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Incidence of nonarteritic anterior ischemic optic neuropathy among adults treated with GLP-1 receptor agonists: A systematic review and single-arm proportion meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 August 2025 and was last updated on 3 August 2025.

INTRODUCTION

Review question / Objective In adults exposed to Glucagon Like Peptide -1 receptor agonists, what is the incidence of new-onset nonarteritic anterior ischemic optic neuropathy during the observed follow-up periods, as reported in randomized trials or observational cohorts?

Rationale The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially approved for type 2 diabetes mellitus, has significantly increased in recent years following their regulatory approval for weight reduction. This class of medications has demonstrated proven benefits in reducing weight, leading to expanded indications and widespread use. Recently, large cohort studies showed cumulative non-arteritic anterior ischemic optic neuropathy (NAION) of 0.04-0.08%, with similar rate of 0.09% in other cohorts.

The incidence of NAION events remain rare, and current literature is fragmented across heterogeneous cohorts, limiting precision of absolute risk estimates. Individual observational studies and smaller case series yield wide confidence intervals, and randomized trials are underpowered to detect this rare outcome. A systematic meta-analysis of proportions across observational and trial data would allow rigorous pooling of event counts and denominators, providing a statistically powered estimate of cumulative NAION incidence following GLP-1 RA exposure. This approach addresses a critical evidence gap, enabling more accurate risk communication, improved pharmacovigilance, and informed clinical decisions regarding the ophthalmic safety profile of GLP-1 therapies.

Condition being studied New-onset nonarteritic anterior ischemic optic neuropathy.

METHODS

Search strategy The search strategy will be assessed the predefined databases, using the following boolean string system or combination of

the words depending on the database search system:

-((Nonarteritic Anterior Ischemic Optic Neuropathy) OR (NAION)) AND ((Semaglutide) OR (glucagon-like peptide-1 agonist))
-(Nonarteritic Anterior Ischemic Optic Neuropathy) AND (Semaglutide)
-(NAION) AND (Semaglutide)
-(Nonarteritic Anterior Ischemic Optic Neuropathy) AND (glucagon-like peptide-1 agonist)
-(NAION) AND (glucagon-like peptide-1 agonist)

Moreover, the reference of previous systematic reviews will be assessed.

Participant or population Adults exposed to Glucagon Like Peptide -1 receptor agonists.

Intervention Glucagon Like Peptide -1 receptor agonists.

Comparator None.

Study designs to be included Experimental and observational.

Eligibility criteria Peer-reviewed journal articles published in English between 2000 and 2025 will be included. Eligible studies must be primary research with an observational or experimental design including a minimum sample size of 10 patients, assessing the incidence of new-onset nonarteritic anterior ischemic optic neuropathy either as a single arm study or in comparison.

Studies will be excluded if they are abstracts, brief comments, letters to the editor, or narrative reviews, or if they have an overlapping population.

Information sources The data bases assessed will be PubMed, Central Cochrane and Clinicaltrials.gov.

Main outcome(s) The incidence of new-onset nonarteritic anterior ischemic optic neuropathy in patients under GLP-1 agonist treatment.

Additional outcome(s) Additional outcomes assessed, will be detailed study-level characteristics for each eligible report, including: participant demographics (e.g. age, sex, diabetes duration, comorbidities); essential study elements (e.g. study design, follow-up duration, outcome definitions); and bibliographic details (author names, institution, publication year, and country).

Data management All the records obtained from the database assessment, will be imported Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA). All the records will be submitted a screening, beginning with a duplicate removal, following with title/abstract assessment using the inclusion/exclusion criteria, and finally a full-text screening using the elegibility criteria, of those records that accomplished the previous phases. Two independent researchers will conduct this screening blinded to the other researcher's decisions. Any disagreements will be solved through a consensus.

Quality assessment / Risk of bias analysis Risk of Bias assessment will be conducted by two researchers, using either the revised Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials; non-randomized observational studies will be evaluated with the Methodological Index for Non-Randomized Studies (MINORS). Any disagreement will be solved through a consensus.

Strategy of data synthesis A univariate single-arm meta-analysis will be conducted with the extracted incidence and sample size using a random-effect model, with the individual study weight estimated using either inverse variance or general linear mixed model depending on the transformation method used (Logit or Freeman-Tukey double arcsine), the between-study variance will be estimated using the restricted maximum likelihood method. The decision to use either Logit transformation or Freeman-Tukey double arcsine, will depend on the systematic review findings, if a incidence of 0 is detected in the studies, a Logit transformation will be employed; moreover, if the incidence of some or different studies include 0 a Freeman-Tukey double arcsine transformation will be employed in the main analysis.

The heterogeneity will be evaluated using Cochran's Q test and Higgins' I2 statistic. I2 values > 50% will be considered significant. To explore potential sources of heterogeneity and possible effect modifiers, different univariate meta-regression models will be conducted, using covariates that will be selected post hoc, based on the systematic review findings.

Subgroup analysis A subgroup analysis could be performed based on the study design or the country were the study were conducted.

Sensitivity analysis Two sensitivity analysis will be conducted, 1) a leave-one-out sensitivity analysis looking for posible influence of individual studies, and, 2) a transformation-based sensitivity will be

conducted in case of use in the main analysis the Freeman-Tukey double arcsine transformation, this sensitivity analysis will consist in conduct another single arm meta analysis using the Logit transformation.

Language restriction English.

Country(ies) involved Mexico.

Keywords Glucagon-Like Peptide 1, semaglutide, Optic Ischaemic Neuropathy, NAION, Nonarteritic Anterior Ischemic Optic Neuropathy, Incidence.

Dissemination plans The dissemination plans include possible congress abstracts and journal peer-review articles.

Contributions of each author

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