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Review article

The risk of glaucoma and serotonergic antidepressants: A systematic review and meta-analysis

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ABSTRACT

Background: : The aim of current study was to conduct a systematic review and meta-analysis to explore the relationship between antidepressant use and glaucoma.

Methods: : Eight major electronic databases were searched from inception until March 19th, 2018 to obtain relevant studies that evaluated associations of antidepressants [including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)] treatment and the risk of primary open-angle glaucoma (POAG) or primary angle-closure glaucoma (PACG) as well as intraocular pressure (IOP), and related anterior chamber parameters compared to participants not exposed to antidepressant treatment. A random-effects meta-analysis was conducted.

Results: : Six case-control studies and one cohort study were eligible (N = 801,754). The use of SSRIs was not associated with a higher risk of glaucoma (k = 7, pooled adjusted odds ratio (pAOR) = 0.956, 95% confidence interval (CI) = 0.807 to 1.133, p = 0.604). In addition, IOP was lower in participants exposed to antidepressants (SSRIs and SNRIs) (k = 4, Hedges' g = -0.519, 95% CI = -0.743 to -0.296, p < 0.001). Finally, pupillary diameter was higher in participants exposed to antidepressant treatment (k = 4, Hedges' g = 0.681, 95% CI = 0.462 to 0.900, p < 0.001).

Limitations: : High heterogeneity of included studies limit the establishment of causal inferences.

Conclusions: : This meta-analysis indicates that a putative association between the use of SSRIs and a higher risk of glaucoma remains to be proven. However, antidepressant drug treatment may be associated with significantly lower IOP and higher pupillary diameter. The mechanisms underpinning these associations deserve further investigation.

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1. Introduction

The glaucoma comprise a heterogeneous group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells that may result in a progressive loss of visual sensitivity, and in some patients, blindness. The hallmark of this group of diseases is optic disc excavation (often referred to as cupping), a characteristic deformation and remodeling of the optic nerve head in response to intraocular pressure (IOP)-related biomechanical stress that can occur at any level of IOP. Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the most frequently types of glaucomatous disease. Whilst trabecular meshwork outflow pathway is accessible to the aqueous humour and is often blocked internally in open-angle glaucoma, it is blocked by the iris in angle-closure glaucoma (Weinreb et al., 2014; Weinreb et al., 2016).

Older age, family history of glaucoma, black race, use of systemic or topical corticosteroids, and high IOP are known risk factors for glaucoma. In addition, some studies have suggested that visual disturbances could be a common side effect of antidepressant drug treatment. Although the use of tricyclic antidepressants is related to a higher risk of developing glaucoma as well an elevated incident of glaucomatous attacks in individuals with pre-existing glaucoma, evidence pertaining to a putative association of treatment with newer generation antidepressants, that is selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), and glaucoma has been less consistent across studies (Carvalho et al., 2016; Richa and Yazbek, 2010). For example, notwithstanding some studies have suggested that the use of newer generation, serotonergic antidepressants could be associated with a higher risk of developing glaucoma (Costagliola et al., 2008), but other studies have failed to replicate those findings (Chen et al., 2015; Zheng et al., 2018). Inconsistent results across studies may therefore raise a certain degree of uncertainty in prescribing newer generation antidepressants to patients at-risk of developing glaucomatous disease. Importantly, it is not known whether SSRIs differ from SNRIs with regard to the risk of development of glaucoma, as both antidepressants exhibit different binding profiles and mechanisms of action (Stahl et al., 2005).

Thus, based upon the current evidences, we hypothesized that the risk of development glaucoma might differ among SSRIs and SNRIs. The aim of the current study is to perform a systematic review and meta-analysis of observational studies and clinical trials that have assessed a putative association of treatment with newer generation antidepressants including SSRIs and SNRIs and glaucoma. Furthermore, evidence pertaining to a possible impact of antidepressant drug treatment on IOP and pupillary diameter was also synthesized.

2. Methods and materials

This study followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) (see Supplementary Table S1). This preliminary meta-analysis followed an *a priori* defined but unpublished protocol. The current meta-analysis followed the requirements of the Institutional Review Board of Tri-Service General Hospital (TSGHIRB: B-105-12).

2.1. Search strategy and study selection

Two authors (HY Wang and PT Tseng) independently performed a systematic literature search of PubMed, ProQuest, ClinicalKey, Embase, ScienceDirect, Cochrane Library, Web of Science, and ClinicalTrials.gov databases from inception until March 19th, 2018 using the keywords "(glaucoma OR intraocular pressure) AND (serotonin OR selective serotonin reuptake inhibitor OR serotonin noradrenaline reuptake inhibitor OR SSRI OR SNRI)". The reference lists of included articles and recent reviews were also searched to identify additional references (Carvalho et al., 2016,2004,2008; Richa and Yazbek, 2010).

Two authors (HY Wang and PT Tseng) independently screened the titles and abstracts of retrieved references for potential eligibility. Both authors reviewed the full text of potentially eligible references, and a final list of included studies was obtained. Any inconsistencies were resolved through discussion with a third reviewer (CS Chu).

2.2. Eligibility criteria

Observational studies and clinical trials that assessed the association of treatment with serotonergic antidepressants and glaucoma, IOP and pupillary diameter were considered for inclusion. The exclusion criteria were: (a) preclinical studies, review articles, meeting abstracts, and non-human studies; (b) studies that did not assess the risk or incidence of glaucoma or changes in IOP associated with treatment with serotonergic antidepressants; and (c) studies that lacked adequate controls.

2.3. Data extraction

Two authors (HY Wang and PT Tseng) independently extracted data of interest following the MOOSE guidelines. The primary outcomes were differences in the risk of glaucoma in subjects receiving SSRIs/SNRIs treatment compared to participants that were not exposed to antidepressant drug treatment (calculated as odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and *p* values). Besides, to adjust for the potential confounding factors in each study, we also extracted adjusted ORs from each included study to calculate the pooled adjusted odds ratio (pAOR).

For the secondary outcome, we analyzed differences in IOP and related parameters obtained through standard procedures that included tonometry, fundoscopy and gonioscopy (including pupillary diameter and chamber volume) in participants who received SSRIs/SNRIs treatment compared to those who were not exposed to antidepressant drug treatment. In this part of meta-analysis, we calculated the effect sizes using Hedges' *g* and corresponding 95% CIs.

When data were not available from included studies, we contacted the primary authors to request the original data. We electronically contacted corresponding authors on two separate occasions one week apart if required.

2.4. Methodological quality appraisal

We used the modified Newcastle–Ottawa scale (modified-NOS) to evaluate the overall quality of the included studies. In brief, the modified NOS is based on a version previously used in a meta-analysis study published and is scored from zero to six points (Anglin et al., 2013). There are total 4 domains with 7 questions. The four domains included methods of selecting study participants, methods of controlling confounding factors, statistical methods, and finally, methods for measuring outcome variables. The higher NOS scores indicated the better quality of study.

2.5. Meta-analysis procedure

Due to the anticipated high heterogeneity across studies, a random-effects models was used to synthesize evidence from included studies (Borenstein et al., 2010). The primary effect sizes (ESs) were estimated as ORs (odds ratios) with 95% CIs, while the secondary ESs were estimated with Hedges' *g* and 95% CIs. We defined the direction of the ES to indicate "a lower risk of glaucoma in participants treated with SSRIs/SNRIs compared to those not exposed to SSRIs/SNRIs treatment" when the value of the OR was less than one. In contrast, we defined the ES to indicate "a lower value of IOP-related parameters in participants treated with SSRIs/SNRIs treatment than in those without SSRIs/SNRIs treatment" when the value of Hedges' *g* was less than zero. The current meta-analyses were conducted using Comprehensive Meta-Analysis