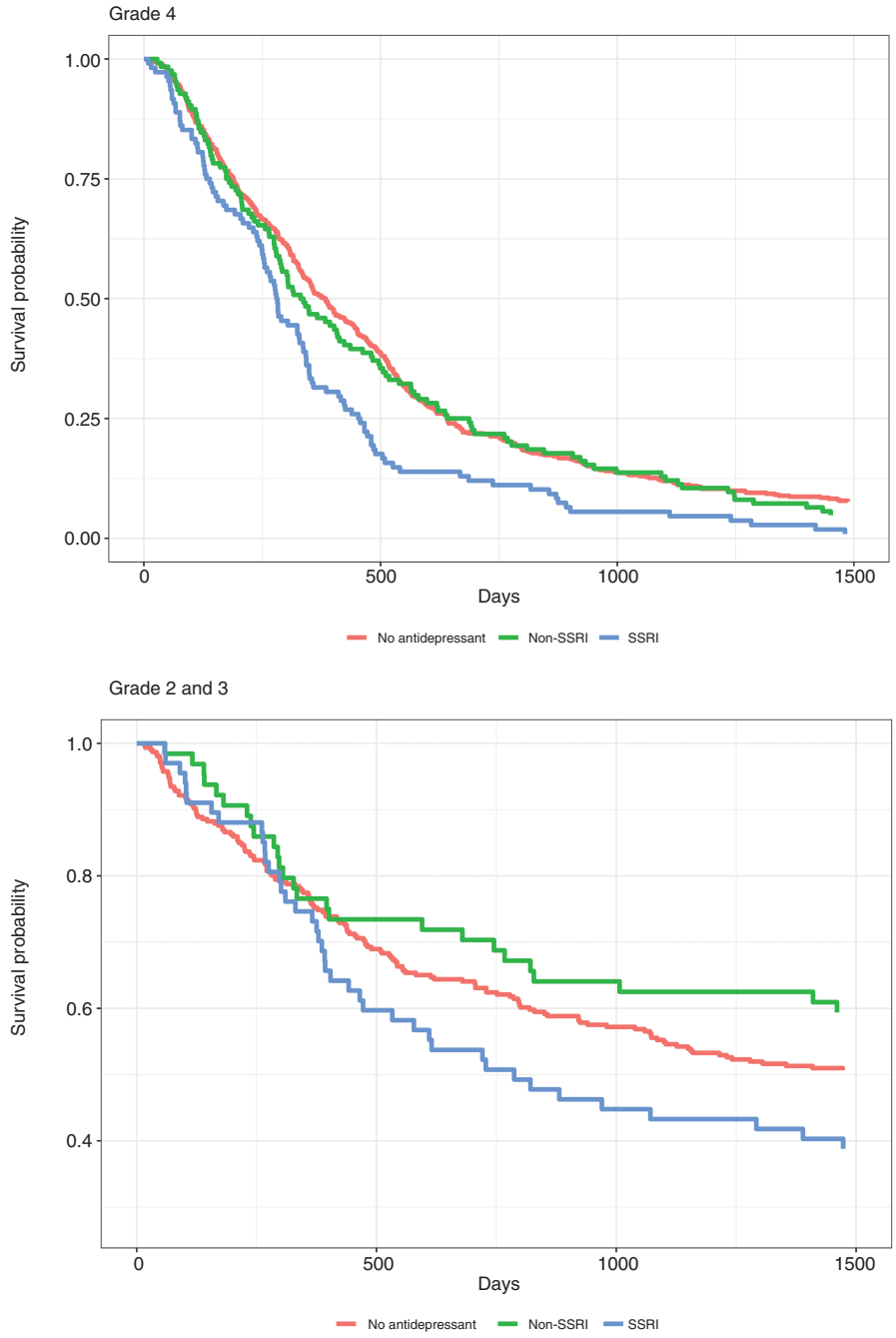

Figure 1. Kaplan-Meyer estimates for survival in grade 4 (top) and grade 2-3 (bottom) treated with selective serotonin reuptake inhibitor (SSRI) (blue) or non-SSRI (green) compared to no antidepressants (red), showing reduced survival in patients treated with SSRI. These estimates are unadjusted and in contrast to the Cox regression, antidepressants are not included as time-dependent covariates.

Table 5. Multivariable Cox Proportional Hazards Model Showing Hazard Ratio for Death in Selective Serotonin Reuptake Inhibitor (SSRI)-Treated Patients With Non-SSRI-Treated Patients Used As a Reference

Grade	HR	CI	*P* value
Grade 4	0.94	0.64–1.37	.737
Grade 2-3	0.42	0.21–0.84	.013

addition, some observations from other cancer forms also suggest the possibility that antidepressant medications may induce changes in tumor microenvironment that may at times have a negative impact on patient survival.[14,20] Consequently, there are multiple pathways through which antidepressants may affect gliomagenesis and possibly also progression of gliomas.

Even though we were able to demonstrate that antidepressants have a clear negative association with survival in glioma patients, we cannot conclusively determine the cause. The relationship between depression, use of antidepressants and survival in glioma is affected by multiple mechanisms and possible confounding factors. It is known that depression is a negative prognostic factor in glioma, and that the causation is multifactorial.[7,21] There is a behavioral aspect of depression, which can negatively affect the general health status of the patient through a reduction in self-care behavior/lifestyle, but also willingness to continue oncological treatment.[5,21–23] The glioma-depression association becomes even more complicated because living with a serious disease with poor prognosis may lead to behaviors and a subjective outlook on life that may mimic depression in otherwise healthy individuals but have other causes.[21] Some further limitations of the present study were that there are factors known to be important when investigating survival in glioma patients that we have not been able to adjust for, such as methylation and performance status. Data as such were not available through the RISK North database. Another limitation is the fact that severity of depression is not adjusted for, and that we were unable to isolate the possible effects of depression per se. Data on dosage of antidepressant medication, compliance to treatment, indices of severity of depression, or where the patient was treated were not available through the registers used in this study.

In conclusion, whether it is the depression/need for antidepressants itself that causes a reduction in survival, or if there are direct pharmacological mechanisms through which antidepressants negatively affect gliomas is still not understood. However, the significant negative association between survival and antidepressants in this study, in combination with frequent prescription warrants further studies, and possibly a more careful consideration of possible risk versus benefit when considering antidepressant treatment for patients with glioma.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Conflict of Interest Statement

None declared.

Authorship Statement

Experimental design: R.L.S., B.M., B.N.H., B.B. Analysis: R.L.S., B.M., B.N.H., S.E. Interpretation of the data: all authors. Drafting of the manuscript: S.E., S.A.S., R.L.S. Revision of manuscript to final version: all authors.

Data Availability

The data sets generated and analyzed in the study can be made available from the corresponding author upon reasonable request. Access to the data will be provided in compliance with applicable data protection and privacy regulations, since they originally were collected and processed in accordance with local ethical guidelines and laws. Researchers interested in accessing the data may contact the corresponding author at rickard.sjoberg@umu.se.

Affiliations

Department of Clinical Sciences, Neurosciences, Umeå University, Umeå, Sweden (S.E., S.A.S., R.L.S.); Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden (B.N.H., M.S., B.M.); Department of Chemistry, Umeå University, Umeå, Sweden (B.B.)

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