Use of tricyclic antidepressants and risk of glioma: a nationwide case–control study

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Background: A protective effect of tricyclic antidepressants (TCAs) against gliomas has been suggested by a small number of studies. We investigated this putative association in a nationwide setting.

Methods: Using a case–control design, we identified all patients with histologically verified glioma (cases) in Denmark between 2000 and 2012 and matched these 1 : 20 to population controls. Conditional logistic regression was used to estimate adjusted odds ratios (ORs) for glioma associated with long-term (>3 years) use of TCAs. Similar analyses were performed for selective serotonin reuptake inhibitors (SSRIs).

Results: We identified 3767 glioma cases and 75 340 population controls. Long-term use of TCAs was inversely associated with risk of glioma (OR 0.72, 95% CI: 0.41–1.25). Long-term SSRI use was not associated with glioma risk (OR 0.93, 95% CI: 0.75–1.16).

Conclusions: Our study indicated that long-term use of TCAs may be associated with a reduced risk of glioma, however, the statistical precision was limited. A similar pattern was not observed for use of SSRIs.

Gliomas constitute about 80% of malignant brain tumours and cause significant morbidity and mortality (Ostrom et al., 2014). Although some progress has been made in identifying risk factors for glioma (Chen et al., 2011; Goodenberger and Jenkins, 2012; Ostrom et al., 2014), the aetiology remains largely unknown. Investigations of the effect of commonly used drugs on glioma risk (Walker et al., 2011; Ferris et al., 2012; Gaist et al., 2013a, b) may improve our understanding of glioma aetiology.

Laboratory studies have indicated that tricyclic antidepressants (TCAs) exert antineoplastic effects (Levkovitz et al., 2005; Jahchan et al., 2013), although the results are equivocal. Thus far, only one epidemiological study has specifically addressed the risk of glioma among users of antidepressants (Walker et al., 2011), reporting a statistically significantly reduced risk of glioma associated with repeat TCA use (odds ratio (OR) 0.59, 95% CI: 0.42–0.81).

To provide further epidemiological data on the potential protective effect of TCA use against gliomas, we conducted a nationwide case–control study of the association between long-term use of TCA and risk of glioma. For comparison, we performed similar analyses for selective serotonin reuptake inhibitors (SSRIs).

MATERIALS AND METHODS

In a nationwide case–control study, we compared the use of TCAs among individuals with incident glioma (cases) with use among cancer-free persons (controls) to estimate ORs for glioma associated with overall or long-term TCA use.

Data sources. We used data from five Danish nationwide registries: the Danish Cancer Registry (Gjerstorff, 2011), the National...
Prescription Registry (Kildemoes et al, 2011), the National Patient Register (Lyne et al, 2011), a register in Statistics Denmark holding information on educational level (Baadsgaard and Quitzau, 2011), and the Civil Registration System (Pedersen, 2011). Detailed information on the included registries is provided in the Supplementary Appendix A, while codes for identification of cases, drug use, and other characteristics are provided in the Supplementary Appendix B.

Cases and controls. From the Danish Cancer Registry, we identified all individuals in Denmark with a first-time diagnosis of glioma between 1 January 2000 and 31 December 2012. The date of cancer diagnosis defined the index date. Case diagnoses were restricted to histologically verified gliomas. Exclusion criteria were age <18 years or >85 years at diagnosis, previous cancer (except non-melanoma skin cancer), and residency outside Denmark within 10 years prior to index date, ensuring at least 10 years of follow-up and a minimum of 5 years of prescription coverage (see Supplementary Appendix A).

We matched each case to 20 population controls on sex and birth year by risk-set sampling, applying the same selection criteria as for cases. Controls were assigned an index date identical to that of their corresponding case. With the nested case–control design and risk-set sampling of control participants, the calculated ORs provide unbiased estimates of the corresponding incidence rate ratios in the underlying source population.

Exposure definition. Our primary exposure was use of TCA (Anatomical Therapeutic Classification (ATC) code N06AA, see Supplementary Appendix C). We disregarded prescriptions redeemed within 1 year prior to the index date, to reduce the possibility of reverse causation (Jørgensen et al). Ever use of TCA was defined as having filled ≥1 prescriptions for any TCA prior to index date. Ever use was further classified into current/recent use (≥1 prescriptions within 1–19.9 years prior to the index date) and past use (≥1 prescriptions >2 years prior to the index date).

Long-term use of TCA was defined as ≥3 years of cumulative duration of use prior to the index date. The duration of each prescription in days was defined as the total number of defined daily doses per prescription.

Main analyses. We used conditional logistic regression to estimate ORs for glioma associated with long-term (≥3 years) use of TCA. We further performed analyses according to the cumulative duration of TCA use in four categories: <1, 1–2, 3–4, and ≥5 years. In all analyses, the reference group was never-users of TCA.

Using prescription, patient, and sociodemographic data (see Supplementary Appendices A and B), disregarding the period of at least 1 year prior to the index date, we adjusted for several potential confounders known or suspected to be associated with risk of gliomas, including (i) use of ≥2 prescriptions of statins, anti-diabetics, low-dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, inhibitors of the renin-angiotensin system, antihistamines, anti-asthma drugs, oral contraceptives, and hormonal replacement therapy; (ii) history of diabetes, stroke, allergy, and asthma; and (iii) highest achieved education.

Supplementary analyses. We performed a number of pre-planned supplementary analyses.

First, we repeated the main analyses with SSRI use as the primary exposure. Further, we performed dose-response analyses for all single antidepressant agents (including non-TCA/SSRIs) used by >100 controls (see Supplementary Appendix C). In these analyses, never use of SSRIs or the individual agent was used as the reference.

Second, we stratified the analyses by type of glioma, that is, glioblastoma multiforme, astrocytoma grade II and III, oligodendroglioma grade II and III, and ‘other types’.

Third, we examined the influence of consistency of TCA use on glioma risk by stratifying long-term TCA use according to the presence or absence of prescription-free periods of ≥1 year within 5 years prior to the index date.

Fourth, we examined associations for glioma with TCA use within subgroups defined by sex, age, or previous polyneuropathy. The latter was done to evaluate the potential influence of confounding by indication on the risk estimates.

Finally, we lagged drug and covariate exposure with 2 or 0 years, respectively, instead of the 1-year lag used in the main analyses.

Other. All analyses were performed using Stata Release 14.0 (StatCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board (Thygesen et al, 2011).

Table 1. Characteristics of cases and their matched controls

|                        | Cases (n = 3767) | Controls (n = 75 340) |
|------------------------|------------------|-----------------------|
| Age, median (IQR)      | 60 (49–68)       | 60 (49–68)            |
| Sex                    |                  |                       |
| Male                   | 2217 (58.9%)     | 44 340 (58.9%)        |
| Female                 | 1550 (41.1%)     | 31 000 (41.1%)        |
| **Glioma subtype**     |                  |                       |
| Glioblastoma multiforme| 2333 (62.5%)     | NA                    |
| Astrocytoma grade II and III | 594 (15.8%)  | NA                    |
| Oligodendroglioma grade II and III | 476 (12.6%)  | NA                    |
| Others                 | 344 (9.1%)       | NA                    |
| **Use of TCA**         |                  |                       |
| Never use              | 3630 (95.4%)     | 72 152 (95.8%)        |
| Ever use               | 137 (3.6%)       | 3188 (4.2%)           |
| Current/recent use     | 36 (0.96%)       | 973 (1.3%)            |
| Past use               | 101 (2.7%)       | 2215 (2.9%)           |
| Long-term use (≥3 years)| 13 (0.35%)       | 373 (0.50%)           |
| Continuous long-term use| 11 (0.29%)      | 292 (0.39%)           |
| **Use of SSRI**        |                  |                       |
| Never use              | 3336 (88.6%)     | 66 118 (87.8%)        |
| Ever use               | 431 (11.4%)      | 9222 (12.2%)          |
| Current/recent use     | 207 (5.5%)       | 4043 (5.4%)           |
| Past use               | 224 (6.9%)       | 5179 (6.9%)           |
| Long-term use (≥3 years)| 89 (2.4%)        | 1932 (2.6%)           |
| Continuous long-term use| 75 (2.0%)        | 1534 (2.0%)           |
| **Drugs**              |                  |                       |
| Statins                | 513 (13.6%)      | 11 290 (15.0%)        |
| Anti-diabetics         | 294 (7.8%)       | 6971 (9.3%)           |
| Low-dose aspirin       | 513 (13.6%)      | 11 856 (15.7%)        |
| NSAIDs                 | 1735 (46.1%)     | 35 533 (47.2%)        |
| Inhibitors of the renin-angiotensin system* | 682 (18.1%) | 14 442 (19.2%) |
| Antihistamines         | 491 (13.0%)      | 10 097 (13.4%)        |
| Anti-asthma drugs      | 556 (14.8%)      | 12 044 (16.0%)        |
| Oral contraceptives    | 449 (11.9%)      | 9013 (12.0%)          |
| Hormone replacement therapy | 514 (13.6%) | 10 984 (14.6%) |
| **Diagnoses**          |                  |                       |
| Diabetes               | 118 (3.1%)       | 3056 (4.1%)           |
| Stroke                 | 65 (1.7%)        | 1452 (1.9%)           |
| Allergy or asthma      | 122 (3.2%)       | 2827 (3.8%)           |
| **Highest achieved education** |             |                       |
| Short (<7–10 years)    | 1302 (34.6%)     | 25 886 (34.4%)        |
| Medium (11–13 years)   | 1539 (40.9%)     | 30 365 (40.3%)        |
| Long (>13 years)       | 813 (21.6%)      | 16 001 (21.2%)        |
| Missing                | 113 (3.0%)       | 3088 (4.1%)           |

*Abbreviations: IQR = interquartile range; NA, not applicable; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

*1 year prior to the index date.

*Angiotensine-converting enzyme inhibitors and angiotensin-receptor blockers.
RESULTS

We identified 4522 incident cases of gliomas during 2000–2012. Exclusions left 3767 eligible cases that were matched to 75 340 controls (Table 1; and flow chart in the Supplementary Results I).

Long-term (>3 years) use of TCA was associated with a statistically non-significant reduced risk of glioma with an adjusted OR of 0.72 (95% CI: 0.41–1.25). There was a tendency towards stronger inverse associations with glioma risk with longer duration of TCA use, although these findings had limited statistical precision (Table 2) and a test for trend did not achieve statistical significance. The corresponding analyses for SSRIs revealed ORs close to unity in almost all strata (Table 2). No clear patterns were seen for individual antidepressants (Supplementary Results II), however, numbers were small.

Subgroup analyses showed some variations, however, the statistical precision was limited. Reduced ORs were observed when the analyses were restricted to men, ages between 65–85 years, or glioblastoma multiforme (OR 0.56, 95% CI: 0.26–1.19; Table 3). The corresponding subgroup analyses for SSRIs showed no material variation in risk estimates, except among subjects aged 65–85 years and with glioma subtype (Supplementary Results III). Varying the lag-time did not affect the OR estimates (data not shown).

As we found the lowest ORs for glioma with TCA use close to the index date, we performed an exploratory post hoc analysis examining the association between ‘current use’ of TCA, defined as use within the last year prior to index date, and glioma risk finding an OR of 1.06 (95% CI: 0.80–1.40). In addition, we performed an analysis of long-term use among such current users, which returned an OR of 0.81 (95% CI: 0.44–1.48).

Table 2. Association between the use of TCA and SSRI and risk of glioma according to various exposure definitions

|                      | Cases | Controls | Crude OR<sup>a</sup> | Adjusted OR<sup>b</sup> |
|----------------------|-------|----------|----------------------|-------------------------|
| **TCA**              |       |          |                      |                         |
| Never use            | 3630  | 72 152   | 1.00 (ref)           | 1.00 (ref)              |
| Ever use             | 137   | 3188     | 0.85 (0.72–1.02)     | 0.89 (0.75–1.06)        |
|                      |       |          | (Current/recent use) |                         |
|                      | 36    | 973      | 0.73 (0.52–1.03)     | 0.76 (0.55–1.07)        |
|                      |       |          | (Past use)           |                         |
|                      | 101   | 2215     | 0.91 (0.74–1.11)     | 0.95 (0.77–1.16)        |
|                      |       |          | (Long-term use)      |                         |
|                      | 13    | 373      | 0.69 (0.40–1.21)     | 0.72 (0.41–1.25)        |
|                      |       |          | (Continuous long-term use) |                   |
|                      | 11    | 292      | 0.75 (0.41–1.36)     | 0.76 (0.42–1.40)        |
| **Cumulative duration** |     |          |                      |                         |
|                      |       |          |                      |                         |
|                      | <1 year | 109 | 2334 | 0.93 (0.76–1.13) | 0.97 (0.80–1.18) |
|                      | 1–2 years | 15 | 481  | 0.63 (0.37–1.05) | 0.65 (0.39–1.09) |
|                      | 3–4 years | 5  | 174  | 0.57 (0.23–1.39) | 0.59 (0.24–1.44) |
|                      | >5 years | 8  | 199  | 0.81 (0.40–1.64) | 0.83 (0.41–1.68) |
| **SSRI**             |       |          |                      |                         |
| Never use            | 3336  | 66 118   | 1.00 (ref)           | 1.00 (ref)              |
| Ever use             | 431   | 9222     | 0.92 (0.83–1.03)     | 0.95 (0.86–1.06)        |
|                      |       |          | (Current/recent use) |                         |
|                      | 207   | 4043     | 1.01 (0.87–1.17)     | 1.04 (0.90–1.20)        |
|                      |       |          | (Past use)           |                         |
|                      | 224   | 5179     | 0.86 (0.75–0.99)     | 0.88 (0.76–1.01)        |
|                      |       |          | (Long-term use)      |                         |
|                      | 89    | 1932     | 0.90 (0.72–1.12)     | 0.93 (0.75–1.16)        |
|                      |       |          | (Continuous long-term use) |                   |
|                      | 75    | 1534     | 0.95 (0.75–1.20)     | 0.98 (0.77–1.24)        |
| **Cumulative duration** |     |          |                      |                         |
|                      |       |          |                      |                         |
|                      | <1 year | 242 | 5266 | 0.91 (0.80–1.04) | 0.93 (0.81–1.07) |
|                      | 1–2 years | 100 | 2024 | 0.98 (0.80–1.20) | 1.00 (0.81–1.23) |
|                      | 3–4 years | 43  | 905  | 0.93 (0.68–1.27) | 0.96 (0.70–1.30) |
|                      | >5 years | 46  | 1027 | 0.86 (0.64–1.17) | 0.89 (0.66–1.20) |

Abbreviations: OR = odds ratio; SSRI = selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. Long-term use is defined as >3 years of cumulative use. In all analyses, prescriptions within the year prior to the index date were disregarded.

<sup>a</sup>Adjusted for age and gender (by design; risk-set matching and conditional analysis).

<sup>b</sup>Further adjusted for (i) use (≥2 prescriptions) of statins, anti-diabetics, low-dose aspirin, non-aspirin NSAIDs, inhibitors of the renin-angiotensin system, antihistamines, anti-asthma drugs, oral contraceptives, and hormonal replacement therapy; (ii) previous diagnoses of diabetes, stroke, allergy, and asthma, and (iii) highest achieved education.

Table 3. Associations between long-term use of TCA (>3 years) and risk of glioma, specified by subgroups

|                     | Cases | Controls | Crude OR<sup>a</sup> | Adjusted OR<sup>b</sup> |
|---------------------|-------|----------|----------------------|-------------------------|
| **Sex**             |       |          |                      |                         |
| Men                 | 4/2164| 149/42 963 | 0.53 (0.20–1.43)    | 0.54 (0.20–1.46)        |
| Women               | 9/1466| 224/29 189 | 0.81 (0.41–1.57)    | 0.84 (0.43–1.64)        |
| **Age**             |       |          |                      |                         |
| 18–49 years         | —/928 | 34/18 478 | —                    | —                       |
| 50–64 years         | 6/1443| 146/28 716 | 0.83 (0.37–1.87)    | 0.83 (0.37–1.89)        |
| 65–85 years         | 5/1259| 193/24 958 | 0.51 (0.21–1.25)    | 0.54 (0.22–1.32)        |
| **Histological subgroup** |     |          |                      |                         |
| Glioblastoma multiforme | 7/2262 | 255/44 905 | 0.54 (0.26–1.15)    | 0.56 (0.26–1.19)        |
| **Comorbidity**     |       |          |                      |                         |
| No polyneuropathy   | 13/3614| 363/71 873 | 0.72 (0.41–1.25)    | 0.74 (0.42–1.28)        |

Abbreviations: OR = odds ratio. In all analyses prescriptions within the year prior to the index date were disregarded.

<sup>a</sup>Adjusted for age and gender (by design; risk-set matching and conditional analysis).

<sup>b</sup>Further adjusted for (i) use (≥2 prescriptions) of statins, anti-diabetics, low-dose aspirin, non-aspirin NSAIDs, inhibitors of the renin-angiotensin system, antihistamines, anti-asthma drugs, oral contraceptives, and hormonal replacement therapy; (ii) previous diagnoses of diabetes, stroke, allergy, and asthma, and (iii) highest achieved education.
DISCUSSION

In this nationwide study, we found an inverse, albeit statistically non-significant, association between TCA use and risk of glioma. However, the statistical precision of our analyses was generally limited.

The main strength of our study is the use of high-quality nationwide registries, whereas the main limitation was the low number of exposed cases limiting the statistical precision and complicating interpretation of subgroup analyses.

The only previous observational study of TCA use and glioma risk reported a statistically significant reduction in glioma risk associated with the use of TCAs with an OR of 0.59 (95% CI, 0.42–0.81) while also showing a statistically significant dose-dependency (Walker et al., 2011). The authors also reported a null association between use of SSRI and glioma risk (OR 0.96; 95% CI: 0.61–1.53) (Walker et al., 2011). Although with less statistical precision, our results are largely compatible with those of the study by Walker et al. (2011).

Biologically plausible explanations supporting these findings appear insufficiently accounted for. Some in vitro studies suggest that antidepressants inhibit the growth of human glioma cell lines (Ishiuchi et al., 2007; Liu et al., 2015). The primary mechanism appears to be related to the overexpression of AMPAR receptors in glioma tissues with TCAs acting as ligands resulting in apoptosis. Autophagy has been suggested as another mechanism of action (Jeon et al., 2011). Study conditions have been heterogeneous, but overall, fluoxetine, paroxetin, sertraline, and clomipramine have demonstrated an enhancing effect on apoptosis in human glioma cell lines (Levkovitz et al., 2005; Tzadok et al., 2010; Liu et al., 2015). No such effect could be demonstrated for imipramine or mianserine (Levkovitz et al., 2005). Other antidepressants have not been subject to comparable studies. As such, we would hypothesise that signals, if any, be present for fluoxetine, paroxetin, sertraline, and clomipramine, but not for imipramine or mianserine. No such pattern was observed (see Supplementary Results II), however, the statistical precision was low in the analyses of individual agents.

Although our findings support the hypothesised protective effect of TCAs on the development of glioma, further substantiation from association studies and elucidation of the biological rationale is required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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