UNIVERSIDADE D
COIMBRA

Ana Sofia Martins Penedones

SYSTEMATIC REVIEW: METHODOLOGICAL ASPECTS OF ITS ROLE IN DRUG SAFETY ASSESSMENT

Tese no âmbito do Doutoramento em Ciências Farmacêuticas, ramo de Farmácia Clínica orientada pelo Professor Doutor Francisco Jorge Batel Marques e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Março de 2020

Faculdade de Farmácia
da Universidade de Coimbra

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All the research work presented in this thesis was performed in strict collaboration of the Laboratory of Social Pharmacy and Public Health, Faculty of Pharmacy, University of Coimbra and the Centre for Health Technology Assessment and Drug Research, Association for Innovation and Biomedical Research on Light and Image, under the supervision of Professor Francisco Jorge Batel Marques.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CRD	Centre for Reviews and Dissemination
CIs	Confidence Intervals
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
cGMP	cyclic Guanosine Monophosphate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drugs Administration
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
GTP	Guanosine Triphosphate
HR	Hazard Ratio
INN	International Non-proprietary Name
JAMA	Journal of the American Medical Association
JBC	Joanna Briggs Collaboration
JBI	Joanna Briggs Institute
JGIM	Journal of General Internal Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NAION	Nonarteritic Anterior Ischemic Optic Neuropathy
NO	Nitric Oxide
OR	Odds Ratio
PDE5	phosphodiesterase type 5
PDE6	phosphodiesterase type 6
PIC	Population, phenomenon of Interest, Context

PICO	Population, Interventions, Comparators, Outcomes
PICOS	Population, Interventions, Comparators, Outcomes, Study design
PICOT	Population, Interventions, Comparators, Outcomes, Time frame
PRISMA	Preferred Reporting Items of Systematic reviews and Meta-Analysis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUG	Panel for Updating Guidance for systematic reviews
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
QUOROM	QUality Of Reporting Of Meta-analyses
RCT	Randomized Controlled Trials
RR	Relative Risk
RoB	Risk of Bias
sGC	soluble Guanylate Cyclase
SPIDER	Sample, Phenomenon of Interest, Design, Evaluation, Research type
SOC	System Organ Class
US	United States
WHO	World Health Organisation

Publications

- Penedones A, Alves C, Batel Marques F. Recommendations to conduct and report systematic reviews in medical literature: a scoping review. BMC Med Res Methodol. 2019;19(1):234. doi: 10.1186/s12874-019-0870-1. *(date of submission: 20 Nov 2017)*

- Penedones A, Batel Marques F. Methodologic Assessment of the Systematic Reviews of Ophthalmic Adverse Drug Reactions Published in Ophthalmology Journals: A Systematic Review. Ophthalmic Res. 2018;60(2):55-68. doi: 10.1159/000489932. *(date of submission: 23 Apr 2018)*

- Penedones A, Alves C, Batel Marques F. A comparison between two recommendations to conduct and report systematic reviews on drug's safety. Systematic Reviews. 2019;8(1):238. doi: 10.1186/s13643-019-1167-5. *(date of submission: 21 Mar 2019)*

- Penedones A, Alves C, Batel Marques F. Risk of nonarteritic ischemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis. Acta Ophthalmol. 2020;98(1):22–31. doi: 10.1111/aos.14253. *(date of submission: 30 May 2019)*

Note: The articles were submitted according to the work sequence of this thesis. However, the date of publication is not sequential since time of discussion between the authors and the journals' editors differed.

Abstract

The systematic review is a research method that aims to identify, select, characterize and analyse all available evidence to answer a research hypothesis. It is performed according to a rigorous methodology to minimize bias, increase transparency and present reliable and robust results. The systematic review can be used as a method to summarise data useful in clinical decision process, for healthcare professionals and consumers, or in regulatory decision process, for regulatory authorities.

Pharmacovigilance is the science that study drugs' safety. It aims to identify, characterize, assess and act on the adverse drug effects. Drugs' safety monitoring is performed in all phases of the drugs' lifecycle. Several methods are available to pharmacovigilance. Common adverse drug effects are detected in pre-marketing phase. Nonetheless, due to the disadvantages of the pre-marketing clinical studies, such as reduced sample size, homogenous sample of subjects and time horizon, drugs' safety profile is essentially characterised at post-marketing phase. Spontaneous reporting, observational clinical studies or published case reports are some of the available post-marketing studies. The systematic review can combine data from the different studies.

Several systematic reviews on drug's safety have been published. However, drug's safety monitoring has special issues, namely in the management of different study designs. Moreover, to produce high quality systematic reviews, a recommendation describing the methodology to perform it should be followed.

This thesis aimed to assess systematic review in drug's safety, namely to study if the available recommendations to conduct and report a systematic review are prepared to be used in drug's safety assessment.

Systematic reviews methodology has become well established. Several research groups are entirely dedicated to this. However, the role of the systematic review in drug's safety is not yet defined. There are few recommendations to conduct and/ or to report a systematic review in drug's safety and their methods are still under development.

Several issues need further research. There are no strategies to search several sources of information to retrieve data on drug's safety. It is also important to define how to combine data from different study designs. In addition, the available methodological quality scales are not prepared to evaluate study designs such as case reports,

spontaneous reports or some designs of observational studies, which are important studies in drug's safety monitoring.

In order to avoid bias and misleading information provided by the methodological differences identified in the available recommendations, systematic reviews in drug's safety assessment may benefit from a single recommendation to conduct and/or to report it.

Resumo

A revisão sistemática é um método de investigação que pretende identificar, selecionar, caracterizar e avaliar toda a evidência disponível de forma a responder a uma hipótese de investigação. A revisão sistemática é elaborada de acordo com uma metodologia rigorosa a fim de minimizar o risco de viés, aumentar a transparência e apresentar resultados robustos e de confiança. A revisão sistemática pode ser usada como um método de síntese de informação, útil na tomada de decisão clínica, para profissionais de saúde e utentes, ou na tomada de decisão regulamentar, para as autoridades reguladoras.

A farmacovigilância é a ciência que estuda a segurança dos medicamentos. Esta tem como objetivos identificar, caracterizar, avaliar e atuar sobre os efeitos adversos a medicamentos. A monitorização da segurança do medicamento é feita em todas as fases do ciclo de vida do medicamento. Vários métodos estão disponíveis em farmacovigilância. Os efeitos adversos a medicamentos mais comuns são detetados na fase de pré-comercialização. No entanto, devido às desvantagens dos estudos clínicos na fase de pré-comercialização, tais como uma amostra de indivíduos homogénea e reduzida ou o curto horizonte temporal, o perfil de segurança dos medicamentos é essencialmente caracterizado na fase de pós-comercialização. A notificação espontânea, os estudos clínicos observacionais e os casos de efeitos adversos descritos na literatura são alguns exemplos de estudos conduzidos na fase de pós-comercialização.

Algumas revisões sistemáticas têm sido elaboradas, avaliando a segurança de medicamentos. Contudo, a avaliação da segurança de medicamentos apresenta alguns desafios, nomeadamente na combinação de dados de estudos com diferentes desenhos. Adicionalmente, deve ser seguida uma recomendação para elaborar e reportar revisões sistemáticas, de modo a produzir revisões de elevada qualidade.

Esta tese teve como objetivo avaliar a revisão sistemática na monitorização de segurança de medicamentos, nomeadamente analisar se as recomendações atuais para elaborar e reportar revisões sistemáticas são adequadas para serem usadas na monitorização de segurança de medicamentos.

A metodologia da revisão sistemática tem sido bem estabelecida. Vários grupos de investigação dedicam-se inteiramente ao estudo da revisão sistemática. Todavia, a utilização da revisão sistemática na monitorização de segurança de medicamentos ainda

não está bem definida. Existem poucas recomendações para elaborar e/ ou reportar uma revisão sistemática na monitorização de segurança de medicamentos. Os seus métodos diferem e ainda não estão adaptados às necessidades que se verificam durante a avaliação de segurança de medicamentos.

Vários aspetos metodológicos necessitam de mais investigação. Estratégias de pesquisa em diferentes fontes de informação, para os diferentes desenhos de estudo sobre segurança de medicamentos, devem ser definidas. Como combinar os dados provenientes dos diferentes tipos de estudos é também um desafio. Adicionalmente, as atuais escalas de avaliação da qualidade metodológica não permitem avaliar estudos que são importantes na monitorização de segurança de medicamentos, tais como os casos descritos na literatura, a notificação espontânea ou outro tipo de estudos observacionais.

Uma única metodologia reduziria o risco de viés e evitaria gerar informação incorreta. Deste modo, uma única recomendação para elaborar e reportar uma revisão sistemática beneficiaria a utilização da revisão sistemática na avaliação da segurança de medicamentos.

Chapter I - Systematic Review

1.1. Definition

A systematic review aims to identify, collate, characterize, and summarize all available information to answer a research question. The selection of the information is based on pre-specified eligibility criteria and may include several types of data. It is a rigorous methodology used to minimize bias, increase transparency, and present reliable results. Therefore, a systematic review produces evidence that can be the basis of informed decisions (Antman et al, 1992; Oxman and Guyatt, 1993; Aromataris and Munn, 2017).

1.2. Historical framework

The first clinical systematic review was published in 1955 in the Journal of the American Medical Association (JAMA) (Beecher, 1955). However, the collection of several studies is known before this date. In 1753, James Lind presented an essay about scurvy by describing "Critical and Chronological View of what has been published on the subject" (Lind, 1753). He compiled data from several sources of information to better understand what was published about the disease (Clarke and Chalmers, 2018). Afterward, other reviews of individual studies were conducted including statistical analysis of the results. In 1904, Pearson et al published their research on the effects of a vaccine against typhoid by combining the results of eleven studies (Pearson, 1904). Although the methodology used was not systematic, the concept of combining the results of studies to be aware of the latest data is the same.

As the role of pooling results from individual studies was growing, the need for the publication of high-quality reviews have also emerged (Clarke and Chalmer, 2018). Systematic reviews offering a robust search and analysis of all available information become more popular. In the decades of 1970 and 1980, several systematic reviews were performed (Bastian et al, 2010). Some assessments of the used methodologies in the elaboration of systematic reviews were also published. The quality of the systematic reviews was proportional to the quality of individual studies. One of the first systematic reviews of randomized controlled trials (RCT), in the healthcare field, was published by Chalmers et al (1989) on "Effective Care During Pregnancy and Childbirth" (Chalmers et al, 1989). In 1994, Dickersin et al (1994) published strategies to search for RCTs on

literature databases. Other systematic reviews and methodological papers have been published since then (Dickersin et al, 1994).

Several research groups have developed systematic reviews and dedicated their research to improve systematic reviews methodology. In 1993, the Cochrane Collaboration was created with the goal of "prepare, maintain, and disseminate systematic reviews" by Ian Chalmers (Higgins et al, 2019). This organisation spreads internationally with the collaboration of more than 15.000 individuals in 100 countries (Allen et al, 2007). Later, the "Cochrane Handbook for Systematic Reviews of Interventions", a guide to support the elaboration of systematic reviews of high quality was developed and published by this research group (Higgins et al, 2019).

Other research groups were also emerged to develop and to study systematic reviews. The Centre for Reviews and Dissemination (CRD) is a department at the University of York, United Kingdom. This group has performed more than 200 systematic reviews, some of them with an impact on healthcare policy decisions (University of York, 2019). In 2009, the CRD published its own guidance on systematic reviews: "Systematic Reviews CRD's guidance for undertaking reviews in healthcare" (Centre for Reviews and Dissemination, 2009). The Joanna Briggs Institute (JBI) accommodates The Joanna Briggs Collaboration (JBC) since 1996 (Jordan et al, 2006). This organisation has now collaboration from more than 70 academic and hospital entities in 39 countries (JBI) (Jordan et al, 2006). In addition, the JBC also established guidelines to perform systematic reviews, "The JBI Reviewer's Manual" (Aromataris and Munn, 2017).

In 2009, a research group defined guidance on the reporting of systematic reviews. The Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) statement was an update of guidance published ten years earlier on the reporting of meta-analysis (Moher et al, 2009). Since then, the PRISMA group has been developing specific recommendations on the reporting of systematic reviews, such as abstracts, equity, harms, diagnostic test accuracy, among others (Moher et al, 2009).

1.3. The need to perform a systematic review

New studies are published every day. MEDLINE, one of the largest biomedical literature databases, indexed more than 810.000 articles only in 2017 (US National Library of Medicine, 2019a). In twenty years, the number of published citations almost duplicated (Figure 1) (US National Library of Medicine, 2019a). Bastian et al (2010) estimated that 75 clinical trials are published per day (Bastian et al, 2010). With this large amount of

information published, to keep updated on all information has become impracticable.

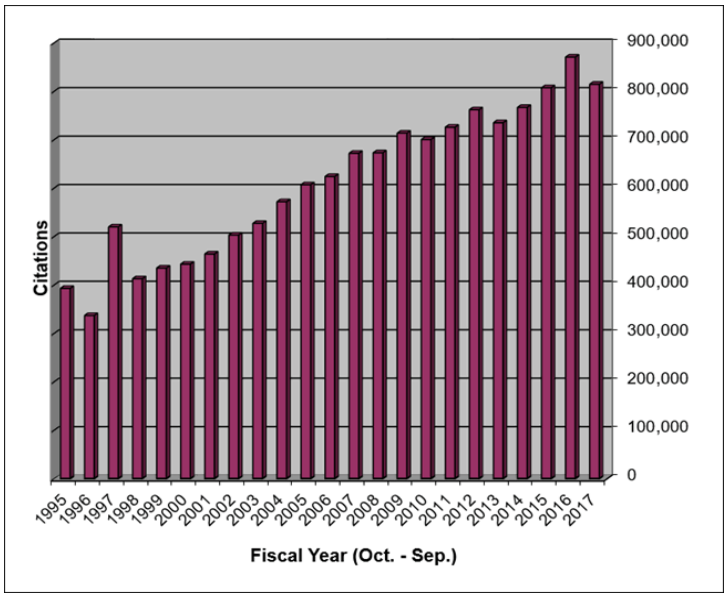

Figure I.1 *- Number of citations published on Medline by fiscal year (Source: US National Library of Medicine, 2019).*

To read and interpret a study requires knowledge. There are varied sources of information and types of studies. The methodological differences found among the individual studies, along with bias, demand a comprehensive analysis of the results of studies. To search and analyse all studies, make almost impossible for all interested parties to become aware of the latest data (Centre for Reviews and Dissemination, 2009). These reasons emphasize the role of the systematic review. As a research synthesis method, systematic reviews can be useful for healthcare professionals, patients, researchers and, also, regulatory authorities (Mulrow, 1994, Moher et al, 2009).

Healthcare professionals need to be constantly updated, as new advances in both science and medicine happen every day (Mulrow, 1994; Moher et al, 2009). Systematic reviews allow healthcare professionals to make informed choices. For instance, if a new class of drugs is approved, it is not feasible for healthcare professionals to make an informed decision without knowing the efficacy and safety profiles of this new class of drugs (Penedones et al, 2014).

Patient empowerment has emerged in the last years. The World Health Organisation (WHO) has defined patient empowerment has "a process through which people gain greater control over decisions and actions affecting their health" (WHO, 1998). Systematic reviews can be important as a summary of information for patients and their caretakers in their informed decisions (Moher et al, 2009).

A systematic review can also be important in research. In general, to summarize the knowledge on a certain subject is the starting point of any project. It can also help research funders to decide to fund the research project (Moher et al, 2009). In addition, systematic reviews are useful to formulate new research hypotheses (Petticrew and Roberts, 2006).

Regulatory authorities can decide about the best practice and take decisions based on the latest information by accessing a systematic review (Mulrow, 1994). For instance, if a new drug is requiring authorisation for commercialization, the regulatory authority can request a summary of all efficacy and safety data to better decide this drug's benefit-risk ratio (Moher et al, 2009).

1.4. Characteristics of systematic review

There are two types of reviews: narrative reviews and systematic reviews. A systematic review differs from a narrative review in many aspects (Table 1). A narrative review doesn't have a research hypothesis, neither a prespecified research methodology. A systematic review distinguishes by constituting a synthesis of all available evidence, using clearly methods of research and analysis of results, to answer a formulated research hypothesis (Higgins et al, 2019). The results of the systematic review are reproducible and, therefore, can be applied to support decisions (Petticrew and Roberts, 2006).

Table 1.1 *- Characteristics of narrative review and systematic review (Source: Higgins et al, 2019).*

Characteristics	**Narrative review**	**Systematic review**
Type of question	Broad	Narrow
Sources and filters on a literature search	Not specific	Based on predefined search literature
Study selection	Random	Based on predefined eligibility criteria
Evidence evaluation	Not performed	Based on scales or other tools
Bias	Large chance of occurrence	Less chance of occurrence
Synthesis	Qualitative	Qualitative/ Quantitative
Interferences	Sometimes based on scientific evidence	Always based on scientific evidence

1.4.1. Meta-analysis

A systematic review can use quantitative methods in the analysis of evidence. The term 'meta-analysis' is used to denote any statistical methods to analyse the results of the individual studies (Glass, 1976). A meta-analysis provides a more precise estimate of the

effects, assesses heterogeneity among studies, and allows to increase sample size and statistical power (Centre for Reviews and Dissemination, 2009; Higgins et al, 2019). A systematic review does not necessarily proceed a meta-analysis. Chalmers and Altman (1995) suggested that the technique could be independent of a systematic review process (Chalmers and Altman, 1995).

To perform a meta-analysis, it is necessary to define the effect size measure (e.g.: odds ratio; risk ratio), to choose the statistical model (e.g.: fixed-effects meta-analysis; random-effects meta-analysis), to describe if a meta-regression between two variables was evaluated, to describe if a cumulative meta-analysis was used, to assess the between-study heterogeneity, and to assess the publication bias (Chalmers and Altman, 1995).

1.5. How to perform a systematic review

1.5.1. Recommendations to perform and/ or to report a systematic review

In order to guide researchers to perform and/ or to report a high-quality systematic review, some recommendations were elaborated. These recommendations assure that all methods to perform and report a systematic review are followed, avoiding bias in the elaboration of the systematic review and assuring transparency in the reporting of the results (Moher et al, 2009; Higgins et al, 2019).

As mentioned above, several organisations developed guidance that helps the researchers to perform and/ or to report a systematic review. Some of these recommendations are the "Cochrane Handbook for Systematic Reviews of Interventions" (Higgins et al, 2019), the "Systematic Reviews CRD's guidance for undertaking reviews in healthcare" (Centre for Reviews and Dissemination, 2009), "The JBI Reviewer's Manual" (Aromataris and Munn, 2017), and the PRISMA Statement (Moher et al, 2009). Many other organisations and individual research groups developed their own guidance. There are a large variety of recommendations adapted to a specific area, such as economic evaluations of health technologies, diagnostic, prognostic, medical tests, aetiology or safety studies.

1.5.2. Steps to perform a systematic review

Before starting a systematic review, the authors must choose a recommendation to conduct and report the systematic review, followed by the elaboration of an *a priori* protocol of their research. The methodology used should be clearly defined.

A. Background

The purpose of the systematic review should be described. For instance, if a previous systematic review on the same research question was already published, the authors need to justify the elaboration of the new systematic review. Moreover, the authors must clarify in which way the systematic review is innovative compared with the current knowledge. A summary of what is known, and the limitations of the research hypothesis should also be described. In addition, the authors should define the perspective in which the systematic review will be performed (e.g.: healthcare professionals, patients, regulatory authorities) (Higgins et al, 2019; Centre for Reviews and Dissemination, 2009; Moher et al, 2009).

A structured research hypothesis must be defined, not only to help researchers to perform their systematic review, but also to help readers to understand clearly the goal of the systematic review. For quantitative reviews, this is, for those who evaluate measures of effect, a strategy named PICO (Population, Interventions, Comparators, Outcomes) was commonly used. This strategy clearly indicates the aim of the systematic review (e.g.: Table 2) (Higgins et al, 2019; Centre for Reviews and Dissemination, 2009; Moher et al, 2009). Other variants of PICO are also available, such as PICOT (T for time frame) and PICOS (S for study design) (Stern et al, 2014). For qualitative reviews, this is, for those using textual data, other strategies can be used, such as PIC (Population, phenomenon of Interest, Context) (Stern et al, 2014) and SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) (Cooke et al, 2012).

Table 1.2 *– Research question: free form question vs. PICO question.*

PICO	**Freeform question:** "This study is aimed at characterizing the safety profile of ophthalmic biologics, in both pre- and post-marketing settings, by carrying out a systematic review based on experimental and observational data." (Penedones et al, 2014)
Population	People with ocular diseases
Intervention	Ophthalmic biologics
Comparator	Active comparator or placebo
Outcome	Safety

B. Methods

The authors must report which recommendation to conduct and/ or to report a systematic review will be used in the elaboration of the systematic review (Moher et al, 2009).

Literature search:

The authors must define the inclusion criteria used to select the studies. This will be helpful to construct the search strategy. Similar to the research hypothesis, the eligibility criteria could be based on PICO or PIC strategy, for quantitative or qualitative reviews, respectively (Aromataris and Riitano, 2014). Thereby, the search strategy will be based on the keywords identified both on the research hypothesis and eligibility criteria.

To perform the search literature, several databases are available (Lu, 2018). Each one has specific characteristics (Table 1.3). Some are bibliographic databases and include millions of published papers. Others comprise abstracts from conferences and other types of grey research. Moreover, there are specific databases depending on the type of study, such as clinical trials registries and spontaneous reports of suspected adverse drug reactions databases.

Table 1.3 *– Example of databases to perform a search literature.*

Databases	
Bibliographic databases	
PubMed *(Canese and Weis, 2013)*	- https://www.ncbi.nlm.nih.gov/pubmed/ - Free resource; - Developed by the National Center for Biotechnology Information (NCBI); - Biomedical citations; - Includes more than 29 million citations; - Includes MEDLINE and PubMed Central (PMC); - Uses MeSH (Medical Subject Headings).
EMBASE *(Elsevier, 2019)*	- https://www.embase.com/ - Developed by Elsevier; - Biomedical and pharmacological citations; - Includes more than 35 million citations; - Includes grey literature (conference abstracts); - Uses Emtree (Embase subject headings).
Cochrane Library *(Cochrane Library, 2019)*	- https://www.cochranelibrary.com/ - Free resource; - Developed by the Cochrane Collaboration; - Includes Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL); - Uses MeSH (Medical Subject Headings).
SCOPUS *(Scopus, 2019)*	- https://www.scopus.com/home.uri - Developed by Elsevier; - Includes more than 69 million citations; - Science, technology, medicine, social sciences, and arts and humanities citations.

Databases	
Toxline (Toxicology Literature Online) *(US National Library of Medicine 2019b)*	- https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE - Free resource; - Developed by the National Library of Medicine; - Includes more than 4 million citations; - Biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals citations.
Web of Science *(Clarivate Analytics, 2019)*	- https://www.webofknowledge.com/ - Developed by Clarivate Analytics; - Includes more than 33 000 journals; - Sciences, social sciences, arts, and humanities citations.
Search engines	
Google Scholar *(Falagas et al, 2008)*	- https://scholar.google.com/ - Free resource; - Developed by Google Inc.; - Biology, life sciences and environmental sciences, business, administration, finance and economics, chemistry and materials science, engineering, pharmacology, veterinary science, social sciences, arts and humanities citations; - Includes grey literature (conference abstracts).
Microsoft Academic Search *(Microsoft, 2019)*	- https://academic.microsoft.com/home - Free resource; - Developed by Microsoft Corporation; - Includes more than 222 million citations; - Covers several topics; - Includes grey literature (conference abstracts).
TRIP Medical database *(Trip, 2019)*	- https://www.tripdatabase.com/; - Developed by Jon Brassey and Chris Price; - Includes medical citations; - Includes citations from several bibliographic databases (e.g. PubMed).
Grey literature	
OpenGrey *(OpenGrey, 2019)*	- http://www.opengrey.eu/search/; - System for Information on Grey Literature in Europe; - Free resource; - Developed by the *Institut de l'Information Scientifique et Technique*; - Includes science, technology, biomedical science, economics, social science, and humanities citations; - Includes more than 700.000 citations; - Includes grey literature (e.g.: technical or research reports, doctoral dissertations, conference papers, official publications).
Clinical Trials registries	
ClinicalTrials.gov	- https://clinicaltrials.gov/; - Free resource; - Maintained by the National Library of Medicine;

Databases	
(ClinicalTrials.gov, 2019)	- Includes clinical studies (mostly from the United States); - Information is provided by the sponsor or principal investigator of the clinical study.
International Clinical Trials Register Platform *(World Health Organisation, 2019)*	- http://apps.who.int/trialsearch/; - Free resource; - Developed by the World Health Organisation; - Includes clinical studies (from several countries); - Information is retrieved from several clinical trials registries in the world.
Spontaneous reports of suspected adverse drug reactions	
EudraVigilance *(European Medicines Agency, 2019)*	- http://www.adrreports.eu/en/index.html; - European database for suspected of adverse drug reactions reports; - Free resource; - Developed by the European Medicines Agency; - Includes spontaneous reports from European Economic Area countries.
VigiAccess *(VigiAccess, 2019)*	- http://www.vigiaccess.org/; - Free resource; - Developed by the World Health Organisation; - Maintained by the Uppsala Monitoring Centre; - Includes data from VigiBase®; - Includes spontaneous reports from 110 countries worldwide.

To perform a comprehensive search is necessary to select more than one database. Several studies pointed out that searching in just one bibliographic database retrieves incomplete information to answer a research question (Baudard et al, 2017; Falagas et al, 2018). At first, not all studies are indexed to all databases. Secondly, studies of large dimensions (and higher weight in the combination of the results) can be missed. Besides, some bibliographic databases are more accurate and provide more updated data than others (Falagas et al, 2018). Searching for clinical trials registries and grey literature can be hard, since there are numerous sources of information on the web and, also, it is difficult to adapt the search strategy to each type of sources (Mahood et al, 2014). However, it is possible to extract results of studies not selected on bibliographic databases and avoid bias publication (Mahood et al, 2014).

Study selection and data extraction:

The process of study selection and data extraction should be peformed by at least two reviewers, independently. This assures transparency and reproducibility of the systematic review (Moher et al, 2009).

The study selection is based on the predefined inclusion criteria. The PICO or PIC components (population, intervention, comparator, outcome), along as other criteria such as language, time horizon and type of study, are used to include the relevant studies (Porritt et al, 2014). In order to avoid the evaluation of all search results, the duplicates should be identified and then a first screening of titles and abstracts is performed. A final screening of the full text determines the inclusion of the study.

To extract data from the included studies, several options are available. These could include predefined forms by the authors, web-based software, or electronic databases (Elamin et al, 2009). The data extracted can include the reference of the included study and descriptive details, such as characteristics of the population, the results of the outcomes, methods of evaluation, among others (Munn et al, 2014).

Methodological quality assessment:

When conducting a systematic review, the methodological quality of the included studies should be performed. Not only to assess the validity and risk of bias of the studies, but also to best combine and interpret the results of these studies and, consequently, the results of the systematic review (Porritt et al, 2014).

The methodological quality allows to evaluate in which way the study adopts measures to reduce bias, i.e., systematic errors (Khan et al, 2013). There are several types of bias (Table 1.4). The bias can be related to the incorrect study design, the conduct of the study or the analysis of the results of the study.

Table 1.4 *– Types of bias: examples (Source: Centre for Evidence-Based Medicine, 2019).*

Type of bias	Description
Allocation bias	Systematic difference in how participants are assigned to comparison groups in a clinical trial.
Attrition bias	Unequal loss of participants from study groups in a trial.
Detection bias	Systematic differences between groups in how outcomes are determined.
Language bias	Publication of research findings in a particular language.
Misclassification bias	Occurs when a study participant is categorised into an incorrect category altering the observed association or research outcome of interest.
Performance bias	Systematic differences in the care provided to members of different study groups other than the intervention under investigation.
Publication bias	When the likelihood of a study being published is affected by the findings of the study.
Recall bias	Systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences.
Reporting bias	The selective reporting of pre-specified outcomes in published clinical trials.

Type of bias	Description
Selection bias	Occurs when individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome.

To assess the methodological quality, several tools are available. They can be applied according to their characteristics, for instance, based on the type of study (Table 1.5), type of assessment (qualitative or quantitative), or components assessed (bias, reporting, among others). Some tools are checklists, other are scales or domains to be evaluated. Most of these tools were developed by research groups, but also by organisations dedicated to systematic reviews methodology, such as the JBI and The Cochrane Collaboration (Page et al, 2018).

Table 1.5 *– Examples of tools to assess methodological quality according to the type of study.*

Type of study	Tools
Randomized controlled trial	- RoB 2: A revised Cochrane risk-of-bias tool for randomized trials - Modified Jadad Score - JBI Critical Appraisal Checklist for Randomized Controlled Trials
Non-randomized trial	- Downs and Black checklist - Newcastle-Ottawa Scale - ROBINS-I tool: Risk Of Bias In Non-randomized Studies - of Interventions
Cohort study	- Downs and Black checklist - Newcastle-Ottawa Scale - ROBINS-I tool: Risk Of Bias In Non-randomized Studies - of Interventions - JBI Critical Appraisal Checklist for Cohort Studies
Case-control study	- Downs and Black checklist - Newcastle-Ottawa Scale - ROBINS-I tool: Risk Of Bias In Non-randomized Studies - of Interventions - JBI Critical Appraisal Checklist for Case-Control Studies
Economic study	- JBI Critical Appraisal Checklist for Economic Evaluations - Drummond Checklist - Evers Checklist
Diagnostic test study	- QUADAS: Quality Assessment of Diagnostic Accuracy Studies - JBI Critical Appraisal Checklist for Diagnostic Test Accuracy studies
Case report	- JBI Critical Appraisal Checklist for Case Reports
Systematic review	- AMSTAR 2: A MeaSurement Tool to Assess systematic Reviews - JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis

JBI: Joanna Briggs Institute.

Data synthesis:

The combination of the data extracted from the included studies can be performed qualitatively or quantitatively. Both techniques allow explore differences between comparison groups and discuss the reasons for these inconsistencies (Munn et al, 2014).

The type of synthesis is dependent on the type of evidence. Studies of high quality, such as RCTs, can be combined through meta-analysis. However, studies of low quality should be combined through qualitative synthesis, since the quality of individual studies could affect meta-analysis. (Munn et al, 2014). The technique of meta-analysis is described at 1.4.1. Meta-analysis.

C. Results

The authors should describe the four main results:

- Selection of individual studies. This could be performed through a narrative description or, most commonly used, through a flow diagram (Figure 1.2.). This description intends to maintain the transparency and reproducibility of the systematic review.

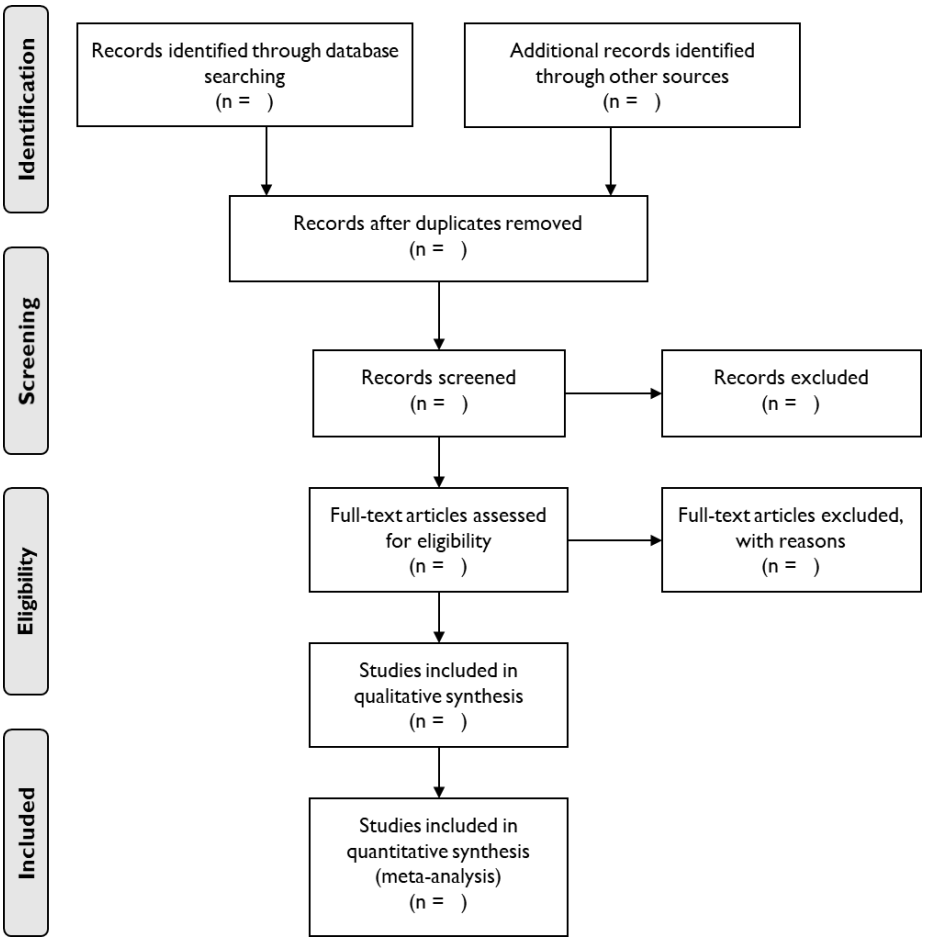

Figure 1.2 *– PRISMA Flow Diagram template (Source: Moher et al, 2009).*

- Characteristics of the individual studies.
- Methodological quality assessment. Tables, figures, graphics, or other schematic diagrams are examples of ways to present these results.
- Results of the systematic review. The summary of data that answers to the research hypothesis should be presented according to the analysis predefined and described in the methods section of the systematic review.

D. Discussion

A brief summary of the results of the systematic review should be presented. These results need to be discussed according to the perspective adopted at the beginning of the systematic review. The limitations found in the elaboration of the systematic review, whether inherent to the systematic review or to individual studies, should also be discussed, since these limitations may influence the interpretation of the results (Robertson-Malt, 2014).

At last, the authors should describe the funding sources and any conflicts of interest. This topic is particularly important since many authors are affiliated to industry, academic institutions, among others. These financial relationships or conflicts of interests can, sometimes, biased the outcomes results' reporting or the study's conclusions (Bekelman et al, 2003). Therefore, in order to ensure the systematic review's transparency, this should be reported.

1.6. Limitations of systematic reviews

Some limitations can be found when performing and reporting a systematic review. Most of the limitations and challenges are associated with the individual studies (Bartolucci and Hillegass, 2010).

The methodological quality of the individual studies can influence the quality of the systematic review. Combining different types of studies, make difficult to pool studies' results. This also can lead to subjective interpretation of the pooled results and draw biased conclusions (Garg et al, 2008). The same can be observed even if the studies present the same study design (Bartolucci and Hillegass, 2010). A meta-analysis is not always possible to conduct (Mallet et al, 2012).

Another limitation is access to information since most of the databases required a fee to access data (Mallet et al, 2012). Searching grey literature is also a challenge once

this literature is spread on the web (Mallet et al, 2012). In the same way, some papers are published in another language than English, which makes it difficult to access the studies' results (Morrison et al, 2012).

Since to perform and report a systematic review is a rigorous process, which intends to make all process transparent and reproducible, this can be complex in certain ways. It requires a multidisciplinary team, time and resources (Mallet et al, 2012).

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Chapter 2 - Systematic Review in drug's safety and clinical assessment

2.1. Pharmacovigilance

Pharmacovigilance can be defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (World Health Organisation, 2002).

Pharmacovigilance or drug safety monitoring is present at all phases of the drug development and clinical practice. Its application on clinical use is of major importance (World Health Organisation, 2004). The main goal is to identify the risks (adverse effects) of drugs. It also allows to establish an organized system to monitor the risks and benefits of drugs (assuring that the risks are inferior to benefits), to identify and characterize new risks, to generate safety signals, and to educate health professionals and consumers to detect and report adverse effects (Kumar, 2017).

An adverse effect can be distinguished into adverse event (AE) as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment" and an adverse drug reaction as "a response to a medicinal product which is noxious and unintended" (European Medicines Agency, 2017), which have a causal relationship with the treatment. An adverse drug reaction can be classified into six types (Table 2.1).

Table 2.1 – *Classification of adverse drug reactions (Source: Kaufman, 2016; Waller and Harrison-Woolrych, 2017).*

Type		Characteristics	Example
A	Augmented	Dose-related Pharmacologically predictable Common	Bleeding with warfarin
B	Bizarre	Not dose-related Unpredictable (immune-mediated, idiosyncratic) Uncommon High mortality	Anaphylaxis with penicillin
C	Chronic	Cumulative dose Time related Uncommon	Adrenal suppression with corticosteroids
D	Delayed	Occurs sometime after use of the drug Difficult to detect	Tardive dyskinesia with neuroleptics
E	End of use	Occurs after withdrawal of the drug Uncommon	Withdrawal reactions with benzodiazepines
F	Failure	Dose-related Common Often caused by drug interactions	Oral contraceptive when used with an enzyme inducer

In addition, an adverse drug reaction can be classified according to their seriousness, expectedness and causal relationship with the suspected drug (Figure 2.1.). A serious adverse drug reaction can be defined as "an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect" (European Medicines Agency, 2017). The expectedness of an adverse drug reaction is determined according to their previous knowledge and description on the Summary of Product Characteristics of the suspected drug (European Medicines Agency, 2017). There are several methods to determine the causal relationship between an adverse drug reaction and a suspected drug, such as global introspection by a panel of experts and the use of algorithms or Bayesian models (Macedo et al, 2006). None of the methods are universally consensual. One of the most commonly used is the one from the World Health Organisation (WHO) (Waller and Harrison-Woolrych, 2017).

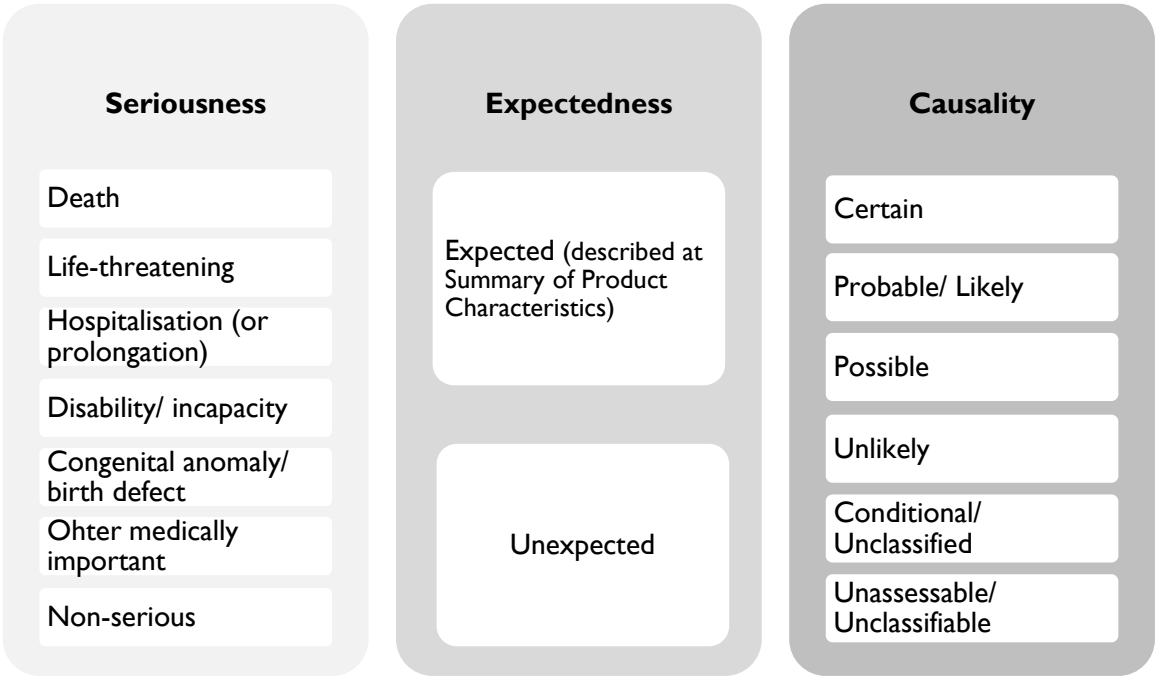

Figure 2.1 – *Criteria used in the classification of suspected adverse drug reactions according to their seriousness, expectedness and causality (based on WHO methodology).*

Adverse effects have a serious impact on public health. In the European Union (EU), it is estimated that 197000 patients die per year. Adverse drug reactions are the 5th cause of death among hospitalized patients and are responsible for 5% of patient hospital admissions (Commission of the European Communities, 2008). Among hospitalized patients, 0.006 to 13.3 (per 100 patients) are preventable ADRs (Wolfe et al, 2018). In

the United States (US), spontaneous reports increased 2.6-fold, and fatal adverse drug reaction increased 2.7-fold, in a period of seven years (Moore et al, 2007). Adverse drug reactions have also a huge economic burden. A study estimated that the "direct costs" in ambulatory varied from €702.21 to €40,273.08, and the in-hospital from €943.40 to €7,192.36 (Batel Marques et al, 2016).

The first report of an adverse effect occurred in 1848, in England. A young female patient died after chloroform anaesthetic exposure. Other cases of adverse effects were sent by health professionals to publishers of scientific Journals. These cases were published to keep aware of other health professionals (Fornasier et al, 2018). In the 1960's, thousands of cases of congenital malformation in babies following thalidomide exposure in pregnancy occurred. This was known as the thalidomide tragedy. After this disaster, several measures to monitor drug's safety were implemented, namely the organised systems to collect spontaneous reports of suspected adverse drug reactions, the development of legislation, the development of authorities able to perform pharmacovigilance activities and the involvement of health professionals and consumers on pharmacovigilance activities (Fornasier et al, 2018; World Health Organisation, 2002).

Since then, several adverse drug reactions have been identified through systematic reviews, meta-analysis, experimental and non-experimental studies, case reports and spontaneous reports (Alves et al, 2013). However, spontaneous reporting continues to be the method that generates more drug safety signals and, consequently, supports drug safety alerts and regulatory authorities' decisions (Alves et al, 2013; Penedones et al, 2015).

Several drugs were withdrawn from the market. A systematic review identified 462 drugs withdrawn from the market between 1953 and 2013 (Onakpoya et al, 2016). Some of these drugs are described in Table 2.2. The most common adverse drug reactions were hepatic disorders, immune system disorders, nervous system disorders, and cardiac disorders. A large percentage of these withdrawals were supported by case reports (McNaughton et al, 2014; Onakpoya et al, 2016).

Table 2.2 – *List of some drugs withdrawn from the market due to safety reasons (Source: McNaughton et al, 2014; Onakpoya et al, 2016).*

Drug	Adverse reaction	Length of time on market	Evidence level*
Aprotinin	Anaphylaxis	48 years	4
Benfluorex	Cardiotoxicity	33 years	3

Drug	Adverse reaction	Length of time on market	Evidence level*
Buflomedil	Neurological and cardiac disorders	37 years	4
Carisoprodol	Intoxication; Psychomotor impairment; Addiction; Misuse	48 years	4
Celecoxib	Increased risk of serious cardiovascular events	8 years	3
Cerivastatin	Renal, musculoskeletal disorders	4 years	4
Chlormezanone	Skin, drug dependence, liver	36 years	4
Domperidone (injectable)	Cardiovascular, drug overdose, endocrine, nervous system disorders	6 years	4
Drotrecogin alfa (activated)	Insufficient evidence; bleeding risk	10 years	1
Grepafloxacin	Cardiovascular disorders	2 years	4
Lumiracoxib	Hepatotoxicity	4 years	4
Nefazodone	Hepatotoxicity	9 years	4
Orciprenaline	Cardiac disorders	49 years	4
Pemoline	Hepatotoxicity	45 years	4
Rimonabant	Psychiatric disorders	2 years	1
Rofecoxib	Thrombotic events	5 years	1
Rosiglitazone	Cardiovascular disorders	10 years	1
Sibutramine	Cardiovascular disorders	11 years	4
Sitaxentan	Hepatotoxicity	4 years	4
Thioridazine	Cardiac disorders; Retinopathy	47 years	4
Valdecoxib	Cardiovascular and cutaneous disorders	2 years	2
Veralipride	Neurological and psychiatric disorders	28 years	4
Ximelagatran	Hepatotoxicity	3 years	2

* Based on Centre for Evidence-Based Medicine (2009) Levels of Evidence: 1 - Systematic review of randomized trials, systematic review of nested case-control studies; 2 - Individual randomized trial or (exceptionally) observational study with dramatic effect; 3 - Non-randomized controlled cohort/follow-up study (post-marketing surveillance); 4 - Case-series (and poor quality cohort and case-control studies).

2.2. Methods in Pharmacovigilance

Pharmacovigilance acts in all phases of the drug's lifecycle, from pre- to post-marketing phase. It begins with the selection of the first dose in humans and with the protection of the human subject in clinical trials, including the informed consent and the periodic safety data monitoring. During the clinical development, the safety profile is identified and characterized (Beninger, 2018). However, pre-marketing clinical trials have limitations such as the reduced sample size, the homogenous population, and the duration of the clinical trials that makes difficult to identify and characterize the drug's safety profile (Härmark and Edwards, 2009). Nonetheless, almost 80% of the adverse drug reactions described in the SmPC is identified during the pre-marketing clinical development and are

adverse drug reactions of type A (Beninger, 2018). At post-marketing phase, through methods besides clinical trials, such as observational studies and spontaneous reporting, new adverse drug reactions are identified, namely those of type B, C, D, E and F (Nóren and Edwards, 2009; Beninger, 2018).

There are two types of methods in Pharmacovigilance: descriptive and analytic methods. The descriptive methods are useful to generate hypothesis, this is to identify new potential adverse drug reactions. Spontaneous reporting is an example of a descriptive method. This method is part of national pharmacovigilance systems (Waller and Harrison-Woolrych, 2017). Health professionals and consumers can identify suspected adverse drug reaction during drug's clinical practice utilisation. Therefore, this suspicion is spontaneously reported to the regulatory authorities or market authorisation holders. Then, the spontaneous report is assessed and transmitted to a database. Several techniques are applied to spontaneous reporting databases in order to detect and generate a safety signal (Härmark and von Grootheest, 2008). This method is cheap and can generate earlier hypothesis based on data from drug's clinical practice (Strom, 2006). Other example of a descriptive method is the intensive monitoring. Along as spontaneous reporting, this method is used in clinical practice including real world data from several groups of patients. However, the monitored drugs and period of follow-up time are previously defined before starting the intensive monitoring. This method allows to quantify incidence of adverse drug reactions and identify safety signals (Härmark and Grootheest, 2008).

The analytical methods are useful to test hypothesis, this is to confirm new adverse drug reactions by describing the causal association between an adverse drug reaction and a drug. Post-marketing clinical studies are an example of an analytical method. Since post-marketing clinical trials, to observational studies, such as cohort studies and case-control studies, to post-authorization safety studies; there are several study designs that, depending on the research hypothesis, can be applied to confirm a safety signal (Waller and Harrison-Woolrych, 2017).

Some of the methods described above are both descriptive and analytical such as clinical studies. Databases of health records are another example. There are four main types of databases, depending on the source of information: spontaneous reporting databases (e.g. VigiBase, Eudravigilance, etc.); intensive monitoring databases (e.g. Drug Safety Research Unit, Intensive Monitoring Medicines Program, etc.); large administrative

databases or electronic health records (e.g. healthcare insurance claims databases); and electronic medical records databases (e.g. General Practice Research database, etc.). These databases allow to identify and to confirm safety signals. In general, they are dependent on the quality of the sources of information (Nóren and Edwards, 2009).

In Table 2.3. are presented some examples of post-marketing descriptive and analytical methods and both their advantages and disadvantages.

Table 2.1 *– Post-marketing methods in pharmacovigilance (Härmark and von Grootheest, 2008; Nóren and Edwards, 2009; Waller and Harrison-Woolrych, 2017).*

Methods	Advantages	Disadvantages
Spontaneous reporting	Less expensive Easy to apply All healthcare professionals and consumers can participate Can study all population Can generate safety signals earlier	Cannot be used for test safety signals Potential for underreporting Potential for selective reporting Incomplete information
Intensive monitoring	Non-interventional Can study all population Can generate safety signals	Cannot be used for test safety signals Studied drugs are previously defined Potential for underreporting Estimate event rates (instead of incident rates) No control group
Databases	Can generate safety signals Can test safety signals	Dependent on the limitations of sources of information
Clinical trials (post-marketing)	Low risk of bias (due to allocation, randomization, blinding, control group)	Homogenous population Reduced sample size Short duration
Cohort studies	Can study multiple outcomes Can study uncommon exposures Selection bias less likely Unbiased exposure data Incidence data available	Possibly biased outcome data More expensive If done prospectively, may take years to complete
Case-control studies	Can study multiple exposures Can study uncommon diseases Logistically easier and faster Less expensive	Control selection problematic Possibly biased exposure data

2.3. Role of systematic review in pharmacovigilance

Besides descriptive and analytical methods, there are other research methods that can be used in pharmacovigilance. Systematic reviews and meta-analysis can combine data from several studies (Higgins et al, 2019). Meta-analysis can also test research hypotheses by applying statistical techniques to data from several studies (Chalmers and Altman, 1995).

Systematic reviews can be used by healthcare professionals in their clinical decision process, making it faster. For instance, O'Mathúna (2010) described the role of the systematic review in clinical decision by nurses in the hypothetical situation of a child with fever. Moreover, several systematic reviews assess specific questions related with drug's safety, including risk estimates, which are important data useful in clinical decision process (Alves et al, 2017; Alves et al, 2019).

Several drugs were withdrawn from the market based on the results of systematic reviews. Some examples include ketoconazole withdrawn by hepatotoxicity, rimonabant by psychiatric reactions, rofecoxib by cardiotoxicity, and rosiglitazone by cardiac reactions (Onakpoya et al, 2016).

The results of the systematic reviews can also be used to develop clinical practice guidelines. The European Association of Urology defined some guidance to help performing systematic reviews to enable clinical practice guidelines development (Knoll et al, 2018). Similarly, a systematic review can identify already published clinical practice guidelines. Lin et al (2019) identified 11 recommendations to manage musculoskeletal pain by performing a systematic review.

In research, systematic reviews can identify potential gaps in knowledge and, consequently, generating future research hypothesis (Moher et al, 2009). This allows to answer clinical questions and to improve the quality of the available evidence, by reviewing its methodological limitations (Haddaway and Pullin, 2014).

Challenges

Although the recognized value of systematic reviews in pharmacovigilance, they present some challenges. These are mainly related with systematic review's methodology (Nicholson et al, 2017).

At first, the investigators need to choose a recommendation to conduct and to report the systematic review, which will determine the methodological quality of the systematic review (Anderson and Jayaratne, 2015; Nicholson et al, 2017).

Secondly, drug's safety is characterized by different types of data, from randomized controlled trials (RCT) to case reports, and consequently involves searching in several sources of information and appraise results of different study designs (Anderson and Jayaratne, 2015; Nicholson et al, 2017).

2.5. Objectives of this thesis

A single recommendation to conduct and/or report systematic reviews is of major importance. How to plan and conduct a systematic review evaluating several types of studies on drug's safety evaluation and to understand the limitations and advantages of the actual recommendations is also a priority in order to produce systematic reviews more accurately and robust, and capable to support decisions both in regulatory and clinical settings.

The research question of this thesis is the following:

- Are the available recommendations to conduct and report a systematic review prepared to be used in drug's safety assessment?

In order to answer the research question, this work was divided into five stages:

1- A scoping review was conducted to identify, review and characterize the published recommendations to conduct and/or to report a systematic review in medical interventions area (first article, chapter 3);

2- Considering Ophthalmology as a case study, a systematic review was conducted to characterize and review the methodology of the systematic reviews reporting ophthalmic adverse drug reactions (second article, chapter 4).

3- A comparison of the methodologies of the two most commonly used recommendations to conduct and report systematic reviews on drug's safety was performed (third article, chapter 5).

4- Two systematic reviews and meta-analysis were conducted according to the two most commonly used recommendations to conduct and report systematic reviews on drug's safety. The association of non-arteritic ischemic optic neuropathy with phosphodiesterase type 5 inhibitors exposure was used as a case study. We report the results of the two systematic reviews in chapter 6 (fourth article) and chapter 7.

5- Discussion on the issues of performing and reporting a systematic review on drug's safety, based on the methodology of the existing recommendations (chapter 8).

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Chapter 3 - Recommendations to conduct and report systematic reviews in medical literature: a scoping review

3.1. Abstract

Background: This scoping review aims to identify, review and characterize the published recommendations to conduct and/or to report a systematic review in medical interventions area.

Methods: A search was carried out in PubMed, EMBASE and Cochrane Library databases, using systematic reviews search filters. The search comprises all recommendations to conduct and/or report a systematic review. Data on methods were extracted from each recommendation. A descriptive analysis was performed.

Results: Eighty-three recommendations were identified. Approximately 60% of retrieved references were published in the last 6 years. Recommendations to both conduct and report a systematic review were issued in 47% studies. The guidance presented in each recommendation to conduct and/ or report a systematic review varied. Almost 96% of the recommendations offer guidance on systematic review methods section. The need and time for updating was only recommended in 29% of recommendations. Forty percent of recommendations endorsed their methods to any subject related to medical interventions. Half of the studies did not specify the design of studies to be included in a systematic review.

Conclusion: Several recommendations to conduct and/or report a systematic review were published and offered different guidance. Further research on the impact of such heterogeneity can improve systematic reviews quality.

3.2. Introduction

A systematic review aims to collect evidence from the research literature, using systematic and explicit methods, to answer a clearly formulated research question (Antman et al, 1992; Oxman and Guyatt, 1993). It is a rigorous methodology used to identify, select, assess methodological quality, analyse and discuss relevant studies (Antman et al, 1992; Oxman and Guyatt, 1993). These characteristics distinguish a systematic review from other type of reviews, since the systematic appraisal of studies based on methodological quality can provide useful information to clinical decision

process, regulatory decisions, and clinical guidelines (Antman et al, 1992; Oxman and Guyatt, 1993; Moher et al, 2009).

The first clinical systematic review was published in 1955 in the Journal of the American Medical Association (JAMA) (Beecher, 1955). At the end of 80s, it was published the first systematic review and meta-analysis in the health field entitled 'Effective Care during Pregnancy and Childbirth' (Chalmers et al, 1989). In the year of 2015, approximately 950 reviews were published only on the Cochrane Database of Systematic Reviews (Cochrane Collaboration, 2018).

Several groups have been dedicated to develop and improve systematic review methodology. In the 90s, the Cochrane Collaboration was created with the goal of "prepare, maintain, and disseminate systematic reviews" (Cochrane Library, 2018). Later, this group published the "Cochrane Handbook for Systematic Reviews of Interventions" (Higgins and Green, 2011). Other main groups developed their own guidance on systematic reviews, such as the Centre for Reviews and Dissemination (CRD) which published "Systematic Reviews CRD's guidance for undertaking reviews in healthcare" (Centre for Reviews and Dissemination, 2009); and The Joanna Briggs Institute (JBI) which developed the "The JBI Reviewer's Manual" (Aromataris and Munn, 2017). In 1999, a group developed guidance on the reporting of meta-analysis (the QUOROM, QUality Of Reporting Of Meta-analyses) (PRISMA, 2018). Ten years later, this guidance was updated and included recommendations on the reporting of systematic reviews (PRISMA, Preferred Reporting Items of Systematic reviews and Meta-Analyses) (PRISMA, 2018). Since then, the PRISMA group has been developing specific recommendations on the reporting of systematic reviews, such as abstracts, equity, harms, diagnostic test accuracy, among others (PRISMA, 2018). The PRISMA Statement has been endorsed by several scientific journals as the recommend guidance to report a systematic review (PRISMA, 2018).

The selection of a methodology will depend on the research question and type of review (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017). It is recognized that the majority of the recommendations to conduct a systematic review follow four primary steps: 1) review of the literature; 2) selection of criteria to include studies for analysis; 3) extraction of the data from the selected studies; and 4) analysis of the extracted data (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017).

Since several recommendations are available to help to conduct and/or reporting a systematic review, the knowledge of each recommendation along with the specificity and individuality of each area (for instance by disease or by type of intervention) could define the best methodology to adopt on the conduct and/or report of a systematic review.

The objective of this scoping review is to identify, review and characterize the recommendations available in healthcare literature to conduct and/or to report a systematic review.

3.3. Methods

This scoping review was developed according to the recommendations of The Joanna Briggs Institute Reviewer's Manual – Methodology for Scoping Reviews (Aromataris and Munn, 2018).

3.3.1. Literature search and data selection

A search was carried out in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (https://www.embase.com/), and Cochrane Library (http://cochranelibrary-wiley.com/cochranelibrary/search/advanced) databases. The databases were searched since its inception until July 17, 2018. The search terms comprised systematic reviews methodology. A filter was applied to restrict the search to English articles. The reference list of all identified articles was also hand searched for additional studies. The literature search and search strategy are listed in the Appendix, Table 1.

Articles were selected for inclusion if they meet the following selection criteria: published in English language; conducted in humans; and were recommendations to conduct and/or to report a systematic review of healthcare interventions (e.g., drugs, medical, surgical, behavioural and occupational therapy, and diagnostic testing). Articles describing exclusively the use of qualitative evidence were excluded. Articles such as editorials, letters, commentaries, and abstracts from congresses, and articles describing recommendations on how to read or to interpret a systematic review were also excluded. A recommendation could be described in a series of articles or in a single article, this is, in one or more references.

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. Disagreement was resolved by discussion and consensus.

3.3.2. Data extraction

The following information was extracted independently from each article:

A. Reference, including authors' names and year of publication;

B. Methodological design used to develop a recommendation to conduct and/or report a systematic review, classified between review or consensus study;

C. Name attributed to the recommendation, if applicable;

D. Type of recommendations: to conduct and/or report a systematic review. A recommendation to conduct a systematic review describes the steps to perform it; instead of a recommendation to report a systematic review which describes on how it should be write;

E. Suggested methodology to conduct and/or report a systematic review; the methodological recommendations analysed were divided into the following sections: 1) introduction; 2) identification of the research question; 3) definition of research protocol; 4) definition of eligibility criteria; 5) execution of literature search; 6) identification of sources of information; 7) data selection; 8) data extraction; 9) risk of bias/methodological quality assessment; 10) data analysis; 11) presentation of results; 12) interpretation of results; 13) discussion/conclusion of results; 14) need and time for updating; 15) helpful material;

F. The subject of the methods issued, for example by disease or study area;

G. Type of studies to be included in the systematic review, for instance, randomized controlled trials (RCT), observational studies, among others;

H. Study group's name, this is who issued the methodology, if applicable.

3.3.3. Data analysis

Data were analysed using descriptive statistics. Statistical analyses were conducted with Microsoft Excel 2010 (Microsoft Corporation, Santa Rosa, CA).

3.4. Results

A total of 3,034 potentially relevant references were yielded from literature search. Twenty additional references were identified. Based on the above inclusion criteria, 210 references were selected for full-text further inclusion. A final sample of 131 references covering 83 different recommendations met the inclusion criteria (some recommendations were described in a series of references, this is, in more than one article). The selection of references is shown in Figure 3.1. The references of the included and excluded studies are listed in the Appendix, Table 2.

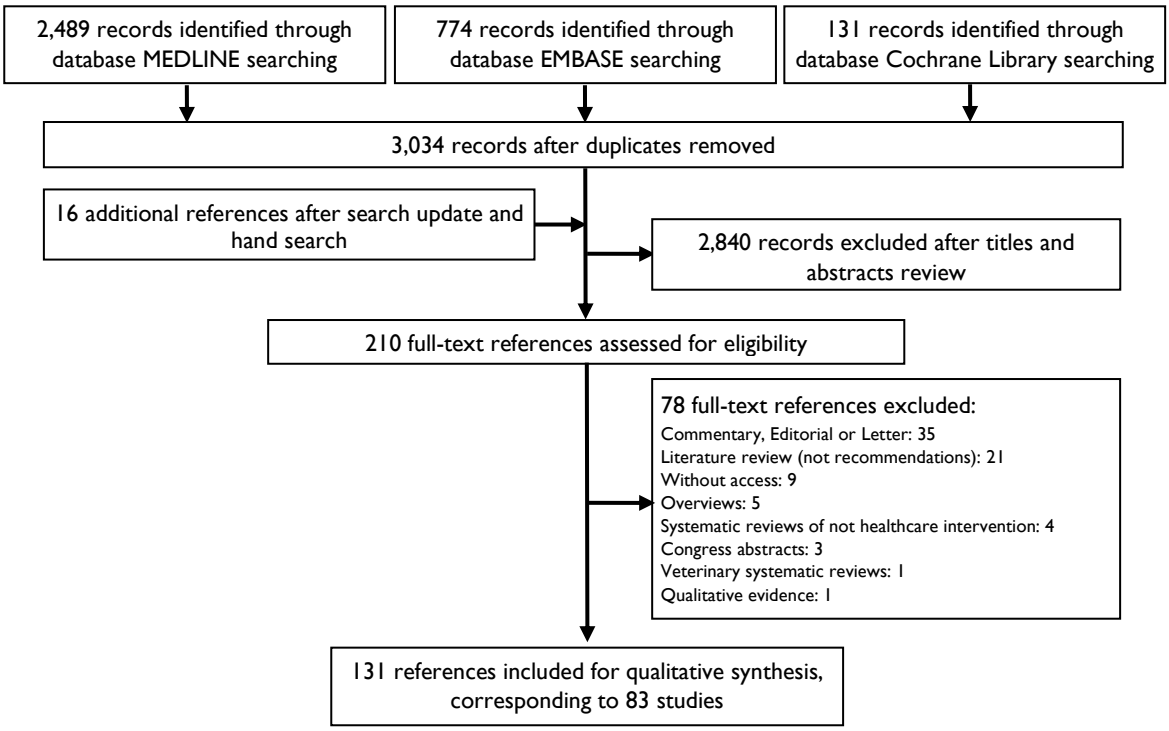

Figure 3.1 *- Flow diagram of Literature search.*

Sixty-three percent (n = 83/131) of retrieved articles were published since 2012 (Appendix-Table 3). Sixty out of 83 (72%) recommendations were developed through a review study, whereas 23 (28%) as a consensus study.

Guidance to conduct and report a systematic review were issued in 39 (47%) recommendations. Only 10% (n = 8/83) of recommendations described guidance on how to report a systematic review. The type of recommendations is described in Figure 3.2. A detailed description of the recommendations is presented in Appendix-Table 3.

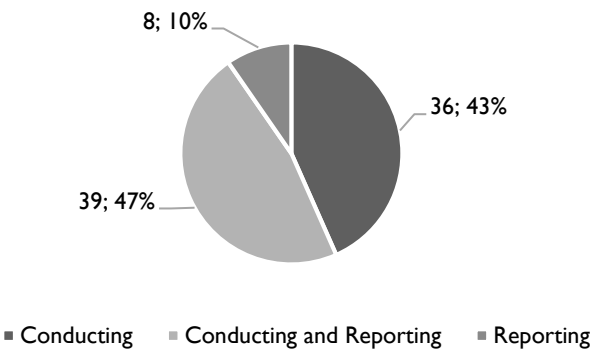

Figure 3.2 *- Type of recommendations, to conduct and/or report a systematic review.*

Table 3.1 describes the methods' sections to conduct and/or report a systematic review for which the recommendations offered guidance.

Methodological steps to analyse data, assess risk of bias/ methodological quality and define eligibility criteria were addressed by most of the recommendations (between 98% and 99% of recommendations). The definition of an a priori research protocol was less often recommended (59 (71%) recommendations). An orientation about how to prepare an introduction, including the background and purpose of systematic review, was only comprised in 38 (46%) recommendations. Guidance about the need and time for updating the systematic review were included in only 24 (29%) recommendations. Thirty (36%) recommendations made available supportive material to conduct and/or report a systematic review, such as tables, graphics, methodological quality assessment scales, and/or flowcharts.

Table 3.1 *- Methods to conduct and/or report a systematic review as suggested in each study.*

Methods to conduct and/or report a systematic review	**N (%)[¥]**
Introduction (background, purpose)	38 (46%)
Identification of the research question	78 (94%)
Definition of research protocol	59 (71%)
Definition of eligibility criteria	81 (98%)
Execution of literature search	79 (95%)
Identification of sources of information	76 (92%)
Data selection	79 (95%)
Data extraction	73 (88%)
Risk of bias/methodological quality assessment	81 (98%)
Data analysis	82 (99%)
Presentation of results	75 (90%)
Interpretation of results	66 (80%)
Discussion/conclusion of results	60 (72%)
Need and time for updating	24 (29%)
Helpful material (tables, graphics, methodological quality assessment scales, flowcharts)	30 (36%)

[¥]The table presents the number of recommendations that issued each specified method.

Thirty-three (39.8%) recommendations endorsed their methods to any subject related to healthcare interventions. Twenty (24%) recommendations are specific of a

clinical subject, such as cardiology, pain, nephrology, and sports medicine and orthopaedic surgery. Eleven (13.2%) recommendations addressed guidance on the conduction and/or report of systematic reviews about investigation procedures. Other subjects, such as economic evaluation, were also studied. The subject of recommendations is presented in Table 3.2.

Table 3.2 *- Subject of the methods issued to conduct and/or report a systematic review by each study.*

Subject of methods	**N (%)**
Any	33 (39.8%)
Any, Adverse effects, Economic evidence, Qualitative research, Public health and health promotion[¥]	1 (1.2%)
Any, Diagnostic tests, Prognostic tests, Public health interventions, Adverse Effects, Economic evaluations, Qualitative evidence[¥]	1 (1.2%)
Any, Qualitative evidence, Quantitative evidence, Economic evidence, Textual and non-research evidence, Text and opinion data[¥]	1 (1.2%)
Clinical Subject	20 (24.0%)
Cardiology	4 (4.8%)
Pain	2 (2.4%)
Nephrology	2 (2.4%)
Sports medicine and orthopaedic surgery	2 (2.4%)
Geriatric	1 (1.2%)
Neck and back pain, and related spinal disorders	1 (1.2%)
Nutrition	1 (1.2%)
Ophthalmology	1 (1.2%)
Pathology	1 (1.2%)
Plastic and Reconstructive Surgery	1 (1.2%)
Pregnancy and childcare	1 (1.2%)
Radiology	1 (1.2%)
Tuberculosis	1 (1.2%)
Urology	1 (1.2%)
Investigation procedures subject	11 (13.2%)
Diagnostic test	5 (6%)
Diagnostic test and prognostic test	2 (2.4%)
Medical tests, genetic tests, and prognostic tests	1 (1.2%)
Radiography	1 (1.2%)
Surgical procedures	1 (1.2%)
Toxicology	1 (1.2%)
Other healthcare interventions	8 (9.6%)
Rehabilitation	3 (3.6%)
Nursing practice	2 (2.4%)
Paediatric practice nursing	1 (1.2%)
Physiotherapy	1 (1.2%)
Occupational therapy	1 (1.2%)
Others	8 (9.6%)
Economic	2 (2.4%)
Harms	2 (2.4%)
Anatomy	1 (1.2%)
Complex multicomponent health care interventions	1 (1.2%)
Patient-reported outcome measures	1 (1.2%)
Prediction model performance	1 (1.2%)
Total	**83 (100%)**

[¥]Each recommendation develop methods for several types of systematic reviews.

Fifty-two (62.7%) recommendations did not specify the studies' design to be included in the systematic review. Among those addressing this issue, clinical trials and randomized controlled trials were the type of study preferred to conduct a systematic review (n=9; 10.8%). The type of studies eligible for inclusion in the systematic review is presented in Table 3.3.

Table 3.3 *- Type of studies eligible for inclusion in the systematic review recommended by each study.*

Type of studies	**N (%)**
Any	52 (62.7%)
RCT	6 (7.2%)
Diagnostic test studies	6 (7.2%)
Clinical trials	3 (3.6%)
Economic evaluations	2 (2.4%)
Diagnostic and prognostic studies	2 (2.4%)
Adverse events	1 (1.2%)
Aetiology studies	1 (1.2%)
Anatomical studies	1 (1.2%)
Evidence on equity	1 (1.2%)
Medical tests, genetic tests, and prognostic tests	1 (1.2%)
Network meta-analysis	1 (1.2%)
Observational studies	1 (1.2%)
Observational studies reporting prevalence and cumulative incidence data	1 (1.2%)
Protocols	1 (1.2%)
RCT, observational studies, diagnostic tests*	1 (1.2%)
Studies of older people	1 (1.2%)
Validation studies	1 (1.2%)
Total	**83 (100%)**

*The recommendation developed methods to conduct a systematic review with each type of study.

Sixty-seven percent of the recommendations were issued by individual groups/authors, without being affiliated with any particular organisation researching in methods used in systematic review. Some organisations such as The Joanna Briggs Institute, The Cochrane Collaboration, The Centre for Reviews and Dissemination, and the Agency for Healthcare Research and Quality also developed, at least one, recommendation to conduct and/or report a systematic review. The distribution of the recommendations by study groups is presented in Table 3.4.

Table 3.4 *- Study groups, who issued the methods to conduct and/or report a systematic review.*

Study group	N (%)
PRISMA	7 (8.4%)
The Joanna Briggs Institute	6 (7.2%)
The Cochrane Collaboration	4 (4.8%)
AHRQ	3 (3.6%)
AHRQ and JGIM	1 (1.2%)
American Heart Association	1 (1.2%)
Centre for Reviews and Dissemination, University of York	1 (1.2%)
COSMIN	1 (1.2%)
European Association of Urology	1 (1.2%)
World Association of Laser Therapy	1 (1.2%)
Other (individual groups/authors)	57 (67.5%)
Total	83 (100%)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; AHRQ: Agency for Healthcare Research and Quality; JGIM: Journal of General Internal Medicine; COSMIN: Consensus-based Standards for the selection of health Measurement Instruments.

3.5. Discussion

In the last years, several organisations and individual groups have published recommendations to conduct and/or report a systematic review. In general, they can be applied to study any healthcare intervention, combining different types of evidence. The recommendations focus on the methods of the systematic review.

In the present study, only orientations about systematic review were identified, characterized and reviewed; however, some of the recommendations include guidance to conduct and/or to report a meta-analysis.

More than half of the recommendations evaluated in this study were published in the last six years. The volume of information and new studies is growing. In MEDLINE, one of the largest databases of medical literature, more than 8 million of articles where indexed in 23 years (Page et al, 2016). In addition, systematic reviews synthesize several types of study, such as network meta-analysis, adverse events, economic studies, among others (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017). The need for specific recommendations addressing this type of studies was also increased over time. This can explain the growth of certain organisations such as the Cochrane Collaboration or the JBI and the development of such specific recommendations (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017). Moreover, regulatory authorities required a compilation of various individual studies in the health technology assessment, for instance in market access (Kumar et al, 2014), in its re-evaluation and to monitoring its benefit-risk ratio (European Medicines Agency, 2013). A systematic review becomes a recognized need to support informed decisions in medicine. A study by Bastian et al.

estimated that 11 systematic reviews are published per day (Bastian et al, 2010). Therefore, guidance on how to conduct and/or report a systematic review of any kind becomes essential.

According to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, the development of a recommendation should include a review of all existing evidence on the research question and an evaluation of this data by a panel of experts. After that, a consensus is achieved on which steps a recommendation should follow (GRADE Working Group, 2004). However, among the recommendations analysed in this study, approximately 70% were published under a review study, and only 30% were developed based on a consensus of a panel of experts.

Some organisations were created to study and develop guidance on the best synthesis of different types of information and, thereafter, the elaboration of systematic reviews (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017). In this review, nearly 32% of the recommendations were issued by these organisations. The other 68% were issued by individual groups/authors. The growth in publication of scientific studies reflects the need to conduct methodological well/structured reviews of the literature (Page et al, 2016). This may also result in the increase of recommendations to conduct and/or report systematic reviews, particularly recommendations for a specific area, such as safety or economic evaluations.

A recommendation to conduct and/or report a systematic review should list and detail all fundamental steps to help authors to write, or scientific journals to appraise a systematic review. From the recommendations characterized in this review, between 88% and 99% developed guidance on methods (from the definition of eligibility criteria to data analysis). The elaboration and publication of a systematic review protocol improves transparency and avoids duplication of work (Higgins and Green, 2011). In this review, only half of the recommendations addressed the elaboration of a protocol. Nowadays, there are several ways to publish a systematic review protocol, such as registration in PROSPERO (International prospective register of systematic reviews) or publication of the protocol in peer-reviewed journals (Moher et al, 2009). However, a significant proportion (44%) of the recommendations issuing the elaboration of a protocol was published during the last four years (since 2015). This becomes interesting since it shows the importance of continuing to address this step in the recommendations to conduct and/or report a systematic review. Despite the majority of the recommendations offer

orientations on how to define the research question, the elaboration of the Introduction was the step less described. Describing the background and the purpose of the systematic review may help readers to understand the research question and make a most properly judgement of the results, increasing the systematic review quality (Moher et al, 2009; Page et al, 2016). Approximately 76% of the recommendations present guidance on the interpretation and discussion of the results. This proportion seems to be low, since systematic reviews' main goals are to inform and help the interested parties in the decision-making processes. 'Need and time for updating' was the step less recommended. Systematic reviews are constantly out of date with new evidence published every day (Shojania et al, 2007). Recently, the panel for updating guidance for systematic reviews (PUGs) group had illustrated the importance of update systematic reviews and developed some guidance that can help authors and readers to understand when to update a systematic review (Garner et al, 2016). Moreover, in 2014, the concept of living systematic review emerged (Elliott et al, 2017). This intended to continually updated a systematic review (of any type). It predisposes a periodic search and the constant update since new data arises (Elliott et al, 2017). Nonetheless, despite some guidance for updating systematic reviews are available, it is still necessary to include this step in the recommendations to conduct and/or report a systematic review.

In this review, all recommendations presented some differences in methodology which may lead to some bias, such as reporting bias. This bias reflects the influence on their reporting, which can lead to a misunderstanding of the results (Cochrane Methods Bias, 2017). If the recommended methodology to conduct a systematic review is not clear enough, the results and conclusions of the produced systematic review could be flawed, limiting its importance and objective (Page et al, 2016). Such methodological impairments may compromise the comparability of systematic reviews addressing the same research question, eligibility criteria, search criteria, and time of research, but which follow different recommendations (Siontis et al, 2013). Therefore, their results, based on the same studies, may be biased and presented in different ways. Thus, each systematic review could present its own conclusions, introducing confounding in health decision-making (Siontis et al, 2013).

Eight recommendations were specifically developed to address the reporting of systematic reviews. Seven of these recommendations were developed by PRISMA working group. Currently, PRISMA has becoming a wide-scale adopted guideline, used by authors

to report and by scientific journals to appraise a systematic review (PRISMA, 2018). The PRISMA, a guideline created to increase the quality of reporting a systematic review, aims at enhancing transparency, reliability, and ease of reading (PRISMA, 2018). Several studies demonstrated the poor quality of systematic reviews when they are not compliant with a reporting guideline (PRISMA, 2018). Despite the publication and dissemination of PRISMA, there are several studies showing the suboptimal compliance to this guidance when reporting a systematic review (Page and Moher, 2017; Pussegoda et al, 2017). Moreover, one of the PRISMA extensions, PRISMA of Diagnostic Test Accuracy (PRIMSA-DTA), has recently being update in order to improve the reporting in systematic reviews of this type (McGrath et al, 2019).

The safety of healthcare interventions is of major importance. The knowledge of their safety profile should be continuously updated to keep healthcare professionals, consumers, and healthcare regulators informed (Higgins and Green, 2011; Centre for Reviews and Dissemination, 2009; Aromataris and Munn, 2017). To characterize the safety profile, several types of information provided by distinct sources need to be consulted. In opposite to efficacy data, safety data is mainly obtained from post-marketing surveillance data sources, which comprises several types of studies, such as post-marketing clinical trials, observational studies, case reports, and spontaneous reports of adverse events (Penedones et al, 2015). Combining evidence from these several sources presupposes some specific methodology in conducting and/or reporting systematic reviews. This review identified four recommendations addressing how to conduct and/or report systematic reviews of adverse events.

Some other relevant areas related to healthcare interventions were also taken into consideration, such as economic evaluations of healthcare interventions. Expenditure with pharmaceuticals may account for a significant amount of health spending, depending on the countries (OECD Data, 2018). Thereafter, pharmacoeconomic studies become essential in supporting the appraisal of medical interventions, medicines and their market access (Kumar et al, 2014). A systematic review of these studies is important for healthcare policy making (Gomersall et al, 2015). However, the role of systematic review to synthesize economic evaluations has been questioned (Anderson, 2010). Not only due to the specific design of economic evaluations, such as type of analysis, perspective adopted, among others, but also because economic evaluations already synthesize

information (Anderson, 2010). Thus, the elaboration of specific recommendations to conduct and/or report a systematic review of economic evaluations may be valuable.

Almost half of the analysed recommendations did not specify the design of studies to be included in a systematic review. Some recommendations only endorse the inclusion of randomized controlled trials, because of its classification such as the highest level of evidence (Centre for evidence-based medicine, 2009). Nonetheless, the type of studies selected must reflect the objective of the systematic review. In a systematic review evaluating the effectiveness of investigation procedures, such as diagnostic tests, studies evaluating the accuracy of diagnostic tests must be chosen (Leeflang, 2014). Naturally, the methodological quality level of the evidence chosen will be varied. However, an evaluation of the risk of bias or methodological quality of the studies included must be conducted. Hereafter, the results of this evaluation must be included in the interpretation of the results of the systematic review (Moher et al, 2009; Higgins and Green, 2011).

This scoping review has several limitations. An a priori protocol was not previously published. The search was conducted according to the PubMed, EMBASE and Cochrane Library databases indexed terms for studies about systematic reviews' methodology. These indexed terms may not comprise all recommendations published in literature. Despite the combination of these terms with free terms such as "methods", the search strategy may not be comprehensive and some references may not have been included. References from other languages than English were not analysed. In addition, grey literature was not searched. This could lead to the exclusion of some recommendations. Therefore, the results must be interpreted carefully. This review offers an overview of what is published and does not intend to address criticism or influence the choice of a specific recommendation. The preliminary results of this study were presented at ISPOR Europe 2018: New Perspectives for Improving 21st Century Health Systems (Penedones et al, 2018).

3.6. Conclusion

Several recommendations to conduct and/or report a systematic review are available to combine evidence from diverse healthcare areas. Such recommendations differ in some methodological aspects. Further research on the implications of such heterogeneity seems important, in order to guarantee systematic review transparency, quality and its role in healthcare.

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3.8. Appendix

Appendix - **Table 1** - Search literature and Search strategy.

Search	Equation	Results
MEDLINE		
#1	"Review Literature as Topic"[Majr]	4,189
#2	"methods"[MeSH Terms] OR "methods"[All Fields] OR "method"[All Fields]	7,857,103
#3	#1 AND #2	2,639
#4	#3 AND English[lang]	2,489
COCHRANE LIBRARY		
#1	"Review Literature as Topic"[Majr]	180
#2	"methods"[MeSH Terms] OR "methods"[All Fields] OR "method"[All Fields]	638,931
#3	#1 AND #2	131
#4	#3 AND English[lang]	131
EMBASE		
#1	'systematic review (topic)'/mj	800
#2	'systematic review (topic)'/mj AND [english]/lim	774

Date: Since databases' inception until July 17, 2018.

Definitions on search terms according to databases websites:

"*Review Literature as Topic*" - Works about published materials which provide an examination of recent or current literature. These articles can cover a wide range of subject matter at various levels of completeness and comprehensiveness based on analyses of literature that may include research findings. The review may reflect the state of the art and may also include reviews as a literary form.

"Methods" - A series of steps taken in order to conduct research.

'systematic review (topic)' - used for items that discuss systematic reviews.

Databases of websites:

MEDLINE: https://www.ncbi.nlm.nih.gov/pubmed/

Cochrane Library: http://cochranelibrary-wiley.com/cochranelibrary/search/advanced

EMBASE: https://www.embase.com/

Appendix - **Table 2** – List of references from included and excluded studies

Included studies

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Appendix ***- Table 3*** *- Detailed description of the recommendations to conduct and/or report a systematic review.*

Recommendation (citations)	Type of study	Purpose	Subject	Organisation	Studies included
Aromataris E and Pearson A, 2014[1] Stern C et al, 2014[2] Aromataris E and Riitano D, 2014[3] Porritt K et al, 2014[4] Munn Z et al, 2014[5] Robertson-Malt S, 2014[6]	Review	Conducting and Reporting	Nursing practice	The Joanna Briggs Institute	Any
Brown PA et al, 2012[7]	Review	Conducting	Rehabilitation research	-	Any
Campbell JM et al, 2015[8]	Consensus study	Conducting	Diagnostic test	The Joanna Briggs Institute	Diagnostic test accuracy studies
Centre for Reviews and Dissemination's guidance, 2009[9]	Review	Conducting and reporting	Any, Diagnostic tests, Prognostic tests, Public health interventions, Adverse Effects, Economic evaluations, Qualitative evidence	Centre for Reviews and Dissemination, University of York	Any
Chalmers I et al, 1993[10]	Review	Conducting	Pregnancy and childcare	-	RCT
Chou R et al, 2018[11]	Consensus study	Conducting and Reporting	Harms	AHRQ	Adverse events
Cochrane Back and Neck Group, 2003, 2009, 2014, 2015[12-15]	Consensus study	Conducting and reporting	Neck and back pain, and related spinal disorders	The Cochrane Collaboration	Clinical trials
Cochrane Diagnostic Test Accuracy Working Group, 2008[16]	Consensus study	Conducting and reporting	Diagnostic accuracy	The Cochrane Collaboration	Diagnostic test accuracy studies
Cochrane Handbook for systematic reviews of interventions, 2011[17]	Review	Conducting and reporting	Any, Adverse effects, Economic evidence, Qualitative research, Public health and health promotion	The Cochrane Collaboration	Any
Cook DA and West CP, 2012[18]	Review	Conducting and Reporting	Any	-	Any
COSMIN guideline, 2018[19]	Consensus study	Conducting	Patient-reported outcome measures	COSMIN	Any
Cronin P et al, 2018[20]	Review	Conducting	Diagnostic accuracy (imaging)	-	Diagnostic imaging studies
Cronin P, 2008[21]	Consensus study	Conducting and Reporting	Any	-	Any
Crowther DM, 2013[22]	Review	Conducting and Reporting	Any	-	Any
Crowther M et al, 2010[23]	Review	Conducting	Any	-	Any
Da Costa BR and Jüni P, 2014[24]	Review	Conducting and Reporting	Any	-	RCT
Davis D, 2016[25]	Review	Conducting and Reporting	Any	-	Any
de Vet HC et al, 2005[26]	Consensus study	Conducting	Physiotherapy	-	RCT
Debray TPA et al, 2017[27]	Review	Conducting and Reporting	Prediction model performance	-	Validation studies

Recommendation (citations)	Type of study	Purpose	Subject	Organisation	Studies included
Dijkers MP et al, 2012[28]	Review	Conducting and reporting	Rehabilitation research	-	Any
Fares M et al, 2016[29]	Review	Conducting	Cardiology	-	Any
Gomersall et al, 2015[30]	Consensus study	Conducting	Economic	The Joanna Briggs Institute	Economic evaluations
Goodacre S, 2009[31]	Review	Conducting	Any	-	Any
Guise JM et al, 2014 (a)[32] Guise JM et al, 2017 (b)[33] Kelly MP et al, 2017[34] Butler M et al, 2017[35] Viswanathan M et al, 2017[36] Pigott T et al, 2017[37] PRISMA-CI: Guise JM et al, 2017 (c) [38]; Guise JM et al, 2017 (d)[39]	Consensus study	Conducting and Reporting	Complex multicomponent health care interventions	AHRQ	Any
Haase SC, 2011[40]	Review	Conducting and Reporting	Any	-	Any
Harris JD et al, 2014[41]	Review	Conducting and Reporting	Sports medicine and orthopaedic surgery	-	Any
Henderson LK et al, 2010[42]	Consensus study	Conducting and Reporting	Nephrology	The Cochrane Collaboration	Any
Hoffmann S et al, 2017[43]	Review	Conducting and Reporting	Toxicology	-	Any
Hopp L and Rittenmeyer L, 2015[44]	Review	Conducting and Reporting	Any	-	Any
Joanna Briggs Institute Reviewers' Manual, 2017[45]	Consensus study	Conducting and reporting	Any, Qualitative evidence, Quantitative evidence, Economic evidence, Textual e non-research evidence, Text and opinion data	JBI	Any
Jones T and Evans D, 2000[46]	Review	Conducting	Nursing practice	-	RCT
Kalra R et al, 2017[47]	Review	Conducting and Reporting	Cardiology	-	Any
Kelley BP and Chung KC, 2018[48]	Review	Conducting and Reporting	Plastic and Reconstructive Surgery	-	Any
Khan KS et al, 2003[49]	Review	Conducting	Any	-	Any
Khan KS, 2005[50]	Review	Conducting	Diagnostic test accuracy	-	Diagnostic test accuracy studies
Koretz RL and Lipman TO, 2017[51]	Review	Conducting and Reporting	Any	-	RCT
Kranke P, 2010[52]	Review	Conducting	Any	-	Clinical trials
Leeflang MM, 2014[53]	Review	Conducting	Diagnostic test accuracy	-	Diagnostic test accuracy
Lipp A, 2003[54]	Review	Conducting and Reporting	Surgical face marks*	-	RCT
Liu Z et al, 2013[55]	Review	Conducting	Diagnostic test and prognostic test	-	Diagnostic and prognostic test accuracy evaluations
Manchikanti L et al, 2009 (a)[56] Manchikanti L et al, 2009 (b)[57]	Review	Conducting and Reporting	Interventional pain management	-	RCT, Observational studies, Diagnostic tests

Recommendation (citations)	Type of study	Purpose	Subject	Organisation	Studies included
Manchikanti L et al, 2009 (c)[58]					
Marchevsky AM and Wick MR, 2015[59]	Review	Conducting	Pathology	-	Any
Marshall G and Sykes AE, 2011[60]	Review	Conducting and Reporting	Radiography	-	Any
Matchar DB, 2012[61] Samson D and Schoelles KM, 2012[62] Segal, 2012[63] Relevo R, 2012[64] Santaguida PL et al, 2012[65] Hartmann KE et al, 2012[66] Singh S et al, 2012[67] Trikalinos TA et al,2012 (a)[68]. Trikalinos TA and Balion CM, 2012[69]. Trikalinos TA et al, 2012 (b)[70]. Jonas DE et al, 2012[71]. Rector TS et al, 2012[72]	Review	Conducting	Medical tests, Genetic tests, Prognostic tests	AHRQ and JGIM	Medical tests, genetic tests, and prognostic tests
Menzies D, 2011[73]	Review	Conducting and Reporting	Tuberculosis	-	Any
Methodology of the European Association of Urology, 2018[74]	Consensus study	Conducting	Urology	European Association of Urology	Any
Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014[75]	Consensus study	Conducting and reporting	Any	AHRQ	Any
Milner KA, 2015[76]	Review	Conducting and Reporting	Any	-	Any
Moola S et al, 2015[77]	Consensus study	Conducting	Any	The Joanna Briggs Institute	Aetiology studies
Munn Z et al, 2015[78]	Consensus study	Conducting	Any	The Joanna Briggs Institute	Observational studies reporting prevalence and cumulative incidence data
Neely JG et al, 2010[79]	Review	Conducting and Reporting	Any	-	Any
Nguyen NH and Singh S, 2018[80]	Review	Conducting and Reporting	Any	-	Any
Nicholson PJ, [81]	Review	Conducting and Reporting	Occupational therapy	-	Any
Noordzij M et al, 2011[82]	Review	Conducting	Nephrology	-	Any
Pollock A and Berge E, 2018[83]	Review	Conducting	Stroke (rehabilitation)	-	Any
PRISMA, 2009, 2010[84-93]		Reporting	Any	PRISMA	Any
PRISMA Harms, 2016[94]	Consensus study	Reporting	Adverse events	PRISMA	Any
PRISMA-DTA, 2018[95]	Consensus study	Reporting	Any	PRISMA	Diagnostic Test Accuracy Studies
PRISMA-E, 2012, 2015, 2016[96-98]	Consensus study	Reporting	Any	PRISMA	Evidence on equity

Recommendation (citations)	Type of study	Purpose	Subject	Organisation	Studies included
PRISMA-IPD, 2015[99]	Consensus study	Reporting	Any	PRISMA	Any
PRISMA-NMA, 2015, 2016[100,101]	Consensus study	Reporting	Any	PRISMA	Network meta-analysis
PRISMA-P, 2015[102,103]	Consensus study	Reporting	Any	PRISMA	Protocols
Ravindran V and Shankar S, 2015[104]	Review	Conducting and Reporting	Any	-	Any
Rew L, 2011[105]	Review	Conducting	Paediatric nursing	-	Any
Riesenberg LA and Justice EM, 2014[106, 107]	Review	Conducting	Any	-	Any
Rudnicka AR and Owen CG, 2012 [108]	Review	Conducting	Ophthalmology	-	Any
Sambunjak D and Franić M, 2012[109]	Review	Conducting	Orthopaedic surgery	-	Any
Sayers A, 2008 (a)[110] Sayers A, 2007 (b)[111] Sayers A, 2008 (c)[112] Sayers A, 2007 (d)[113]	Review	Conducting	Any	-	Any
Schweizer ML and Nair R, 2017[114]	Review	Conducting and reporting	Any	-	Any
Scientific Statement from the American Heart Association, 2017[115]	Consensus study	Conducting	Cardiac Prevention and Treatment	American Heart Association	Any
Shenkin SD et al, 2017[116]	Review	Conducting and Reporting	Healthcare of older people	-	Studies of older people
Sousa MR and Ribeiro AL, 2009[117]		Conducting and reporting	Diagnostic and prognostic	-	Diagnostic and Prognostic Studies
Standards of World Association of Laser Therapy, 2006[118]		Conducting and Reporting	Low-Level Laser Therapy for Musculoskeletal Pain and Disorders	World Association of Laser Therapy	Clinical trials
Staunton M, 2007[119] Halligan S and Altman DG, 2007[120]	Review	Conducting	Radiology	-	Any
The EBA process, 2016[121]	Review	Conducting and Reporting	Anatomy	-	Anatomical studies
Thrift AG, 2010[122]	Review	Conducting	Any	-	Observational studies
Uman LS, 2011[123]	Review	Conducting and Reporting	Any	-	Any
Umscheid CA, 2013[124]	Review	Conducting	Any	-	Any
van Mastrigt GA et al, 2016[125] Thielen FW et al, 2016[126] Wijnen B et al, 2016[127]	Review	Conducting	Economic	-	Economic evaluations
Wanden-Berghe C and Sanz-Valero J, 2012[128]	Review	Conducting	Nutrition	-	Any
White A and Schmidt K, 2005[129]	Review	Conducting	Any	-	Any
Wieseler B and McGauran N, 2010[130]	Review	Reporting	Any	-	Any
Yanagawa B et al, 2018[131]	Review	Conducting	Cardiac surgery	-	Any

AHRQ: Agency for Healthcare Research and Quality.

Chapter 4 - Methodologic Assessment of the Systematic Reviews of Ophthalmic Adverse Drug Reactions Published in Ophthalmology Journals: A Systematic Review

4.1. Abstract

Introduction: This systematic review aims to characterize and review the methodology of the systematic reviews reporting ophthalmic adverse drug reactions.

Methods: This systematic review followed the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analyses guide. MEDLINE and EMBASE databases were searched, by all Ophthalmology journals. All systematic reviews reporting ophthalmic adverse drug reactions in the last decade were included. Data on methodology were extracted. Methodological quality was assessed through A MeaSurement Tool to Assess systematic Reviews 2 scale. Descriptive analysis was performed.

Results: Twenty-one systematic reviews were identified. Almost 60% of the systematic reviews reported non-ophthalmic drugs. Nine (43%) systematic reviews did not follow any recommendation. A search filter was not applied in 48% systematic reviews. Observational data was the source of information most included. The methodological quality was assessed in 57% systematic reviews. A meta-analysis was performed in 57% systematic reviews. The protocol's elaboration, the explanation of the sources of information and the list of excluded articles were the domains less performed in the systematic reviews.

Conclusion: The systematic reviews reporting ophthalmic adverse drug reactions diverged in some methodological aspects. Such an issue deserves further investigation, since discrepancies may lead to biased conclusions and, consequently, impact clinical and/or regulatory decisions.

4.2. Introduction

A systematic review uses systematic, rigorous and accountable methods to identify, select and critically appraise evidence from the research literature to answer an explicit formulated clinical question (Antamn et al, 1992; Oxman and Guyatt, 1993). Therefore, systematic reviews keep all interested parties, such as healthcare professionals, researchers and regulators up dated (Moher et al, 2009). The systematic review

constitutes a useful tool in the clinical decision process, including drug's benefit risk assessment; to support regulatory decisions; and to develop clinical guidelines (Moher et al, 2009).

A drug's safety must be evaluated combining different types of studies and sources of evidence to identify and characterize both common and rare adverse drug reactions (EUNETHA, 2015). In general, clinical trials often preclude definite and robust conclusions on drugs' safety owing to their limited duration and their strict inclusion/exclusion criteria that can result in a homogenous set of patients. However, the most frequent adverse reactions can be identified in clinical trials. Other types of studies, such as observational studies, case reports and spontaneous reports, can be more useful in the detection of rare and/or long-term adverse reactions, in different sets of patients (Strom, 2006; Singh and Loke, 2012).

In spite of the eye being a small and contained organ, protected by several blood-ocular barriers, a minimal damage can lead to substantial impairment (Miguel et al, 2014; Penedones et al, 2015). Ophthalmic adverse drug reactions may be induced by both ophthalmic and non-ophthalmic drugs (Miguel et al, 2014; Penedones et al, 2015). These reactions are rare and often unanticipated (Miguel et al, 2014; Penedones et al, 2015). Some cases were related with the use of well-recognizable drugs or class of drugs, for instance, intraoperative floppy iris syndrome was caused by tamsulosin and angle-closure glaucoma was caused by topiramate among others (Miguel et al, 2014; Penedones et al, 2015). Sometimes these reactions can be serious, and occasionally permanent; for instance, optic atrophy caused by ethambutol or optic neuropathy caused by amiodarone are permanent impairments (Miguel et al, 2014).

Due the difficulty involved in recognizing ophthalmic adverse drug reactions, namely, those caused by nonophthalmic drugs, data from ophthalmic adverse drug reactions is generally recorded from spontaneous reports (Miguel et al, 2014; Penedones et al, 2015). Sixty-six percent of the safety alerts of ophthalmic drug reactions issued by regulatory authorities were supported by spontaneous reports (Penedones et al, 2015). However, other sources of information, such as observational studies, may also represent an important role specially when studying the causality relation between the adverse drug reaction and the suspected drug (Miguel et al, 2014; Penedones et al, 2015).

The systematic review has been used to synthesize information on a drug's safety in Ophthalmology (Penedones et al, 2014). However, a universally accepted guideline to

perform and/or to report systematic reviews is not available. After the publication of Cochrane's first guideline (Higgins and Green, 2011), several others have been produced. These guidelines describe, in detail, the methodology to perform and/or to report systematic reviews of drug's efficacy (Golder et al, 2006). Since a drug's safety should be characterized by several heterogenous data sources, which leads to different searches to identify data sources and different methodological quality assessments, how to perform and report a systematic review on drug's safety is a recognized need (Golder et al, 2006).

This systematic review aims to assess the methodology of systematic reviews. All existing systematic reviews reporting ophthalmic adverse drug reactions induced by ophthalmic and non-ophthalmic drugs, published in Ophthalmology journals, are reviewed and characterized.

4.3. Methods

This systematic review followed the recommendations of the Cochrane's Collaboration (Higgins and Green, 2011) to perform a systematic review and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to report a systematic review (Moher et al, 2009).

4.3.1. Literature Search and Data Selection

MEDLINE and EMBASE databases were searched. A last search was conducted in December 2017. Search terms comprised the name of all Ophthalmology journals with an impact factor, as described in Journal Citation Reports (Clarivate Analytics, 2018). The search was also combined with "systematic review" indexed term (MeSH term in MEDLINE and Emtree term in EMBASE). Only articles published in the last 10 years (from 2008 to 2017) were considered. No language restrictions were applied. The search strategy is listed in Appendix – Table 1. Additionally, all ophthalmology journals websites and references of included articles were also reviewed.

Articles were included if they were systematic reviews evaluating ophthalmic adverse drug reactions resulting from ophthalmic or non-ophthalmic drugs as a primary outcome. Congress abstracts of systematic reviews were excluded, since the full text is required to assess methodology.

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. Disagreement was resolved by discussion and consensus.

4.3.2. Data Extraction and Quality Assessment

Data was extracted from each included systematic review by 2 investigators independently. The following information was extracted from each systematic review: reference and year of publication; drugs under evaluation; adverse drug reaction assessed; recommendation followed to conduct and/or to report the systematic review; databases searched; search characteristics; type of included studies; methodological quality scale used; and if a meta-analysis was performed.

The drugs evaluated were coded according to the second- and third-level therapeutic subgroup of the Anatomical Therapeutic Chemical classification system (WHO, 2017).

The adverse drug reactions were coded in the high-level term and in the preferred-term, according to the Medical Dictionary for Regulatory Activities, version 20.1 (MedDRA, 2017).

The databases searched were divided into bibliographic databases of articles, clinical trials registries platforms, and grey literature.

Search characteristics retrieved include length of time, search terms (free or indexed terms) and search filters (such as language, study design among others).

The methodological quality was assessed using the instrument "A MeaSurement Tool to Assess systematic Reviews" 2 (Shea et al, 2017). The instrument consists of 16 domains assessing the risk of bias that may have arisen through poor conduct of the systematic reviews of both randomized controlled clinical trials and non-randomized studies (Shea et al, 2017).

4.3.3. Data Analysis

Information retrieved was analysed using descriptive statistics. Statistical analyses were conducted with Microsoft Excel 2016 (Microsoft Corporation, Santa Rosa, CA, USA).

4.4. Results

A total of 1,333 potentially relevant references were yielded from literature search. One additional reference was identified after search update and hand search. After reviewing titles and abstracts, 71 full-text references were assessed for eligibility. A final sample of 21 references met the inclusion criteria. The selection of references is shown

in Figure 4.1. The references of the included and excluded studies are listed in the Appendix – Table 2.

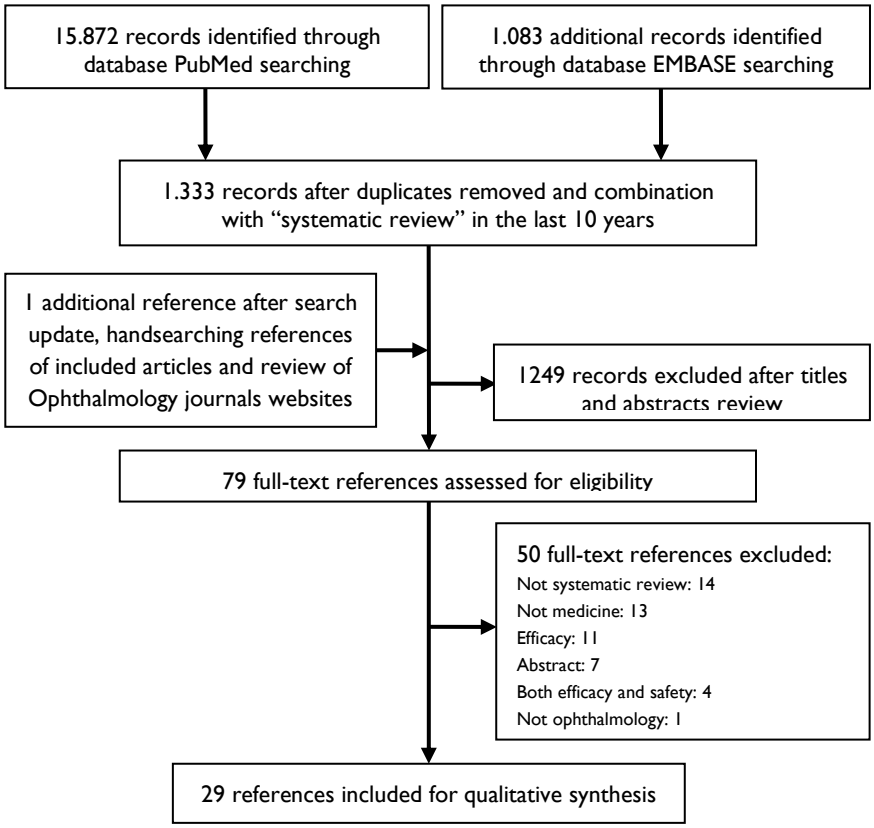

Figure 4.1 *- Flow diagram of Literature search.*

Systematic Reviews' Characteristics

Fourteen (67%) systematic reviews were published in the last 4 years.

The therapeutic subgroups of the drugs evaluated are presented in Table 4.1. Non-ophthalmic drugs were evaluated in 12 (57%) systematic reviews. Among the non-ophthalmic drugs, "antineoplastic agents" (n = 4; 19%) was the most evaluated therapeutic subgroup. "Ocular vascular disorder agents" (n = 5; 23%) were the ophthalmic drugs most frequently evaluated.

Four (19%) systematic reviews evaluated any "Eye disorder." Retinal disorders and "Glaucomas (excl congenital)" were assessed in 3 (14%) systematic reviews each. Three (14%) systematic reviews assessed both ocular and non-ocular disorders. The adverse drug reactions evaluated are described in Table 4.2.

Table 4.1 *- Therapeutic subgroups of drugs evaluated in included systematic reviews (ATC 2nd level).*

ATC 2nd level	**N (%)**
Ophthalmologicals	16 (55%)
Antineoplastic agents	4 (14%)
Antithrombotic agents	2 (7%)
Lipid modifying agents	1 (3%)
Antibacterials for systemic use	1 (3%)
Ophthalmological and otological preparations	1 (3%)
Several drugs*	1 (3%)
Immunostimulants	1 (3%)
Analgesics	1 (3%)
Diagnostic radiopharmaceuticals	1 (3%)
Total	29 (100%)

*One systematic review assessed several drugs of different therapeutic subgroups, such as acetazolamide, anorexiant mix (consisting of phendimetrazine tartrate, caffeine-ephedrine mixture, l-carnitine, green tea extract, and orthosiphon powder), aspirin, basic detox nutrient (a dietary supplement containing methyl-sulfonyl-methane and several other ingredients), bupropion, cabergoline, citalopram, chlorthalidone, dipivefrine, ecstasy, ecstasy and marijuana, escitalopram, flavoxate, flucloxacillin, glycopyrrolate, hydrochlorothiazide (also known as disothiazide), hydrochlorothiazide and triamterene, indapamide, mefanamic acid, methazolamide, metronidazole, oseltamivir, paroxetine, promethazine, sulfasalazine, sulfamethoxazole/trimethoprim, topiramate, topiramate and sulfamethoxazole/trimethoprim, and venlafaxine.

Table 4.2 *- Safety concerns evaluated in the included systematic reviews (MedDRA SOC) by therapeutic subgroups of drugs (ATC 2nd level).*

MedDRA (SOC)/ ATC 2nd level	**N (%)**
Eye disorders	**15 (52%)**
Ophthalmologicals	5 (17%)
Antineoplastic agents	3 (10%)
Antithrombotic agents	2 (7%)
Antibacterials for systemic use	1 (3%)
Analgesics	1 (3%)
Several drugs	1 (3%)
Diagnostic radiopharmaceuticals	1 (3%)
Immunostimulants	1 (3%)
Vascular disorders, and Cardiac disorders$^{\alpha}$	**3 (10%)**
Ophthalmologicals	3 (10%)
Ocular and non-ocular disorders*	**3 (10%)**
Ophthalmologicals	3 (10%)
Cardiac disorders	**2 (7%)**
Ophthalmologicals	2 (7%)
Investigations, and Eye disorders¥	**2 (7%)**
Ophthalmological and otological preparations	1 (3%)
Lipid modifying agents	1 (3%)
Non-ocular disorders*	**2 (7%)**
Ophthalmologicals	2 (7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)$^{\beta}$	**1 (3%)**
Antineoplastic agents	1 (3%)
Vascular disorders	**1 (3%)**
Ophthalmologicals	1 (3%)
Total	29 (100%)

α Three systematic reviews assessed both vascular and cardiac disorders. *Some systematic reviews evaluated any ocular and/or non-ocular disorders. ¥ Refers to intraocular pressure increased and glaucoma. β Refers to extraocular tumour.

Methodology of the Systematic Reviews

The methodology of the systematic reviews analysed is described in Table 4.3.

Table 4.3 *- Methodologic characteristics of the systematic reviews included.*

Reference, year	Orientation	Databases	Search terms	Search filter	Study design of included studies	Meta-analysis	Quality scale
Sun et al, 2017	PRISMA	MEDLINE, ClinicalTrials.gov, handsearch	Free	None	RCT	Yes	Cochrane Risk of Bias Tool
Alves et al, 2017	PRISMA	PubMed, Cochrane Library	Free	Language	RCT	Yes	Cochrane Risk of Bias Tool
Morshedi et al, 2016	None	PubMed, handsearch	Free	Language	Observational	No	None
McCann et al, 2016	Moose; PRISMA	MEDLINE, EMBASE, PubMed, Google scholar	Free, Thesarus	Language Humans	Observational	Yes	Newcastle-Ottawa Quality Assessmen t Scale
Chatziralli et al, 2016	None	PubMed	Free	None	RCT, observational	Yes	None
Shin et al, 2016	Moose; PRISMA	PubMed, EMBASE, Cochrane Library	Free	None	Experimental Observational	Yes	Newcastle-Ottawa Quality Assessmen t Scale
Alves et al, 2016	PRISMA	MEDLINE, Cochrane Library, ClinicalTrials.gov, handsearch	Free, Thesarus	Language	RCT, observational	Yes	Downs and Black checklist
Caldeira et al, 2015	PRISMA	MEDLINE, Cochrane Library, SciELO collection, Web of Science databases, handsearch	Free, Thesarus	None	RCT	Yes	Cochrane Risk of Bias Tool
Murphy et al, 2016	None	PubMed	Free	Language	Observational	No	Naranjo scale ranges
Lim et al, 2015	None	PubMed, EMBASE, Cochrane Library, handsearch	Free	None	Observational	No	None
Penedones et al, 2014	PRISMA	PubMed, Cochrane Library, International Clinical Trials Registry Platform, EudraVigilance	Free	Language	RCT, experimental, observational	No	Downs and Black checklist
Liu et al, 2014	None	Lexicomp, PubMed	Free	Study design	Experimental Observational	No	None
Ye et al, 2014	None	MEDLINE, Web of Science, Cochrane Library, EMBASE, handsearch	Free	Language	RCT, observational	Yes	Downs and Black checklist
Smith et al, 2014	Stroup et al, 2000	PubMed, Scopus, Science Citation Index and Conference Proceedings	Free, Thesarus	Humans	Observational	No	None

Reference, year	Orientation	Databases	Search terms	Search filter	Study design of included studies	Meta-analysis	Quality scale
		Citation Index-Science, handsearch					
Kiddee et al, 2013	PRISMA	MEDLINE, EMBASE, Cochrane Library, handsearch	Free	Language Humans	RCT, observational	Yes	Cochrane Risk of Bias Tool
Smith and Smith, 2013	Stroup et al, 2000	PUBMED, SCOPUS, Science Citation Index and Conference Proceedings Citation Index—Science, handsearch	Free, Thesarus	Humans	Observational	No	None
Fragoso et al, 2011	PRISMA	MEDLINE, PubMed, Scopus, Index Medicus, Biomed Central, Ebsco Fulltext, LILACS, Scielo and the Cochrane Database of Systematic Reviews	Free	None	Observational	No	None
van der Reis, 2011	Cochrane	PubMed, EMBASE, Toxline, and the Cochrane library, FDA and EMA websites, handsearch	Free, Thesarus	Language	Experimental Observational	No	None
Schmucker et al, 2011	None	MEDLINE, EMBASE, Cochrane Library, handsearch, ClinicalTrials.gov, International Clinical Trials Registry Platform	Free, Thesarus	None	RCT, experimental, observational	Yes	Centre for Reviews and Disseminat ion
Siesky et al, 2009	None	MEDLINE	Not clear	Humans	Experimental	Yes	None
Honrubia et al, 2009	None	MEDLINE, EMBASE, Cochrane Library	Free, Thesarus	Language	RCT	Yes	Jadad Score

MOOSE, Meta-analysis Of Observational Studies in Epidemiology. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. RCT, Randomized Controlled Trials.

Nine (43%) systematic reviews did not follow (or report) any recommendation to conduct and/or to report a systematic review. Among those following a recommendation, 43% (n = 9) applied the PRISMA statement to report a systematic review, and 14% (n = 3) followed a guideline to conduct a systematic review (Cochrane Collaboration and Stroup et al). Only 2 (10%) systematic reviews followed both types of recommendations.

The Cochrane Library and PubMed database were the bibliographic databases most searched (n = 12; 57%), followed by MEDLINE database (n = 10; 48%), and EMBASE database (n = 8; 38%). In median, each systematic review searched 2 (range 1–9)

bibliographic databases. Six (29%) systematic reviews searched only one bibliographic database.

Four (19%) systematic reviews were searched in clinical trials registries.

Seven (33%) systematic reviews were searched for additional information on grey literature, and 12 (57%) systematic reviews were also hand searched on the references list from included studies.

Eighteen (86%) systematic reviews did not apply any date restriction in their searches. Free terms were used in search strategies of 12 (57%) systematic reviews. Eight (38%) systematic reviews used both free and indexed terms.

Ten (48%) systematic reviews did not apply any search filter. Among those studies which apply a search filter, the filter "Language" was applied in 10 (48%) systematic reviews, "Humans" in 5 (24%), and "Study design" in 1 (5%).

Sixteen (76%) systematic reviews included observational data in their reviews, of which 7 (33%) included only observational data. Randomized controlled trials (RCT) were the second most preferred type of study in the analysed systematic reviews (n = 10; 48%), being the only study type included in 4 (19%) systematic reviews.

Nine (43%) systematic reviews did not evaluate the methodological quality of the included studies. The "Cochrane Risk of Bias Tool" was used to assess the risk of bias of included studies in 4 (19%) systematic reviews, and the "Downs and Black checklist" in 3 (14%).

Twelve (57%) systematic reviews performed a meta-analysis in the quantitative analysis of their results.

Methodological Quality Analysis

The results of the methodological quality assessment are illustrated in Table 4.4. The systematic reviews from McCann et al. (2016) and Ye et al. (2014) were the studies most compliant with methodological quality. Both studies have only one negative domain, which included, respectively, the presentation of the list of excluded articles and reasons of exclusion (domain 7), and the elaboration and publication of a protocol of the systematic review (domain 2) (Ye et al, 2014; McCann et al, 2016). All systematic reviews included the components of Population, Intervention, Comparator, Outcome in the description of research question and inclusion criteria (domain 1), described the results in detail (domain 8), using tables, and graphics if necessary, and reported any potential sources of conflict of interest (domain 16). Only 3 (14%) systematic reviews prepared

and/or published a protocol of the systematic review (domain 2). Fifteen (71%) systematic reviews did not explain their selection of the study designs for inclusion in the review (domain 3). The list of excluded articles and reasons of exclusion (domain 7) was not described in 14 (67%) systematic reviews.

Table 4.4 *- Methodological quality assessment for each systematic review, according to the AMSTAR 2 scale.*

Reference/ Domains*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sun et al, 2017	Y	PY	N	PY	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Alves et al, 2017	Y	N	N	PY	N	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y
Morshedi et al, 2016	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y
McCann et al, 2016	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Chatziralli et al, 2016	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	N	Y
Shin et al, 2016	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Alves et al, 2016	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Caldeira et al, 2015	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	Y	Y
Murphy et al, 2016	Y	N	N	N	N	N	Y	Y	Y	N	N	N	Y	N	N	Y
Lim et al, 2015	Y	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	Y
Penedones et al, 2014	Y	N	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	N	Y
Liu et al, 2014	Y	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	Y
Ye et al, 2014	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Smith et al, 2014	Y	N	N	Y	Y	Y	N	Y	N	N	N	N	N	Y	N	Y
Kiddee et al, 2013	Y	N	N	Y	Y	Y	N	Y	Y	Y	N	N	N	Y	N	Y
Smith and Smith, 2013	Y	N	N	Y	Y	Y	N	Y	N	N	N	N	N	Y	N	Y
Fragoso et al, 2011	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Y
van der Reis, 2011	Y	N	Y	Y	N	N	N	Y	N	N	N	N	Y	Y	N	Y
Schmucker et al, 2011	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y
Siesky et al, 2009	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	N	Y
Honrubia et al, 2009	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

Y, yes; PY, partial yes; N, no. *Each domain is fully described in the Appendix 3. 1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

4.5. Discussion

This study was conducted to review the methodology of the systematic reviews reporting ophthalmic adverse drug reactions.

More than a half of the analysed systematic reviews were published in the last 4 years. This result was also reported in previous articles studying the epidemiology of systematic reviews (Golder et al, 2006; Chen and Jhanji, 2012; Golder et al, 2013; Page et al, 2016). Since the volume of information is growing, the number of systematic reviews has also increased (Bastian et al, 2010). A study by Bastian et al. (Bastian et al, 2010) estimated that 75 trials and 11 systematic reviews where published per day. Also, regulatory authorities required a compilation of various individual studies in health technology assessment (Naudet et al, 2017). Nonetheless, the increased publication of systematic reviews may not be interpreted as an improvement on their methodology and role (Ioannidis, 2016; Naudet et al, 2017).

In fact, the publication of several systematic reviews studying the same research question may lead to redundant systematic reviews (Golder et al, 2008; Zorzela et al, 2014).

Ophthalmic drugs were related with 40% of the ophthalmic adverse drug reactions studied in this systematic review. In the last decade, the majority of the safety alerts of ophthalmic adverse drug reactions come mostly from non-ophthalmic drugs (Penedones et al, 2015). "Ocular vascular disorders" were the drugs more frequently assessed in the included systematic reviews, including the anti-vascular endothelial growth factor drugs. A review of systematic reviews in ophthalmology identified a large proportion of systematic reviews published in the field of retina, with 37% of systematic reviews published on age-related macular degeneration (Chen et al, 2012). This corroborated our results since anti-vascular endothelial growth factor drugs were approved for the treatment of age-related macular degeneration (Chen et al, 2012).

Almost 20% of the included systematic reviews did not specify the ophthalmic adverse drug reaction evaluated. This result is in line with that of previous reviews of systematic reviews of adverse drug reactions (16.5–22%) (Golder et al, 2008; Golder et al, 2013; Zorzela et al, 2014).

About 43% of the studied systematic reviews did not follow a recommendation to conduct and/or to report a systematic review. Among the reviews analysed, PRISMA was the most used recommendation to report a systematic review. Nonetheless, some studies suggested that PRISMA was in many cases used erroneously as a recommendation to conduct (instead of to report) a systematic review (Chen et al, 2012; Golder et al, 2013). Despite the recent efforts to harmonize the methodology for conducting and reporting a

systematic review, several research groups have defined their own recommendations (Penedones et al, 2018). With regard to systematic reviews of adverse drug reactions, 4 recommendations (3 to conduct and 1 to report a systematic review) were available (Penedones et al, 2018). From the systematic reviews analysed in this work, only one followed a recommendation specifically designed to conduct a systematic review of adverse drug reactions (van der Reis et al, 2011). Following a recommendation to conduct and/or to report a systematic review was essential, since it can affect the quality of the review (Zorzela et al, 2014; Penedones et al, 2018). In 2014, a study by Zorzela et al. described the poor quality of reporting systematic reviews of adverse drug reactions, when a recommendation to report such reviews was not followed (Zorzela et al, 2014).

The Cochrane Library and PubMed databases were the bibliographic databases most searched in the systematic reviews analysed. Three reviews of systematic reviews of adverse drug reactions had identified MEDLINE as the most searched bibliographic database (Golder et al, 2006; Chen et al, 2012; Zorzela et al, 2014). In our review, the MEDLINE database was the third database most used to search studies. Sometimes, PubMed and MEDLINE are attributed to the same database (US National Library of Medicine, 2018).

In median, 2 bibliographic databases were searched in the systematic reviews included in this review. This result is in line with previous reviews (Golder et al, 2006; Golder et al, 2008; Chen et al, 2012). Since one study may be cited only in one bibliographic database, the literature search must comprise multiple databases (Moher et al, 2009; Higgins and Green, 2011). Moreover, there are a variety of bibliographic databases, which one with their own scope and type of studies (Rathbone et al, 2016). A combination of several bibliographic databases must increase the performance and reliability of the literature search (Aagaard et al, 2016; Rathbone et al, 2016). In this study, a large percentage (almost 30%) of systematic reviews searched only one bibliographic database. In spite of many authors following a recommendation to conduct and/or to report a systematic review, in our study, from the 30% of the systematic reviews that searched only in 1 database, 83% did not follow a recommendation.

The proportion of systematic reviews conducting a search in clinical trials registries is small. Two studies, which evaluated specifically the utilization of clinical trials registries in the selection of studies, found that only 35–38% of systematic reviews incorporated a clinical trials registry into their searches (van Enst et al, 2012; Jones et al,

2014). Clinical trials registries increased the transparency in reporting the results of a clinical trial and help to identify unpublished clinical trials (Jones et al, 2014). In a study by Jones et al (2014), a relevant clinical trial was identified by 79% of the systematic reviews of the major medical journals. For this reason, several recommendations to conduct and/or to report a systematic review suggested clinical trials registries as important sources to identify clinical trials results (Centre for Reviews and Dissemination, 2009; Moher et al, 2009; Higgins and Green, 2011).

Other additional sources to identify adverse drug reactions included grey literature and hand searching. The search for additional data reduces publication bias (Joober et al, 2012). In 2 reviews of systematic reviews reporting adverse drug reactions, 88% of the systematic reviews searched for additional sources of information (Golder et al, 2008; Golder et al, 2013). In our review, the results were more modest (33% systematic reviews searched on grey literature and 57% included hand searching). Data such as case reports describing adverse drug reactions, spontaneous reports and congress abstracts was the type of grey literature that could be searched to a systematic review of adverse drug reactions (Moher et al, 2009; Higgins and Green, 2011).

The reporting of a search strategy is an essential step when reporting a systematic review (Yoshii et al, 2009; Koffel and Rethlefsen, 2016). Assuring the reproducibility of the search strategy implies the description of all search terms, date range, search filters and the person who conducts the search (Yoshii et al, 2009; Koffel and Rethlefsen, 2016). A study compared the search strategies of systematic reviews of adverse drug reactions with other systematic reviews and concluded that poor reporting is a common point; however, systematic reviews of adverse drug reactions include more sources of information and search on more databases (Golder et al, 2014). In our review, few systematic reviews applied a date filter to limit their searches. Highly sensitivity searches composed of both free and indexed terms were performed by 38% of the systematic reviews analysed. Searching with a combination of terms is more reliable and accurate to find data, reducing the possibility of excluding a relevant article (Moher et al, 2009; Higgins and Green, 2011). The filter most applied, in this review, was "Language." The inclusion of English or non-English studies could affect estimates, leading to language bias (Moher et al, 2009; Higgins and Green, 2011).

Observational data, such as observational studies and grey literature, was the type of study most assessed among the systematic reviews analysed. This result is conflicting

with those from reviews of systematic reviews reporting adverse drug reactions, where the RCT were the type of study most used (Golder et al, 2006; Zorzela et al, 2014). Due to their robust methodology, RCTs provide unbiased estimates (Strom, 2006). However, RCTs are well designed to assess efficacy despite safety (Strom, 2006; Singh and Loke, 2012).

Around 45% of the retrieved systematic reviews did not perform a methodological quality assessment of their studies. The assessment is important, since it can determine the validity of the study's results (Moher et al, 2009; Higgins and Green, 2011). The inclusion of several types of studies may be challenging due to the scarcity of recommendations to assess the methodological quality of data such as grey literature (Adams et al, 2016).

Sixty percent of the systematic reviews conducted a quantitative analysis through meta-analysis. This result is also found in other reviews of systematic reviews (Golder et al, 2006; Page et al, 2016). Combining the results of multiple studies can achieve a better estimate of effect (Berlin et al, 2012).

The methodological quality of the systematic reviews analysed in this review varied. The identification of the research question and the potential conflicts of interest were the domains most reported. Some domains related with the methods of the systematic review were not so clear. These domains reflect the transparency and robustness of the systematic review and could influence the results of our review. Previous reviews had illustrated the poor reporting of systematic reviews of adverse drug reactions (Golder et al, 2008; Zorzela et al, 2014). An Editorial in 2014 suggested authors to follow a recommendation to conduct and/or to report a systematic review in Ophthalmology, emphasizing the "deficient methodology" (Li and Bartley, 2014).

This systematic review has some methodological limitations. Our search comprised only 2 bibliographic databases; however, we also searched in the websites of the indexed scientific journals in Ophthalmology. The search was limited to the last 10 years, since major methodological improvements in systematic review were observed in the last decade.

4.6. Conclusion

In general, some discrepancies between systematic reviews can be found, namely, on search strategy, databases searched, studies included, methodological quality

assessment and data analysis. Such issues deserve further investigation, since methodological insufficiencies of systematic reviews may lead to biased conclusions and, therefore, negative impacts on clinical and/or regulatory decisions.

4.7. References

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4.8. Appendix

Appendix - **Table 1** – Search strategy.

Search	Search terms
#1	("Prog Retin Eye Res"[Journal] OR "Ophthalmology"[Journal] OR "JAMA Ophthalmol"[Journal] OR "Am J Ophthalmol"[Journal] OR "Ocul Surf"[Journal] OR "Br J Ophthalmol"[Journal] OR "J Refract Surg"[Journal] OR "Retina"[Journal] OR "Surv Ophthalmol"[Journal] OR "Exp Eye Res"[Journal] OR "Invest Ophthalmol Vis Sci"[Journal] OR "Acta Ophthalmol"[Journal] OR "Clin Exp Ophthalmol"[Journal] OR "Curr Opin Ophthalmol"[Journal] OR "J Cataract Refract Surg"[Journal] OR "J Vis"[Journal] OR "Annu Rev Vis Sci"[Journal] OR "Ocul Immunol Inflamm"[Journal] OR "Graefes Arch Clin Exp Ophthalmol"[Journal] OR "Ophthalmic Physiol Opt"[Journal] OR "Eye (Lond)"[Journal] OR "J Glaucoma"[Journal] OR "Curr Eye Res"[Journal] OR "Transl Vis Sci Technol"[Journal] OR "Mol Vis"[Journal] OR "Cornea"[Journal] OR "J Neuroophthalmol"[Journal] OR "Vision Res"[Journal] OR "Doc Ophthalmol"[Journal] OR "Cont Lens Anterior Eye"[Journal] OR "Ophthalmic Epidemiol"[Journal] OR "Ophthalmologica"[Journal] OR "Vis Neurosci"[Journal] OR "Ophthalmic Res"[Journal] OR "J Ophthalmol"[Journal] OR "Ophthalmic Surg Lasers Imaging Retina"[Journal] OR "J Ocul Pharmacol Ther"[Journal] OR "BMC Ophthalmol"[Journal] OR "Can J Ophthalmol"[Journal] OR "Jpn J Ophthalmol"[Journal] OR "Optom Vis Sci"[Journal] OR "Eur J Ophthalmol"[Journal] OR "Eye Contact Lens"[Journal] OR "J Eye Mov Res"[Journal] OR "Ophthalmic Genet"[Journal] OR "Clin Exp Optom"[Journal] OR "Ophthal Plast Reconstr Surg"[Journal] OR "Cutan Ocul Toxicol"[Journal] OR "Semin Ophthalmol"[Journal] OR "Int J Ophthalmol"[Journal] OR

Search	Search terms
	"Perception"[Journal] OR "Int Ophthalmol"[Journal] OR "J AAPOS"[Journal]) OR "J Pediatr Ophthalmol Strabismus"[Journal] OR "Indian J Ophthalmol"[Journal] OR "Ophthalmologe"[Journal] OR "Klin Monbl Augenheilkd"[Journal] OR "J Fr Ophtalmol"[Journal] OR "Arq Bras Oftalmol"[Journal]) AND Systematic review
#2	#1 Filter: Systematic review; last 10 years

Appendix - **Table 2** - List of included and excluded studies.

Included studies

Alves C, Penedones A, Mendes D, Batel Marques F (2016). A systematic review and meta-analysis of the association between systemic fluoroquinolones and retinal detachment. Acta Ophthalmol; 94(5):e251-9.

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Ye J, Xu Y-F, He J-J, Lou L-X (2014). Association between aspirin use and age-related macular degeneration: a meta-analysis. Invest Ophthalmol Vis Sci; 55(4):2687-2696.

Excluded studies

Not systematic review

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Abstract

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Smith AF, Klotz A, Wormstone M (2015). Cataracts as an adverse event in the drug development process: Findings from a systematic review and economic model. Invest Ophthalmol Vis Sci; 56:7 (4148).

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Chapter 5 - A comparison between two recommendations to conduct and report systematic reviews on drug's safety

5.1. Abstract

Introduction: Several recommendations are available to conduct and report a systematic review of adverse drug reactions. This study is aimed at identifying and comparing the methodologies of the two most commonly used recommendations to conduct and report systematic reviews on drug's safety.

Methods: Two systematic reviews were conducted following the recommendations "Cochrane Handbook for Systematic Reviews of Interventions" and "Systematic Reviews' Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare". The methods of each recommendation were characterized and the results and the discussion of each systematic review were also evaluated.

Results: The methodologies of both recommendations are similar. The review question was structured. Both recommendations suggest to include pre- and post-marketing data. The recommended data sources differed and, consequently, the results of the systematic reviews (37 vs. 35 studies). Other aspects of search literature were identical. Different tools are suggested to evaluate the methodological quality of the included studies. For case reports, both recommendations only report some questions that may be helpful to assess risk of bias. The reporting of the results and discussion is also identical for both recommendations.

Conclusions: Few methodological differences were observed between the analysed recommendations to conduct a systematic review on drug's safety. Combining their methods into a single and recognized recommendation could be of great value.

5.2. Introduction

A systematic review can constitute an important tool in pharmacovigilance (EUNETHA, 2015). A rigorous methodology is used to systematically summarize the available evidence on drug's safety (Oxman and Guyatt, 1993). Data on the common and expected adverse drug reactions can be obtained from clinical trials (Singh and Loke, 2012). Observational studies, case reports and spontaneous reports are valuable to detect rare and/or long-term adverse drug reactions (Strom, 2006). Combining this information using a systematic methodology, which identify, select and critically appraise all available

evidence, can expand and strength drug's safety profile (EUNETHA, 2015). Healthcare professionals, patients and also regulatory authorities can keep up to date and make informed decisions (Moher et al, 2009).

To conduct and/or report a systematic review, a defined methodology should be *a priori* selected. The choice of the recommendation to conduct and/or to report a systematic review is dependent on the review question. For instance, if the aim of a systematic review is to study drug's efficacy or safety, health economics, diagnostic test accuracy, among others, the methods will be specific and applied to each area (Centre for Reviews and Dissemination, 2009; Higgins and Green, 2011; Agency for Healthcare Research and Quality, 2014). There are different recommendations to conduct and/or report a systematic review (Penedones et al, 2018a). Nevertheless, each recommendation presents different methodology (Penedones et al, 2018a). In a previous study, between 88% and 99% of the recommendations offer guidance on methods (from eligibility criteria to data analysis) (Penedones et al, 2018a). However, some aspects, such as elaboration of an *a priori* protocol, definition of background, interpretation and discussion of the results and the need and time for updating the systematic review, presented several discrepancies (Penedones et al, 2018a).

Three recommendations are available to conduct and report a systematic review of drug's safety (Centre for Reviews and Dissemination, 2009; Higgins and Green, 2011; Agency for Healthcare Research and Quality, 2014). Each one was developed by an organisation created to study and develop guidance on the best synthesis of different types of information (Centre for Reviews and Dissemination, 2009; Higgins and Green, 2011; Agency for Healthcare Research and Quality, 2014). The "Cochrane Handbook for Systematic Reviews of Interventions", developed by the Cochrane Collaboration and last updated on March 2011 (Higgins and Green, 2018), and the "Systematic Reviews' Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare", developed by the Centre for Reviews and Dissemination (CRD) on 2009 (Centre for Reviews and Dissemination, 2009), were the recommendations most used to conduct and to report systematic reviews in this field (Penedones et al, 2018a). In 2016, the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) group also developed a guideline to reporting systematic reviews of adverse drug reactions (Moher et al, 2009).

This study is aimed at identifying and comparing the methodology of the two most commonly used recommendations to conduct and report a systematic review of adverse drug reactions.

5.3. Methods

In a previous work, we had identified three recommendations "Cochrane Handbook for Systematic Reviews of Interventions", "Systematic Reviews' CRD guidance for undertaking reviews in healthcare" and the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" developed by the Agency for Healthcare Research and Quality (AHRQ)) used to conduct and/or report a systematic review of adverse drug reactions (Penedones et al, 2018a). The recommendations developed by the Cochrane Collaboration (Higgins and Green, 2011) and the CRD (Centre for Reviews and Dissemination, 2009) are the most commonly used and were included to study their methodology. We did not include the recommendation developed by the AHRQ. Although it can be applied to conduct systematic reviews on drug's safety, this guidance is specific for comparative effectiveness reviews of interventions under the Effective Health Care Program (Agency for Healthcare Research and Quality, 2014).

The two chosen recommendations were named as (A) for "Cochrane Handbook for Systematic Reviews of Interventions" (Higgins and Green, 2011) and (B) for "Systematic Reviews' CRD guidance for undertaking reviews in healthcare" (Centre for Reviews and Dissemination, 2009). We conducted two systematic reviews addressing the methodologies defined by the recommendations A and B. Two authors performed both systematic reviews independently, while a third author validated all methodology and results.

At first, a search strategy was defined between consensus among the three authors and replied in each database. The selection of studies and extraction of results were conducted by two authors independently. Disagreements were resolved by discussion and consensus with the third author. The results in each systematic review were analysed using descriptive analysis, and, when it is possible, using meta-analysis. Details of the elaboration of each systematic review are available in the Additional file. At the end, the methods of each recommendation were characterized and evaluated. We categorized their methods into 'Introduction', which included 'Background', 'Eligibility criteria', and 'Review question'; 'Identifying evidence', including 'Type of studies', 'Databases', 'Search strategy', 'Data selection', 'Data extraction', 'Quality assessment', and 'Data synthesis';

and 'Reporting', describing the 'Flowchart', 'Characteristics of studies', 'Outcome analysis', 'Quality assessment', 'Discussion', 'Conclusion', 'Funding', and 'Appendix'. Afterwards, a qualitative (exploratory) comparison between the results and impact of these results were performed.

In order to study the influence of different recommendations to conduct a systematic review, the same research question was studied in both systematic reviews. A case study was used to compare both methodologies. We assessed the development of an ophthalmic adverse drug reaction after a suspected medicine exposure. Three regulatory agencies issued a safety alert on the association of non-arteritic anterior ischemic optic neuropathy (NAION) with phosphodiesterase type 5 (PDE5) inhibitors (Penedones et al, 2015). In order to study such association, we defined a research hypothesis, structured according to PICO (Population, Intervention, Comparator, and Outcome) strategy: to assess the risk of developing NAION in individuals taking PDE5 inhibitors. The results of both systematic reviews can be found in the Additional file. Herein, the results of the systematic reviews were compiled into a table. s.

5.4. Results

The methodology suggested by the recommendations A and B to conduct and report a systematic review of adverse drug reactions is summarized in Table 5.1. We highlighted the sections of the systematic review which differed between both recommendations.

In general, the methodology of both recommendations is similar. Both systematic reviews provide a detailed rationale for conducting the review, focusing on the description of the intervention and condition, and their possible association. The review question was structured and follow the PICO strategy. The two recommendations suggest to search studies including pre- and post-marketing data on drug's safety. The bibliographic databases and other sources to search evidence suggested in each recommendation differed. Other aspects of search literature, such as the search strategy, data selection, data extraction, and data synthesis were identical. To evaluate the methodological quality of the included studies, the Cochrane Collaboration developed three scales which evaluate randomized controlled trials, cohort, and case-control studies. The CRD's guideline (B) recommends some tools to evaluate the several types of studies. For case reports, both guidelines report some questions that may be helpful to evaluate the risk of

bias/ quality of the reports. The reporting of the results and discussion is also identical for both recommendations.

Table 5.1 *- Summary of methodology used in each systematic review.*

Step/ Review	A – Cochrane Collaboration	B – Centre for Reviews and Dissemination
Introduction		
Background	Description of the condition; Description of the intervention; How the intervention might work; Why it is important to do this research.	Description of intervention; Description of the condition; Rationale for review.
Eligibility criteria	-Type of participants: Patients for whom a PDE_5 inhibitor is indicated in one of the three approved therapeutic indications; -Type of interventions: PDE_5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil) comparing with placebo, active treatment or no treatment; -Type of outcome measures: Development of NAION.	-Population: Patients for whom a PDE_5 inhibitor is indicated in one of the three approved therapeutic indications; -Intervention: PDE_5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil); -Comparators: Placebo, active treatment or no treatment; -Outcomes: Development of NAION.
Review question	PICO Strategy: To assess the risk of NAION associated with PDE5 inhibitors exposure. A systematic review is carried out based on pre- and post-marketing data.	PICO Strategy: The objective of this systematic review is to assess the risk of NAION associated with PDE5 inhibitors exposure, based on pre- and post-marketing data.
Identifying evidence		
Type of studies	Randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports.	Randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports.
Databases	MEDLINE, EMBASE, Cochrane Controlled Register of Trials (CENTRAL), TRIP*, SCOPUS*, Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform, and VigiBase.	MEDLINE, EMBASE, Toxline, Pharmline*, websites of the manufacturers of drugs and VigiBase.
Search strategy	Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and the ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search.	Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and the ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search.
Data selection	Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion.	Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion.
Data extraction	Data was extracted from each included study by two researchers independently.	Data was extracted from each included study by two researchers independently.

Step/ Review	A – Cochrane Collaboration	B – Centre for Reviews and Dissemination
Quality assessment	Included studies were independently assessed for bias according to the methods described in Chapter 13.5 and Chapter 14.6 of the Cochrane Handbook for Systematic Reviews of Interventions.	For observational studies, the checklist proposed by Downs and Black was used. The case reports were evaluated according to the questions elaborated on the Chapter 4 of the CRD's guidance for undertaking reviews in health care.
Data synthesis	Data analysis followed the guidelines set out in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions.	Data from case and spontaneous reports were analysed using descriptive statistics. A meta-analysis was conducted to analyse data from observational studies.
Reporting		
Flowchart	A predefined flowchart was used. 37 studies were included in the review, 4 observational studies and 33 case reports (and 608 spontaneous reports).	The PRISMA flowchart was used. 35 studies were included in the review, 4 observational studies and 31 case reports (and 608 spontaneous reports).
Characteristics of studies	A descriptive table was elaborated. The following information was extracted: reference; country; study design; population (number and demographic data); intervention (and comparator); number of individuals with the ophthalmic adverse drug reaction; risk factor; and medical history.	A descriptive table was elaborated. The following information was extracted: reference; country; study design; population (number and demographic data); intervention (and comparator); number of individuals with the ophthalmic adverse drug reaction; risk factor; and medical history.
Outcome analysis	A meta-analysis was conducted to assess observational studies. A descriptive statistic was used for case reports and spontaneous reports.	A meta-analysis was conducted to assess observational studies. A descriptive statistic was used for case reports and spontaneous reports.
Quality assessment	A table describing the results of risk of bias assessment was developed.	A table describing the results of risk of bias assessment was developed.
Discussion	Summary of main results; Overall completeness and applicability of evidence; Potential biases in the review process; Agreements and disagreements with other studies or reviews.	Principal findings; Comparison with other research; Strengths and weaknesses of the research.
Conclusion	Implications for practice/ research.	Recommendations/ implications for practice/ further research.
Funding	A financial disclosure was described.	A financial disclosure was described.
Appendix	Search strategy; List of included and excluded studies; Vigibase results; Characteristics of studies and quality assessment results.	Search strategy; List of included and excluded studies; Vigibase results; Quality assessment results.

* Databases not accessible to the authors of the reviews.

5.5. Discussion

There are three recommendations to conduct systematic reviews of adverse drug reactions (Penedones et al, 2018a). In order to assess the methodological differences between those recommendations, in this study, two systematic reviews were conducted following the two most commonly used recommendations. Similar approaches in the elaboration of the two systematic reviews of adverse drug reactions were observed.

One of the characteristics that distinguish systematic reviews from narrative reviews is a structured review question (Centre for Reviews and Dissemination, 2009). In both systematic reviews, a structured question was presented. It predisposes to a focused hypothesis and can also be useful to define eligibility, search, and inclusion criteria, and presentation of results (Zorzela et a, 2016). Similar to efficacy systematic reviews, systematic reviews focusing on drug's safety could present a broad or narrow review question (Zorzela et al, 2016). A systematic review studying the association of a class of medicines with a specific adverse drug reaction (for example, the development of retinal detachment after fluoroquinolones exposure (Alves et al, 2016)) has a narrow focus, while a systematic review studying all adverse drug reactions associated with a class of medicines (for example, the safety profile of ophthalmic anti-angiogenesis inhibitors has a broad focus (Penedones et al, 2014)) (Zorzela et al, 2016).

Both recommendations suggested the selection of several types of evidence. These included experimental and observational data. Depending on the review question, each type of sources of information could be the most appropriate. Clinical trials are a robust source of information (Singh and Loke, 2012). Data on common and anticipated adverse drug reactions could be obtained from these studies (Singh and Like, 2012). Observational studies have some flaws subject of bias in their methodology, such as in the demographic characteristics of the included populations, the follow-up time durations, or the effect size measures used (Strom, 2006); however, they can provide relevant information on the common, rare, and long-term adverse drug reactions (Strom, 2006). Examples of observational data include clinical studies in clinical practice, health-administrative databases studies, cases and series of case reports, and spontaneous reports (Strom, 2006). An example of the importance of observational data on drug's safety assessment is visible in the regulatory decisions. Some safety alerts were issued based only on spontaneous reports (Alves et al, 2013; Penedones et al, 2015). In general, systematic reviews of drug's efficacy contain data from the highest level of evidence, namely

randomized and controlled clinical trials (The Centre for Evidence-based Medicine, 2009); however, in systematic reviews focusing on drug's safety, several types of evidence should be included, in order to obtain a more completed and robust drug's safety profile. The combination of several types of evidence in safety is already used to make better informed decisions (Alves et al, 2013). In 2012, the United States Food and Drug Administration issued a safety alert on statins and cognitive side effects. The evidence supporting the regulatory evaluation consisted on randomized controlled trials, observational studies (cohort studies, case-control studies, cross-sectional studies), case reports, and a review of post-marketing spontaneous reports database. Thereafter, the adverse drug reactions section of the medicines was updated (Alves et al, 2013).

A difference which impact the results of these two systematic reviews was the selection of the bibliographic databases and other sources of information. The authors of the present study only searched in the suggested sources of each recommendation. We also experienced some difficulties in accessing some bibliographic databases. Several studies pointed out the importance of including data from a wide range of bibliographic databases, not only because of their limitations (some databases are more accurate and include newest studies than others), but also because some studies may only be available in one bibliographic database (for instance grey literature is not easily available) (Falagas et al, 2008; Haddaway et al, 2015). At the present work, we observed some discrepancies between the two systematic reviews in terms of the number of included studies. For instance, two case reports were not included in one of the performed systematic reviews. Nonetheless, we studied the risk of development of a rare adverse drug reaction. Therefore, the volume of available information could be reduced compared with that of a common adverse drug reaction. If the information not found were of higher methodological quality than case reports (such as case-control or cohort studies), the impact of not including this data would be substantial. For instance, in both systematic reviews, the same four observational studies were found. A meta-analysis was conducted based on their results. If a study was missed, the results of this meta-analysis would be different and, consequently, the risk estimate could vary for opposite meanings (risk vs. no risk). Conducting a search, using all available sources of information is important, as this will ensure that all relevant data are obtained and evaluated (Zorzela et al, 2016). A systematic review performed by Baudard et al (2017) evaluated the impact of searching on clinical trials registries for additional studies. By analysing a predefined sample of

systematic reviews, this research group found that 52% did not report a search on clinical trials registries (Baudard et al, 2017). After performing searches on clinical trial registries, Baudard et al (2017) found 122 additional randomized controlled trials. If these studies had been included in meta-analysis, the weight of studies would be changed to almost 60% in some systematic reviews (Baudard et al, 2017). Other study conducted by Franco et al (2018) found that 73% of reviews have issues in the definition of literature searches.

The methodological quality assessment for experimental and observational studies, such as cohort and case-control studies, is possible due to a variety of available tools. However, few or no tools are available to assess other types of observational studies, case reports, health-administrative databases studies, case and series of case reports and spontaneous reports (Glasziou et al, 2004). Since a hierarchy of evidence is not yet defined to assess drug's safety, several studies questioned the usefulness of these tools once a combination of several types of studies are included in a systematic review and an evaluation of all is not possible (McIntosh et al, 2004). In addition, the majority of the available risk of bias tools are not prepared to assess studies on adverse drug reactions (Faillie et al, 2017). A systematic review evaluating the quality of reporting in systematic reviews of drug's safety studies found that a large proportion of the analysed systematic reviews failed in reporting risk of bias assessment (Zorzela et al, 2014). Nevertheless, some efforts are being made to improve the methodological quality assessment of studies reporting drug's safety. In addition, a recent study has described a new risk of bias tool to use when conducting systematic reviews of randomized controlled trials, cohort studies, case-control studies and nested case-control studies describing adverse drug reactions (Faillie et al, 2017).

Some studies assessed the quality of systematic reviews reporting adverse drug reactions. In general, systematic reviews reporting adverse drug reactions failed methodologically (Cornelius et al, 2009; Zorzela et al, 2014; Mahady et al, 2015). Definition of adverse drug reaction, design of literature search, bibliographic databases choice and assessment of methodological quality of the included studies are the main divergent steps (Cornelius et al, 2009; Zorzela et al, 2014; Mahady et al, 2015). In most of the studies, only a small proportion has good reporting (Cornelius et al, 2009; Zorzela et al, 2014; Mahady et al, 2015). In a previous work, we analysed the methodology used in systematic reviews reporting ophthalmic adverse drug reactions and found the same methodological issues (Penedones et al, 2018b). In 2016, the PRISMA group developed

guidance to help reporting systematic reviews of adverse drug reactions, the PRISMA Harms (Zorzela et al, 2016). A study performed by Li et al (2019), evaluated the methods of a sample of systematic reviews, one year after the publication of PRISMA Harms. They concluded that a large number of systematic reviews still presented methodological differences (Li et al, 2019). The reinforcement of the use of recommendations to conduct and/ or report a systematic review of adverse drug reactions still continues of major importance.

Limitations of this study

This study has some limitations. Only two recommendations were used to perform a comparison on methods of reviewing drug's safety data. The two systematic reviews were conducted by the authors of the present study. Only an exploratory analysis was performed to compare both recommendations. A statistical analysis of the methodologies of both recommendations will be necessary to better understand the differences among them. In the two systematic reviews, the authors only searched on the recommended bibliographic databases, despite the recommendations suggested that other databases could be included. Therefore, two case reports were not included in one systematic review. This resulted in an example of the non-inclusion of all available evidence and, consequently, differences in the results of the systematic reviews.

Further investigation

Further consideration should be taken on the access of the data, including public bibliographic databases and the selection of all available databases, resulting in a more robust and complete data and, therefore, improving the knowledge provided by the systematic review.

In addition, new tools able to evaluate methodological quality of some studies, such as some type of observational studies and case reports, should be elaborated. Moreover, several sources of information should be recorded and more investigation should be performed to clarify the role of the methodological quality assessment in the context of evaluating the evidence of safety.

Finally, the process of conducting and reporting a systematic review of adverse drug reactions, including the design of the review, data search, selection, extraction and synthesis, should be transparent and independent.

5.6. Conclusions

Few methodological differences were observed among the available recommendations to conduct a systematic review of adverse drug reactions. Combining their methods into a single and recognized recommendation could be of great value. A unique, objective and easy to apply methodology could improve systematic review's role in drug safety. Further research should be considered, namely in granting access to the information and in the methodological quality assessment of the included evidence.

5.7. References

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5.8. Appendix

Step/ Review	A – Cochrane Collaboration	B – Centre for Reviews and Dissemination
Title	Risk of nonarteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis	Risk of nonarteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis
Introduction		
Background	Description of the condition: Ischemic optic neuropathies are the main cause of acute optic nerve injury in Caucasian patients aged 50 years or older.[1-4] Depending on the affected nerve, they can be divided into anterior or posterior ischemic optic neuropathy.[3,4] Ischemic optic neuropathies can also be classified, according to aetiology, into arteritic or non-arteritic.[1-4] The pathophysiology of non-arteritic anterior ischemic optic neuropathy (NAION) remains unknown.[1-3] The hypothesis most accepted is that NAION results from small vessel disease, such as an occlusion, of the short posterior ciliary arteries, which supplied the optic nerve head, resulting in hypoperfusion and infarction of the anterior optic nerve.[1-3] Several factors increase the risk of developing NAION.[1-4] Anomalies in optic nerve anatomy, increased age and genetic predisposition, underlying systemic diseases, such as hypertension, episodic hypotension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnoea, prolonged surgical procedures, cataract surgery, and medication, such as amiodarone, interferon-α, nasal decongestants, several vasopressors or vasoconstricting drugs, and phosphodiesterase type 5 (PDE5) inhibitors.[1-4] The diagnosis of NAION is essentially clinical. NAION is, generally, presented as sudden, painless, and associated with any pattern of visual field loss.[1-4] Patients may present decreased visual acuity, reduced colour vision, visual field defect, or flame-shaped haemorrhages.[2] In the fellow eye, small or absent physiological cup may also happen.[1,3] Description of the intervention: The PDE5 inhibitors are a drug class mainly approved for the treatment of erectile dysfunction. Avanafil, toenail, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil are examples of selective PDE5 inhibitors. Some of PDE5 inhibitors were also	Description of intervention: The phosphodiesterase type 5 (PDE5) inhibitors are a drug class mainly approved for the treatment of erectile dysfunction. Avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil are examples of selective PDE5 inhibitors. Some of PDE5 inhibitors were also approved for the treatment of signs and symptoms of benign prostatic hyperplasia (tadalafil) and pulmonary arterial hypertension (sildenafil and tadalafil).[1] Sildenafil was the first PDE5 inhibitor introduced in the market, in 1998.[2] The PDE5 enzyme potentiates nitric oxide cascade and concentration of cyclic guanosine monophosphate in the smooth muscle cells, resulting in muscle relaxation, increased blood flow, and prolonged erection[1,3], reverse pulmonary artery remodelling and a reduced pulmonary vascular tone[4,5], and modulate the afferent nerve activity, responsible for the regulation of micturition reflex[6,7]. The PDE5 inhibitors are well tolerated and most of their adverse reactions are adjacent to their vascular role.[8] Patients taking nitrate compounds should not use PDE5 inhibitors, since it can result in a sudden hypotension.[8] Headache, flushing, nasal congestion, and dyspepsia are the most common adverse reactions associated with PDE5 inhibitors.[1,3,8] In addition, tadalafil was also related with myalgia and back pain.[8] Patients using PDE5 inhibitors also experienced visual abnormalities, such as changes in colour perception, blurred vision and non-arteritic anterior ischemic optic neuropathy (NAION).[1,3] Description of the condition: The development of NAION is, generally, presented as sudden, painless, and associated with any pattern of visual field loss.[9-12] Patients may present decreased visual acuity, reduced colour vision, visual field defect, or flame-shaped hemorrhages.[10] Few patients, almost 10%, reported pain and headache.[9-12]

	approved for the treatment of signs and symptoms of benign prostatic hyperplasia (tadalafil) and pulmonary arterial hypertension (sildenafil and tadalafil). [5] Sildenafil was the first PDE5 inhibitor introduced in the market, in 1998.[6] Erectile dysfunction is defined as the inability to achieve or maintain an erection able to satisfactory sexual performance.[7] PDE5 enzyme, found in the smooth muscle of the corpus cavernosum, stimulate hydrolysis of cyclic guanosine monophosphate (cGMP) into GMP, decreasing the concentration of cGMP and nitric oxide (NO) cascade and, consequently, the erection.[5,7] PDE5 inhibitors bind to PDE5 enzymes, avoiding cGMP hydrolysis.[5,7] Therefore, it potentiates NO cascade and concentration of cGMP in the smooth muscle cells in corpus cavernosum, resulting in muscle relaxation, increased blood flow and prolonged erection.[5,7,8] The same mechanism of action is observed for the treatment of pulmonary arterial hypertension and signs and symptoms of benign prostatic hyperplasia.[11-14] PDE5 inhibitors play a role in reverse pulmonary artery remodelling and a reduced pulmonary vascular tone and in the micturition and prostate functioning. PDE5 inhibitors.[11-14] The PDE5 inhibitors are well tolerated and most of their adverse reactions are adjacent to their vascular role.[8] Patients taking nitrate compounds should not use PDE5 inhibitors, since it can result in a sudden hypotension.[8] Headache, flushing, nasal congestion, and dyspepsia are the most common adverse reactions associated with PDE5 inhibitors.[5,7,8] In addition, tadalafil was also related with myalgia and back pain.[5,7] Some serious and rare adverse reactions have been described to PDE5 inhibitors, such as priapism (painful erections), sudden hearing loss and visual abnormalities, such as changes in colour perception, blurred vision and NAION.[5,7] How the intervention might work: The association between the use of PDE5 inhibitors and the development of NAION remains unknown.[5,7,10,15] PDE5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION.[10,15] PDE5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation.[10,15] PDE6	Nevertheless, the pathophysiology of NAION remains unknown.[9-11] The hypothesis most accepted is that NAION results from small vessel disease, such as an occlusion, of the short posterior ciliary arteries, which supplied the optic nerve head, resulting in hypoperfusion and infarction of the anterior optic nerve.[9-11] Several factors increase the risk of developing NAION, such as anomalies in optic nerve anatomy like optic nerve head drusen and small cup-to-disc ratio or absence of the cup; increased age and genetic predisposition; underlying systemic diseases like hypertension, episodic hypotension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnoea, and blood loss; prolonged surgical procedures; cataract surgery; and medication like amiodarone, interferon-α, nasal decongestants, several vasopressors or vasoconstricting drugs, and PDE5 inhibitors.[9-12] Rationale for review: NAION causes a serious visual disability with sudden vision. PDE5 inhibitors are the first line treatment for erectile dysfunction, which is a common medical condition. Several studies assessed the association between PDE5 inhibitors intake and the development of NAION. A systematic review and meta-analysis can combine all available evidence and provide a more precise result, helpful to healthcare professionals, patients and, also, regulatory authorities.

	enzyme is present in ocular blood vessels and have an important function in phototransduction. It is thought that PDE5 inhibitors also act on PDE6, being responsible for changes in colour perception.[8,10] Why it is important to do this research: NAION causes a serious visual disability with sudden vision. PDE5 inhibitors are the first line treatment for erectile dysfunction, which is a common medical condition. Several studies assessed the association between PDE5 inhibitors exposure and the development of NAION. A systematic review and meta-analysis can combine all available evidence and provide a more precise result, helpful to healthcare professionals, patients and, also, regulatory authorities.	
Eligibility criteria	-Type of participants: Patients for whom a PDE_5 inhibitor is indicated in one of the three approved therapeutic indications; -Type of interventions: PDE_5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil) comparing with placebo, active treatment or no treatment; -Type of outcome measures: Development of NAION.	-Population: Patients for whom a PDE_5 inhibitor is indicated in one of the three approved therapeutic indications; -Intervention: PDE_5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil); -Comparators: Placebo, active treatment or no treatment; -Outcomes: Development of NAION.
Review question	PICO Strategy: To assess the risk of NAION associated with PDE5 inhibitors exposure. A systematic review is carried out based on pre- and post-marketing data.	PICO Strategy: The objective of this systematic review is to assess the risk of NAION associated with PDE5 inhibitors exposure, based on pre- and post-marketing data.
Identifying evidence		
Type of studies	Randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports.	Randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports.
Databases	MEDLINE, EMBASE, Cochrane Controlled Register of Trials (CENTRAL), TRIP*, SCOPUS*, Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform, and VigiBase.	MEDLINE, EMBASE, Toxline, Pharmline*, websites of the manufacturers of drugs and VigiBase.
Search strategy	Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and the ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search. The databases were searched since its inception until November 19, 2018.	Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and the ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search. The databases were searched since its inception until November 19, 2018.
Data selection	Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion.	Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion.

Data extraction	Data was extracted from each included study by two researchers independently.	Data was extracted from each included study by two researchers independently.
Quality assessment	Included studies were independently assessed for bias according to the methods described in Chapter 13.5 and Chapter 14.6 of the Cochrane Handbook for Systematic Reviews of Interventions.	For observational studies, the checklist proposed by Downs and Black was used. The case reports were evaluated according to the questions elaborated on the Chapter 4 of the CRD's guidance for undertaking reviews in health care.
Data synthesis	Data analysis followed the guidelines set out in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions.	Data from case and spontaneous reports were analysed using descriptive statistics. A meta-analysis was conducted to analyse data from observational studies.
Reporting		
Flowchart	A total of 295 potentially relevant records were yielded from literature search (MEDLINE, EMBASE and CENTRAL). Additionally, 462 records were identified through other resources (Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform). Two potential articles were identified through reference lists of reviews. Based on above inclusion criteria, 87 records were selected for full-text further inclusion. A final sample of 37 references covering 4 observational studies, 3 series of cases reports and 30 case reports met the inclusion criteria. The selection of references is shown in Figure 1. The references of the included and excluded studies are listed in the Appendix 2. The results of the VigiBase search for NAION events were described below.	A total of 293 potentially relevant publications were yielded from literature search (MEDLINE and EMBASE). Additionally, 61 records were identified through other resources (Toxline). Four potential articles were identified through reference lists of reviews. Based on above inclusion criteria, 77 records were selected for full-text further inclusion. A final sample of 35 references covering 4 observational studies, 3 series of cases reports and 28 case reports met the inclusion criteria. The selection of references is shown in Figure 1. The references of the included and excluded studies are listed in the Appendix 2. The results of the VigiBase search for NAION events reported with PDE5 inhibitors were described below.
Characteristics of studies	Studies: No clinical trials were identified. Four observational studies evaluating the association of PDE5 inhibitors with NAION were identified. Three studies were retrospective. One observational study used the case-control design and two studies were case-crossover. Two studies included patients from United States (US) in their evaluations. Three series of case reports comprising 22 case reports along with 30 case reports describing the development of NAION when the patient was exposed to a PDE5 inhibitor were identified. Twenty case reports were from US. A single publication reported 10 case reports from Saudi Arabia. In VigiBase, 689 spontaneous reports of "Eye disorders" were identified (Appendix 3). Participants: All observational studies evaluated males treated for erectile dysfunction. Their mean age was 64.1 years old. A total of 5,396,708 men were	No RCT were identified. Four observational studies evaluating the association of PDE5 inhibitors with NAION were identified (Table 1). Three studies were retrospective. One observational study used the case-control design and two studies were case-crossover. Two studies included patients from United States (US) in their evaluations. All observational studies evaluated males treated for erectile dysfunction. Their mean age was 64.1 years old. A total of 5,396,708 men were included in the 4 studies. From these, 480,700 were exposed to a PDE5 inhibitor and 4,915,781 men were the comparator. From the total of participants, 114 men were their own control in case-crossover studies. Risk factors to develop NAION and medical history were recorded in three studies. In two studies, the PDE5 inhibitors were specified to vardenafil, tadalafil and sildenafil. Three series of case reports comprising 22 case reports along with 28 case reports

	included in the 4 studies. 480,700 were exposed to a PDE5 inhibitor and 4,915,781 men were the comparator. From the total of participants, 114 men were their own control in case-crossover studies. Risk factors to develop NAION and medical history were recorded in three studies. A total of 52 patients exposed to a PDE5 inhibitor with NAION were described in the literature. Forty-seven (90%) patients were men. The average age of the patients were 52.9 years old (min= 7 months; max= 76). Twelve (23%) patients had not risk factors to develop NAION. Hypertension (n=16; 31%), diabetes mellitus (n=12; 23%) and dyslipidaemia (n=11; 21%) were the most described risk factors. Interventions: All observational studies evaluated the use of PDE5 inhibitors for the treatment of erectile dysfunction. In two studies, the PDE5 inhibitors were specified to vardenafil, tadalafil and sildenafil. Forty (77%) case reports described patients treated for erectile dysfunction, and five (10%) case reports described patients treated for pulmonary arterial hypertension. Sildenafil was the PDE5 inhibitor most reported (n=47; 90%) in case reports, followed by tadalafil (n=4; 8%) and udenafil (n=1; 2%). Type of outcome measures: All studies reported the risk of developing NAION with PDE5 inhibitors exposure. In case reports, the unit of analysis was each case report.	describing the development of NAION when the patient was exposed to a PDE5 inhibitor were identified. Eighteen case reports were from US. A single publication reported 10 case reports from Saudi Arabia. A total of 50 patients exposed to a PDE5 inhibitor with NAION were described in the literature. Forty-five (90%) patients were men. The average age of the patients were 52.5 years old (min= 7 months; max= 76). Twelve (23%) patients had not risk factors to develop NAION. Hypertension (n=15; 30%), diabetes mellitus (n=12; 24%) and dyslipidaemia (n=10; 20%) were the most described risk factors. Thirty-nine (78%) case reports described patients treated for erectile dysfunction, and five (10%) case reports described patients treated for pulmonary arterial hypertension. Sildenafil was the PDE5 inhibitor most reported (n=45; 90%) in case reports, followed by tadalafil (n=4; 8%) and udenafil (n=1; 2%). The characteristics of case reports are described in Table 2. In VigiBase, 6692 spontaneous reports on the SOC 'Eye disorders' were identified (Appendix 3). Of these, 608 belong to the PT 'Optic ischaemic neuropathy'.
Outcome analysis	Observational studies: Treatment with PDE5 inhibitors are not associated with an increased risk of NAION (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I2 = 62.6%) (Figure 3; Table 1). Two case-crossover studies evaluated the association of intermittent use of PDE5 inhibitors and development of NAION. Both studies examined the risk of NAION associated with PDE5 inhibitors exposure within 5 half-lives compared with a more prior time period. The results showed that there is an increased risk of NAION within five half-lives of PDE5 inhibitors use (OR 2.20; 95% CI 1.29, 3.76; p = 0.922; I2 = 0%) (Figure 3; Table 1). Nathoo et al (2015), a retrospective nested case-control study, compared the risk of NAION in individuals exposed to PDE5 inhibitors to controls. The results were not statistically significant and	Observational studies: Treatment with PDE5 inhibitors are not associated with an increased risk of NAION (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I2 = 62.6%) (Figure 3; Table 1). Two case-crossover studies evaluated the association of intermittent use of PDE5 inhibitors and development of NAION. Both studies examined the risk of NAION associated with PDE5 inhibitors exposure within 5 half-lives compared with a more prior time period. The results showed that there is an increased risk of NAION within five half-lives of PDE5 inhibitors use (OR 2.20; 95% CI 1.29, 3.76; p = 0.922; I2 = 0%) (Figure 3; Table 1). However, the risk is not statistically significant. Nathoo et al (2015), a retrospective nested case-control study, compared the risk of NAION in individuals exposed to PDE5 inhibitors to controls. The results

	concluded that there is not any association between PDE5 inhibitors exposure and NAION (OR 0.96 95% CI 0.75, 1.23) (Figure 3; Table 1). An identical result was achieved by Margo and French (2007) (OR 1.02; 95% CI 0.92, 1.13) (Figure 3; Table 1). Sensitive analysis: The risk of NAION changed when the analysis included both definitive and possible cases of NAION (OR 1.28; 95% CI 0.95, 1.73; p = 0.012; I2 = 72.4%) (Figure 4). Case reports: In the total of case reports, the administration of PDE5 inhibitors always precedes an event of NAION. A regular administration (≥ 2 months) of PDE5 inhibitors was observed in 25 (48%) case reports, whereas a recent administration was identified in 22 (42%) case reports. From the cases where a regular administration was reported, five patients admitted to double or triple the dose of PDE5 inhibitors. In general, the doses administered to each patient were within the approved. The majority of the cases reported the development of NAION in one eye (right eye = 22; 42%; left eye = 17; 33%). The characteristics and results of case reports are described in Table 2. Spontaneous reports: "Optic ischaemic neuropathy", including NAION, was most reported with sildenafil (n=496), followed by tadalafil (n=79) and vardenafil (n=33) (Table 3).	were not statistically significant and concluded that there is not any association between PDE5 inhibitors exposure and NAION (OR 0.96 95% CI 0.75, 1.23) (Figure 3; Table 1). An identical result was achieved by Margo and French (2007) (OR 1.02; 95% CI 0.92, 1.13) (Figure 3; Table 1). Sensitive analysis: The risk of NAION did not change when the analysis included both definitive and possible cases of NAION (OR 1.28; 95% CI 0.95, 1.73; p = 0.012; I2 = 72.4%) (Figure 3). Case reports: In the total of case reports, the administration of PDE5 inhibitors always precedes an event of NAION. A regular administration (≥ 2 months) of PDE5 inhibitors was observed in 24 (48%) case reports, whereas a recent administration was identified in 22 (44%) case reports. From the cases where a regular administration was reported, four patients admitted to double or triple the dose of PDE5 inhibitors. In general, the doses administered to each patient were within the approved. The majority of the cases reported the development of NAION in one eye (right eye = 22; 44%; left eye = 17; 34%). The results of case reports are described in Table 2. Spontaneous reports: "Optic ischaemic neuropathy", including NAION, was most reported with sildenafil (n=496), followed by tadalafil (n=79) and vardenafil (n=33).
Quality assessment	All case reports were assessed for bias (Appendix 4 – Characteristics of included studies). Despite a plausible biological mechanism can explain the development of NAION associated with PDE5 inhibitors exposure, the results of the observational studies evaluating the risk of such association were not significant. Therefore, none of the case reports have a good predictive value and causality, and cannot be used to demonstrate such association. The risk of bias of each observational study was also assessed (Figure 2). The results are as the follows: *bias due to confounding* - One observational study was assessed as having critical risk of bias. No one of the confounders were controlled. The other three studies were assessed as serious risk of bias; *bias in selection of the participants into the study* - In three studies, the selection process was strongly related with the intervention and the outcome. In the other study, the selection process only	The full description of the methodological quality assessment was described in Appendix 4. The methodological quality was assessed as good for three observational studies and fair for one observational study (Table 4). The study of Margo and French (2007) failed to report clearly the objective of the study. In the four observational studies, the patients were not blind to the exposure, neither the people who measure the outcomes. There was not randomization in any of the studies. The sample size was not estimated in any of the studies. For all case reports, a questionnaire was answered (Appendix 4). The exposure precedes the outcome. In some cases, the exposure was prolonged (≤ 2 months). For one case report, the dose was over those described in the Summary of Product Characteristics. The majority of patients had risk factors to develop

	depended on outcome; *bias in classification of interventions* - All studies were assessed as low risk of bias. The intervention was well defined at the start of the study; *bias due to deviations from intended interventions* - All studies were assessed as low risk of bias. As observational studies, all deviations in study reflected the usual practice; *bias due to missing data* - All studies were assessed as low risk of bias. Data from the studies were complete; *bias in measurement of outcomes*: All studies were assessed as low risk of bias. The methods of assessment were comparable across intervention groups; *bias in selection of the reported result*: The studies did not provide sufficient information to evaluate this risk of bias.	NAION. Insufficient or unclear data on discontinuation and rechallenge was observed in the majority of case reports. In general, there are other factors that can explain the development of NAION.
Discussion	Summary of main results: Some observational studies studied the association of PDE5 inhibitors exposure and the development of NAION. However, their results were not statistically significant, even when compared the intermittent exposure of PDE5 inhibitors with exposure in a more previous time. Several case reports described the development of NAION when the patient was taking a PDE5 inhibitor. The cases occurred mostly in men exposed to sildenafil for the treatment of erectile dysfunction. Almost 75% of patients had risk factors to develop NAION. In the majority of cases, the PDE5 inhibitor exposure was regular. NAION generally occurs in one eye. Overall completeness and applicability of evidence: This review included four observational studies. All of them have serious methodological issues, namely in assuring methods to avoid bias due to confounders, for example, determining the influence of risk factors to develop NAION or co-medications. Another critical issue was the selection of the participants into the study. In the included observational studies, the participants were selected according to the outcome and exposure, this is, the population was chosen according to the specific and pre-established aim leading to a risk of bias in the selection of participants. In the majority of the observational studies, the confounders were not controllable, since the population chosen was representative of the clinical practice. The case reports also describe the events occurred in clinical practice. In general, the	Principal findings: Spontaneous reports were reported describing the development of NAION associated with PDE5 inhibitors exposure. Based on this data, in 2005, three regulatory agencies (European Medicines Agency (EMA), Food and Drug Administration (FDA), and Health Canada) issued a safety alert, warning healthcare professionals and consumers to be aware of visual changes related with sildenafil, tadalafil and vardenafil intake. The sections of the product label "Contraindications", "Warnings and Precautions", "Adverse reactions" and "Patient Counselling Information" were also updated.[16] The association between the use of PDE5 inhibitors and the development of NAION is not yet established.[1,3,17,18] Several physiopathological hypotheses were studied. PDE5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION.[17,18] PDE5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation.[17,18] PDE6 enzyme is present in ocular blood vessels and have an important function in phototransduction. It is thought that PDE5 inhibitors also act on PDE6, being responsible for changes in colour perception.[8,17] A pharmacological rationale can explain the development of NAION after PDE5 inhibitors exposure. In this review, in order to study such association, experimental and observational evidence was searched. We did not find experimental evidence studying this association. Nevertheless, four observational studies, along with 50

	included case reports were well-described. However, some aspects such as causality result in higher risk in using this information to corroborate an association between PDE5 inhibitors use and NAION. The data available on spontaneous reports was scarce, such as the therapeutic indication, patients' past medical history and risk factors, or case's causality assessment. Further, it was not possible to calculate incidences of NAION because no data of the exposed patients to each PDE5 inhibitor was measured. Despite of the methodological problems observed on the available evidence, in 2005, the European Medicines Agency (EMA), the Food and Drug Administration (FDA) and Health Canada issued a safety alert based on spontaneous reports. The sections of the product label "Contraindications", "Warnings and Precautions", "Adverse reactions" and "Patient Counselling Information" were updated.[17] Potential biases in the review process: A protocol of this review was not previously published. The methodological quality level of the included evidence is low. Observational studies, case reports, and spontaneous reports are important tools in pharmacovigilance since they are useful to detect rare and/or long-term adverse reactions. However, observational designs are more likely to be subject of bias. The study search, selection and extraction process were systematic and independent, that should minimize bias. Some sources of information are not available in our university (such as TRIP and Scopus databases) and they need the payment of a fee to access and perform searches. The International Clinical Trials Register Platform and VigiBase are databases, developed and maintained by the World Health Organisation (WHO). The International Clinical Trials Register Platform contains trials registries from several worldwide data providers, such as ClinicalTrials.gov and EU Clinical Trials Register.[17] The VigiBase detain information reported to the WHO Programme for International Drug Monitoring from 120-member countries.[19] The data provided by these two databases may not be completed and doesn't represent all worldwide data.	case reports and 608 spontaneous reports were identified. According to the evidence found in this review, the cases occurred mostly in men exposed to sildenafil for the treatment of erectile dysfunction. NAION generally occurs in one eye after a regular PDE5 inhibitor exposure. The majority of the patients had other risk factors to develop NAION, such as hypertension. When pooled the results from the observational studies into a meta-analysis, the current available published evidence demonstrated to be insufficient to support an association between the development of NAION and PDE5 inhibitors exposure. Comparison with other research: Twenty-two reviews were identified in the search performed to this systematic review and meta-analysis. Of those, 12 (50%) reviewed specifically the association between PDE5 inhibitors exposure and the risk of NAION. Three systematic reviews identified some case reports and observational studies. Despite the present systematic review and meta-analysis has included more studies and case reports, the results of the previous published reviews were similar to those found in this systematic review. One systematic review also performed a meta-analysis with observational studies.[18] An association between PDE5 inhibitors use and the development of NAION was also not found.[18] This review only included observational studies, excluding other type of observational data, such as case and series of case reports and spontaneous reports. This review included the four observational studies identified in our work along with the observational study by French and Margo (2008) which evaluated the association of PDE5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION.[19] The study concluded that there was no increase in risk of NAION in men taking a PDE5 inhibitor with organic nitrates or an alfa-blocker compared with men taking PDE5 inhibitor alone.[19] This observational study was not included in the present systematic review since the aim of this study was to determine if the risk of developing NAION is increased with the co-medication of organic nitrate or alfa-blockers. Another article analysed the spontaneous reporting to the FDA of NAION associated with sildenafil, tadalafil and

	There was different designs and methodologies across the included observational studies. Such differences are usually associated with increased heterogeneity.[20] Therefore, the results should be interpreted cautiously. Nevertheless, case-crossover was the study design more properly used. In this design, each subject is his own control and is possible to estimate the risk of acute adverse events associated with intermittent drug exposures.[21] Agreements and disagreements with other studies or reviews: Twenty-two reviews were identified in the search performed to this review. Of those, 12 (50%) reviewed specifically the association between PDE5 inhibitors exposure and the risk of NAION. Three systematic reviews identified some case reports and observational studies. Despite the present systematic review has included more studies and case reports, the results of the previous published reviews were similar to those found in this systematic review. One systematic review also performed a meta-analysis with observational studies.[22] No association between PDE5 inhibitors use and the development of NAION was found.[22] This review included the observational study by French and Margo (2008) which evaluated the association of PDE5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION.[23] The study concluded that there was no increase in risk of NAION in men taking a PDE5 inhibitor with organic nitrates or an alfa-blocker compared with men taking PDE5 inhibitor alone.[23] This observational study was not included in the present systematic review since it does not allow to measure the risk of PDE5 inhibitors alone. One article analysed the spontaneous reporting to the FDA of NAION associated with sildenafil, tadalafil and vardenafil. The first spontaneous report was reported in 1999 to sildenafil, one year after its marketing authorization. Since then, an increase in spontaneous reports were observed after FDA published the safety alert with cases describing such association. A more detailed and completed cases of NAION after PDE5 inhibitors intake was obtained through spontaneous reports systems.[24]	vardenafil. The first spontaneous report was reported in 1999 to sildenafil, one year after its marketing authorization. Since then, an increase in spontaneous reports were observed after FDA published the safety alert with cases describing such association. A more detailed and completed cases of NAION after PDE5 inhibitors intake was obtained through spontaneous reports systems.[20] Strengths and weaknesses of the research: A key strength of this systematic review and meta-analysis is the combination of the published available evidence on clinical practice, including several types of evidence. Observational studies, case reports, and spontaneous reports are important tools in pharmacovigilance since they are useful to detect rare and/or long-term adverse reactions. A protocol of this work was not previously published. Some sources of information are not available in our university (such as TRIP and Scopus databases) and they need the payment of a fee to access and perform searches. There are few studies evaluating the association between PDE5 inhibitors use and NAION. These studies have serious risk of bias and some limitations. Observational designs are likely to be subject of bias. There was different designs and methodologies across the included observational studies. Such differences are usually associated with increased heterogeneity.[21] Nevertheless, case-crossover was the study design more properly used. In this design, each subject is his own control and is possible to estimate the risk of acute adverse events associated with intermittent drug exposures.[21] Therefore, the results should be interpreted cautiously. The checklist used to assess the methodological quality is one of the checklists proposed by the CRD guidance for undertaking reviews in health care to assess non-randomized controlled trials.[13] However, this checklist may not provide detailed information on the insufficiencies of the studies. For instance, all the observational studies included are subject to exposure misclassification. Two observational studies used data from clinical databases, one observational study applied a questionnaire to patients, and the other observational study did not specify the data source. Since PDE5 inhibitors are, generally, used periodically, data on

		exposure can be subject of exposure misclassification bias and/or recall bias. This bias and the low study power to detect the adverse drug reaction, may have led to the wide confidence intervals in the effect sizes for all studies. New large, prospective and comparative studies evaluating such association are needed. A meta-analysis was conducted as recommended by the CRD guidance for undertaking reviews in health care.[13] Although a small number of studies was available, a quantitative synthesis allows to increase the sample size, narrow confidence interval and increase statistical power.[13] In this review, one of the observational studies detected an association between PDE5 inhibitors exposure and the development of NAION. However, when we pooled the results of all observational studies, the risk of developing this adverse drug reaction was not statistically significant. Thus, the result of the meta-analysis should be interpreted based on the limitations of the studies. We pooled the results according to the study design of the observational studies. We did not perform a meta-analysis to understand the influence of the risk factors, since this information is not clear in all the four observational studies. The VigiBase database was developed and is maintained by the World Health Organisation (WHO). The VigiBase detain information on spontaneous reported to the WHO Program for International Drug Monitoring from 120-member countries.[22] The data provided by this database may not be completed and doesn't represent all worldwide data. The data available on spontaneous reports was scarce, such as the therapeutic indication, patients' past medical history and risk factors, or case's causality assessment. Further, it was not possible to calculate incidences of NAION because no data of the exposed patients to each PDE5 inhibitor was measured.
Conclusion	Implications for practice/ research: There are few studies evaluating the association between PDE5 inhibitors use and NAION. These studies have serious risk of bias and several limitations. New large and comparative studies evaluating such association are needed. Despite the available evidence was scarce, a plausible mechanism can explain the development of NAION resultant from PDE5 inhibitors use. Additionally, several case reports and spontaneous reports have been published	Recommendations/ implications for practice/ further research: In light of the current available evidence, an association between PDE5 inhibitors exposure and NAION was not identified. However, since case and spontaneous reports have been reported, and in the light of a pharmacological rationale, a close monitoring is foreseen of great value.

	in literature. Some of them resulted in the generation of a safety alert from regulatory authorities. A close monitoring of the prescription of PDE5 inhibitors may be of great value in clinical practice.	
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Appendix	Appendix 1 - Search strategy; Appendix 2 - List of included and excluded studies; Appendix 3 - Vigibase results; Appendix 4 - Characteristics of studies and quality assessment results.	Appendix 1 - Search strategy; Appendix 2 - List of included and excluded studies; Appendix 3 - Vigibase results; Appendix 4 - Quality assessment results.
Tables	Table 1 – Observational studies summary. Table 2 – Characteristics and results of case reports. Table 3 – Spontaneous reports of PDE5 inhibitors registered in VigiBase. Table 4 – Scores of the methodological quality assessment of the observational studies.	Table 1 – Observational studies summary. Table 2 – Characteristics and results of case reports. Table 3 – Spontaneous reports of PDE5 inhibitors registered in VigiBase. Table 4 – Scores of the methodological quality assessment of the observational studies.
Figures	Figure 1 – PRISMA flow chart of search strategy and study selection. Figure 2 – Odds Ratios and 95% Confidence Intervals for definitive cases of NAION associated with PDE5 inhibitors. Figure 3 – Odds Ratios and 95% Confidence Intervals for definitive and possible cases of NAION associated with PDE5 inhibitors.	Figure 1 – PRISMA flow chart of search strategy and study selection. Figure 2 – Odds Ratios and 95% Confidence Intervals for definitive cases of NAION associated with PDE5 inhibitors. Figure 3 – Odds Ratios and 95% Confidence Intervals for definitive and possible cases of NAION associated with PDE5 inhibitors.

Chapter 6 - Risk of nonarteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis

This systematic review and meta-analysis were conducted in accordance with the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care (Centre for Reviews and Dissemination, 2009).

6.1. Abstract

Introduction: The development of nonarteritic anterior ischaemic optic neuropathy has been described to phosphodiesterase type 5 inhibitors. The aim of this systematic review and meta-analysis was to assess the risk of non-arteritic anterior ischemic optic neuropathy associated with phosphodiesterase type 5 inhibitors exposure.

Methods: A literature search was performed at MEDLINE, EMBASE, Toxline, and VigiBase. Randomized controlled trials, observational studies, case reports and spontaneous reports describing non-arteritic anterior ischemic optic neuropathy associated with phosphodiesterase type 5 inhibitors exposure were included. The risk of bias was assessed according to Centre for Reviews and Dissemination's guidance. Data were analysed using descriptive statistics and meta-analysis.

Results: Four observational studies, 50 case reports, and 608 spontaneous reports were identified. All observational studies evaluated males treated for erectile dysfunction. Treatment with phosphodiesterase type 5 inhibitors are not associated with an increased risk of definitive non-arteritic anterior ischemic optic neuropathy (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I2 = 62.6%). The methodological quality was assessed as good for three studies. Among case reports, 12 (23%) patients did not have risk factors to develop non-arteritic anterior ischemic optic neuropathy. Thirty-nine (78%) patients were treated for erectile dysfunction. A regular administration of phosphodiesterase type 5 inhibitors was observed in 24 (48%) case reports. All case reports were assessed as higher risk of bias.

Conclusions: According to the available evidence, the treatment with phosphodiesterase type 5 inhibitors was not found to be associated with non-arteritic anterior ischemic optic neuropathy. Further research is needed to study such association, including possible confounding factors.

6.2. Introduction

The phosphodiesterase type 5 (PDE5) inhibitors are a drug class mainly approved for the treatment of erectile dysfunction. Avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil are examples of selective PDE5 inhibitors. Some of PDE5 inhibitors were also approved for the treatment of signs and symptoms of benign prostatic hyperplasia (tadalafil) and pulmonary arterial hypertension (sildenafil and tadalafil) (Huang and Lie, 2013). Sildenafil was the first PDE5 inhibitor introduced in the market, in 1998 (Frederick et al, 2014).

The PDE5 inhibitor potentiates nitric oxide (NO) cascade and concentration of cyclic guanosine monophosphate in the smooth muscle cells, resulting in muscle relaxation, increased blood flow, and prolonged erection (Huang and Lie, 2013; Shamloul and Ghanem, 2013), reverse pulmonary artery remodelling and a reduced pulmonary vascular tone (Montani et al, 2009; Barnes et al, 2017), and modulate the afferent nerve activity, responsible for the regulation of micturition reflex (Gacci et al, 2016; Giuliano et al, 2013).

The PDE5 inhibitors are well tolerated and most of their adverse reactions are adjacent to their vascular role (Ferguson and Carson, 2013). Patients taking nitrate compounds should not use PDE5 inhibitors, since it can result in a sudden hypotension (Ferguson and Carson, 2013). Headache, flushing, nasal congestion, and dyspepsia are the most common adverse reactions associated with PDE5 inhibitors (Huang and Lie, 2013; Shamloul and Ghanem, 2013; Ferguson and Carson, 2013). In addition, tadalafil was also related with myalgia and back pain (Ferguson and Carson, 2013). Patients using PDE5 inhibitors also experienced visual abnormalities, such as changes in colour perception, blurred vision and non-arteritic anterior ischemic optic neuropathy (NAION) (Huang and Lie, 2013; Shamloul and Ghanem, 2013).

The development of NAION is, generally, presented as sudden, painless, and associated with any pattern of visual field loss. Patients may present decreased visual acuity, reduced colour vision, visual field defect, or flame-shaped haemorrhages (Kerr et al, 2009). Few patients, almost 10%, reported pain and headache. Nevertheless, the pathophysiology of NAION remains unknown. The hypothesis most accepted is that NAION results from small vessel disease, such as an occlusion, of the short posterior ciliary arteries, which supplied the optic nerve head, resulting in hypoperfusion and

infarction of the anterior optic nerve (Mathews, 2005; Luneau et al, 2008; Kerr et al, 2009; Peeler and Cestari, 2016).

Several factors increase the risk of developing NAION, such as anomalies in optic nerve anatomy like optic nerve head drusen and small cup-to-disc ratio or absence of the cup; increased age and genetic predisposition; underlying systemic diseases like hypertension, episodic hypotension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnoea, and blood loss; prolonged surgical procedures; cataract surgery; and medication like amiodarone, interferon-α, nasal decongestants, several vasopressors or vasoconstricting drugs, and PDE5 inhibitors (Mathews, 2005; Luneau et al, 2008; Kerr et al, 2009; Peeler and Cestari, 2016).

The objective of this systematic review and meta-analysis is to assess the risk of NAION associated with PDE5 inhibitors exposure, based on pre- and post-marketing data.

6.3. Methods

The systematic review and meta-analysis were conducted in accordance with the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care (Centre for Reviews and Dissemination, 2009). As this paper was a systematic review and meta-analysis of published work, ethical approval was not required.

6.3.1. Eligibility criteria for considering studies for the review

Studies were assessed against the eligibility criteria described in the following sections.

- Population: Patients for whom a PDE5 inhibitor is indicated in one of the three approved therapeutic indications;
- Intervention: PDE5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil);
- Comparators: Placebo, active treatment or no treatment;
- Outcomes: Development of NAION;
- Study design: Randomized controlled trials (RCT), observational studies, case reports or series of cases and spontaneous reports. All longitudinal studies need to report incidences. Case reports or series of cases could also be described in editorials, letters, commentaries, and abstracts from congresses.

6.3.2. Search methods for identifying studies

MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (https://www.embase.com/), Toxline (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm) and VigiBase (http://www.vigiaccess.org/) were searched on November 19, 2018, since its inception until November 19, 2018. The websites of the manufacturers of drugs were also searched for studies with available results. Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search. The literature search and search strategy for each source of information are listed in Appendix - Table 1. The reference lists of studies selected for inclusion were reviewed for relevant additional studies. In VigiBase, the spontaneous reports were searched by INN and selected through the 1st level of the Medical Dictionary for Regulatory Activities (MedDRA) terminology System Organ Class (SOC) 'Eye disorders' and the 4th level of MedDRA terminology Preferred Term (PT) 'optic ischaemic disorder'.

6.3.3. Study selection

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. Disagreement was resolved by discussion and consensus with a third researcher.

6.3.4. Data collection

The following data were extracted from each study: reference; country; study design; population (number and demographic data); intervention (and comparator); number of individuals with the ophthalmic adverse drug reaction; risk factor; and medical history. Data was extracted from each included study by two researchers independently.

6.3.5. Risk of bias assessment

The risk of bias of the retrieved studies was independently assessed. For observational studies, the checklist proposed by Downs and Black (1998) was used. Studies' methodological quality was assessed as good, fair, or poor when the total score was ≥20, from 15 to 19, and ≤14, respectively. When more than one reference was found for the same study, the methodological quality evaluation was based on the total set of information. The case reports were evaluated according to the questions elaborated on

the Chapter 4 of the CRD's guidance for undertaking reviews in health care (Centre for Reviews and Dissemination, 2009).

6.3.6. Data synthesis and analysis

Data from case and spontaneous reports were analysed using descriptive statistics. A meta-analysis was conducted to analyse data from observational studies. Statistical analyses were conducted with Stata version 13.

The meta-analyses were conducted based on the DerSimonian and Laird random-effects model, which was used to pool odds ratios (ORs) with their 95% confidence intervals (CIs) (DerSimonian and Laird 1986). This model was chosen since the validity of tests of heterogeneity can be limited with a small number of component studies and it is more conservative than a fixed-effect model in the presence of between-studies heterogeneity. The effect size estimates available for the shortest time intervals between PDE5 inhibitors exposure and NAION were used. The analysis was conducted by study design and only included the cases of definitive NAION (excluding those as possible NAION).

Studies must have provided risk estimates [relative risk (RR), odds ratio (OR), or hazard ratio (HR)] for patients treated with the suspected drug compared with a control group; or data allowing calculation of such risk estimates. A minimum of three studies was needed in order to carry out a meta-analysis.

The I^2 statistic test was used to assess for heterogeneity between studies, where an I^2 estimate >50% was considered indicative of substantial heterogeneity. A sensitive analysis was conducted to estimate the global risk including both definitive and possible cases of NAION.

6.4. Results

Details of the included and excluded studies

A total of 293 potentially relevant publications were yielded from literature search (MEDLINE and EMBASE). Additionally, 61 records were identified through other resources (Toxline). Four potential articles were identified through reference lists of reviews. Based on above inclusion criteria, 77 records were selected for full-text further inclusion. A final sample of 35 references covering 4 observational studies, 3 series of cases reports and 28 case reports met the inclusion criteria. The selection of references is shown in Figure 6.1. The references of the included and excluded studies are listed in

the Appendix - Table 2. The results of the VigiBase search for NAION events reported with PDE5 inhibitors were described below.

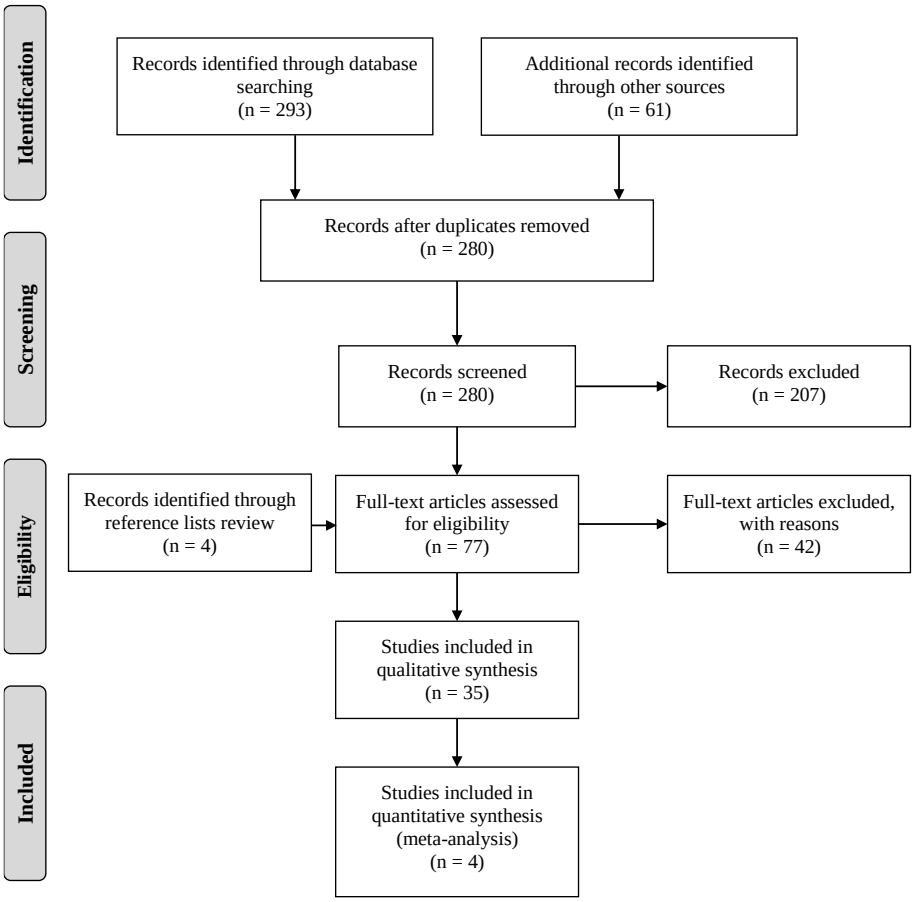

Figure 6.1 *- PRISMA flow chart of search strategy and study selection.*

No RCT were identified. Four observational studies evaluating the association of PDE5 inhibitors with NAION were identified (Table 6.1).[w1-w4] Three studies were retrospective.[w2-w4] One observational study used the case-control design[w3] and two studies were case-crossover[w1,w2]. The four studies included patients from United States (US) in their evaluations. All observational studies evaluated males treated for erectile dysfunction. Their mean age was 64.1 years old. A total of 5,396,708 men were included in the 4 studies. From these, 480,700 were exposed to a PDE5 inhibitor and 4,915,781 men were the comparator. From the total of participants, 114 men were their own control in case-crossover studies. Risk factors to develop NAION and medical history were recorded in three studies and included tobacco use, hypertension, and diabetes. In two studies, the PDE5 inhibitors were specified to vardenafil, tadalafil and sildenafil[w1,w3].

Table 6.1 *- Observational studies summary.*

Reference	Study design	Population			Cases (N)	Control (N)	Interventions	ADR Cases (N)	ADR Control (N)	Measure	95% CI	Risk factor
		Sex	Age (y)	N								
Flahavan et al, 2017[w1]	Prospective case-crossover study	Male	61.5	279	24	24	Tadalafil, vardenafil, sildenafil	11	13	Rate ratio 2.27	0.99–5.20	Tobacco use; alcohol consumption; recreational / illicit drug use
Campbell et al, 2015[w2]	Retrospective case-crossover study	Male	61.1	673	D: 43 D + P: 64	248 374	PDE_5 inhibitor	43 64	- -	Odds ratio 2.15 2.36	1.06–4.35 1.33–4.19	Tobacco use, hypertension, diabetes, concomitant medication
Nathoo et al, 2015[w3]	Retrospective nested case-control study	Male	69.8	1,238,399	1,109	1,237,290	Tadalafil, vardenafil, sildenafil	6.8%	7.4%	Adjusted rate ratio 0.96	0.75–1.23	Diabetes mellitus, hypertension, stroke, myocardial infarction, statins
Margo and French, 2007[w4]	Retrospective cohort study	Male	64	4,157,357	479,489	3,677,868	PDE_5 inhibitor	D: 442 D+P: 670	- -	Risk ratio 1.02 1.10	0.92–1.13 1.01-1.19	No risk-factors described

Table 6.2 *- Characteristics and results of case reports.*

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose[a]	Therapeutic indication
Dehghani et al, 2018[w5]	Iran	1	42	Male	None	OD	Tadalafil	20 mg twice weekly for 8 years	Erectile dysfunction
Vargas-Sánchez et al, 2018[w6]	Spain	1	58	Male	Post-traumatic cervical myelopathy and spastic tetra paresis	OU	Sildenafil	Not clear	Erectile dysfunction
Karimi et al, 2017[w7]	Iran	1	65	Male	None	OU	Sildenafil	20 days before the attack	Erectile dysfunction
Coca et al, 2016[c w8]	US	1	39	Female	Not clear	OU	Sildenafil	20 mg 3 times daily for 3 years	Pulmonary hypertension
Zheng et al, 2016[w9]	Australia	1	56	Female	Arterial hypertension	OS	Sildenafil	10 mg 3 times daily for 7 years	Pulmonary hypertension
Atilgan et al, 2014[w10]	Turkey	1	35	Male	Small optic cup/optic disc ratio	Not know	Sildenafil	Last 3 years	Erectile dysfunction
Gaffuri et al, 2014[c w11]	Italy	1	7 months	Female	Systemic blood pressure was persistently found at upper normal levels for age and Glenn operation	OU	Sildenafil	0.2 mg/kg 3 times daily for 4 weeks	Pulmonary hypertension
Galvez-Ruiz and Arishi, 2013[w12]	Saudi Arabia	10	52	Male	Diabetes mellitus	OD	Sildenafil	100 mg routinely (>2–3 times per month) for 1 year	Not clear
			50	Male	Diabetes mellitus and ischaemic heart disease	OS	Sildenafil	Routinely for 1 year	Not clear
			52	Male	Diabetes mellitus	OS	Sildenafil	He had used Sildenafil regularly for approximately two years (2–3 times per week)	Not clear
			41	Male	Diabetes mellitus	OS	Sildenafil	Regularly (>2–3 times per week)	Erectile dysfunction
			45	Male	Diabetes mellitus	OS	Sildenafil	Regularly (>2–3 times per week) for 6 months	Erectile dysfunction
			38	Male	Diabetes mellitus and dyslipidaemia	OU	Sildenafil	Daily	Not clear
			56	Male	Hypertension and hypercholesterolaemia	OD	Sildenafil	Regularly (>2–3 times per week) for 6– 8 months before	Erectile dysfunction
			51	Male	Diabetes mellitus and dyslipidaemia	OD	Sildenafil	Intake in the days before to the attack	Erectile dysfunction
			52	Male	Diabetes mellitus and hypertension	OD	Sildenafil	Regularly (>2–3 times per week) for over 1 year	Erectile dysfunction
			70	Male	Diabetes mellitus and dyslipidaemia	OD	Sildenafil	Regularly for several months (>2–3 months)	Erectile dysfunction
Kim and Kim, 2012[b w13]	South Korea	1	54	Male	Smoking	OD	Udenafil	100 mg the night before the attack	Erectile dysfunction

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose[a]	Therapeutic indication
Tarantini et al, 2012[w14]	Italy	1	60	Male	Diabetes mellitus	OU	Sildenafil	50 mg in 3 consecutive days before the attack	Erectile dysfunction
El-Domyati et al, 2011[w15]	Egypt	1	48	Male	None	OD	Sildenafil	50 mg 36 hours before the attack	Improve sexual performance
Felekis et al, 2011[w16]	Greece	1	51	Male	Mild hypercholesterolemia and family history (father) with OU attacks of NAION	OD	Sildenafil	Once a week in the previous 6 months	Erectile dysfunction
Ghanem, 2011[w17]	Egypt	1	53	Male	None	OS	Sildenafil	Once a week in the previous 4 months	Erectile dysfunction
Moschos and Margetis, 2011[w18]	Greece	1	55	Male	None	OU	Sildenafil	50 mg, 4–5 times a month in the previous 8 months	Erectile dysfunction
Prat et al, 2011[w19]	Spain	1	63	Female	Aortic valve replacement 8 years ago, atrial fibrillation, arterial hypertension, peripheral vascular disease resulting in amputation of her right toe 2 months before	OS	Sildenafil	50 mg 3 times daily	Pulmonary hypertension
Pepin and Pitha-Rowe, 2008[w20]	US	1	63	Male	Essential hypertension	OS	Sildenafil	25 mg sporadically for the last 5 years; in the night before to the attack the patient took 100 mg	Erectile dysfunction
Su et al, 2008[w21]	Singapore	1	76	Male	Hypertension, hyperlipidaemia, and stroke	OU	Sildenafil	1 capsule once a day or 1 capsule every other day. 36 hours before the attack, patient took 3 capsules (96.66 mg)	Erectile dysfunction
Gedik et al, 2007[w22]	Turkey	1	36	Male	Hypotension and small cup-to-disc ratio	OU	Sildenafil	100 mg for the first time on the night before to the attack	Not clear
Sivaswamy and Vanstavern, 2007[w23]	US	1	6	Female	None	OS	Sildenafil	11 mg three times daily for 15 months	Pulmonary hypertension
Akash et al, 2005[w24]	UK	1	54	Male	None	OS	Sildenafil	200 mg few hours before the attack; 100 mg 2–3 times a week over a few months	Erectile dysfunction
Bollinger and Lee, 2005[w25]	US	1	67	Male	Hypercholesterolemia	OD	Tadalafil	20 mg 2 hours before the attack	Erectile dysfunction
Escaravage et al, 2005[w26]	US	1	59	Male	None	OS	Tadalafil	20 mg 45 hours before the attack	Erectile dysfunction
Peter et al, 2005[w27]	UK	1	59	Male	None	OS	Tadalafil	20 mg 7 days consecutively	Erectile dysfunction
Pomeranz and Bhavsar, 2005[w28]	US	7	59	Male	Hypertension and elevated lipids	OU	Sildenafil	25 mg sporadically, the patient took one dose in the night before the attack	Erectile dysfunction
			58	Male	Hypertension and elevated lipids	OD	Sildenafil	50 mg 1 hour before to the attack	Erectile dysfunction
			67	Male	Hypertension	OD	Sildenafil	Intermittently for 5 weeks, 50 mg in the night before the attack	Erectile dysfunction

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose[a]	Therapeutic indication
			50	Male	Hypertension and hypoplastic optic neuropathy	OS	Sildenafil	50 mg for two consecutive nights, 100 mg in the night before the attack	Erectile dysfunction
			69	Male	Hypertension and retinal detachment on left eye	OS	Sildenafil	50 mg per week in the last 3 months	Erectile dysfunction
			66	Male	Hypertension, diabetes mellitus, elevated lipids and retinal detachment on left eye	OD	Sildenafil	24-36 hours before to the attack	Erectile dysfunction
			60	Male	Hypertension and elevated lipids	OD	Sildenafil	Next morning	Erectile dysfunction
Gruhn and Fledelius, 2004[w29]	Denmark	1	69	Male	Vague right eye visual disturbance (in the day before)	OD	Sildenafil	50 mg 18 hours before the attack	Erectile dysfunction
Sinha et al, 2004[b w30]	UK	1	31	Male	Smoking, disc-at-risk	OD	Sildenafil	The patient doubled the dose to100 mg in the night before the attack	Erectile dysfunction
Boshier et al, 2002[w31]	UK	1	61	Male	Hypertension, elevated lipids, smoking, coronary artery disease and myocardial infarction	OD	Sildenafil	Not clear	Erectile dysfunction
Dheer et al, 2002[w32]	India	1	48	Male	None	OS	Sildenafil	90 minutes before the attack	Erectile dysfunction
Pomeranz et al, 2002[w33]	US	5	52	Male	None	OS	Sildenafil	50 mg 30 minutes before the attack	Erectile dysfunction
			69	Male	Elevated lipids	OD	Sildenafil	45 minutes before the attack	Erectile dysfunction
			42	Male	None	OD	Sildenafil	Next morning	Erectile dysfunction
			62	Male	NAION on left eye	OD	Sildenafil	50 mg per week in the last 15 months	Erectile dysfunction
			59	Male	Diabetes mellitus, smoking and coronary artery disease	OD	Sildenafil	50 mg several hours before the attack	Erectile dysfunction
Cunningham and Smith, 2001[b w34]	US	1	42	Male	Not clear	OD	Sildenafil	Not clear	Erectile dysfunction
Egan and Pomeranz, 2000[α w35]	US	1	52	Male	Smoking	OS	Sildenafil	50 mg 36 hours before the attack	Erectile dysfunction

Three series of case reports comprising 22 case reports along with 28 case reports describing the development of NAION when the patient was exposed to a PDE5 inhibitor were identified. Eighteen case reports were from US. A single publication reported 10 case reports from Saudi Arabia[w12]. A total of 50 patients exposed to a PDE5 inhibitor with NAION were described in the literature. Forty-five (90%) patients were men. The average age of the patients were 52.5 years old (min= 7 months old; max= 76 years old). Twelve (23%) patients had not risk factors to develop NAION. Hypertension (n=15; 30%), diabetes mellitus (n=12; 24%) and dyslipidaemia (n=10; 20%) were the most described risk factors. Thirty-nine (78%) case reports described patients treated for erectile dysfunction, and five (10%) case reports described patients treated for pulmonary arterial hypertension. Sildenafil was the PDE5 inhibitor most reported (n=45; 90%) in case reports, followed by tadalafil (n=4; 8%) and udenafil (n=1; 2%). The characteristics of case reports are described in Table 5.2.

In VigiBase, 6692 spontaneous reports on the SOC 'Eye disorders' were identified (Appendix – Table 3). Of these, 608 belong to the PT 'Optic ischaemic neuropathy'.

Findings of the review

Observational studies

Treatment with PDE5 inhibitors are not associated with an increased risk of NAION (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I2 = 62.6%) (Figure 6.2; Table 6.1).

Two case-crossover studies evaluated the association of intermittent use of PDE5 inhibitors and development of NAION[w1,w2]. Both studies examined the risk of NAION associated with PDE5 inhibitors exposure within 5 half-lives compared with a more prior time period[w1,w2]. The results showed that there is an increased risk of NAION within five half-lives of PDE5 inhibitors use (OR 2.20; 95% CI 1.29, 3.76; p = 0.922; I2 = 0%) (Figure 5.2; Table 6.1)[w1,w2].

Nathoo et al (2015), a retrospective nested case-control study, compared the risk of NAION in individuals exposed to PDE5 inhibitors to controls[w3]. The results were not statistically significant and concluded that there is not any association between PDE5 inhibitors exposure and NAION (OR 0.96 95% CI 0.75, 1.23) (Figure 6.2; Table 6.1)[w3]. An identical result was achieved by Margo and French (2007) (OR 1.02; 95% CI 0.92, 1.13) (Figure 6.2; Table 6.1)[w4].

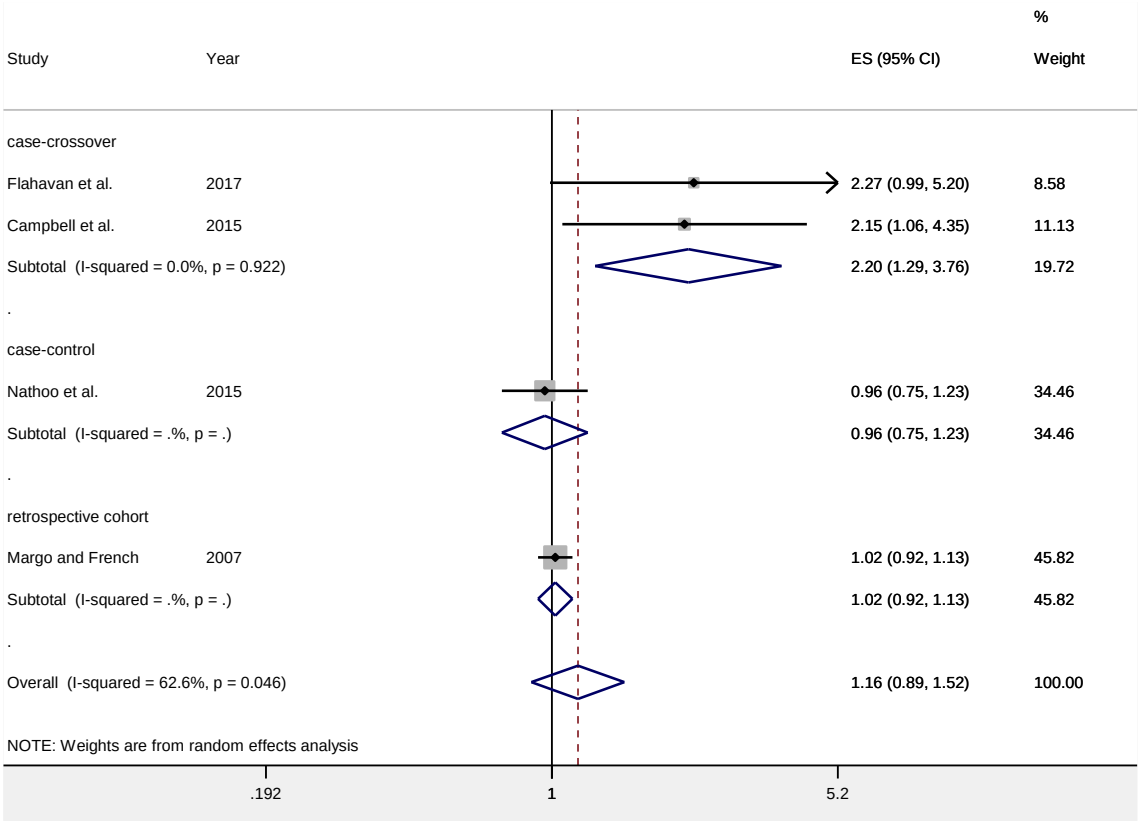

Figure 6.2 *- ORs and 95% CIs for definitive cases of NAION associated with PDE5 inhibitors.*

Sensitive analysis

The risk of NAION did not change when the analysis included both definitive and possible cases of NAION (OR 1.28; 95% CI 0.95, 1.73; p = 0.012; I2 = 72.4%) (Figure 6.3).

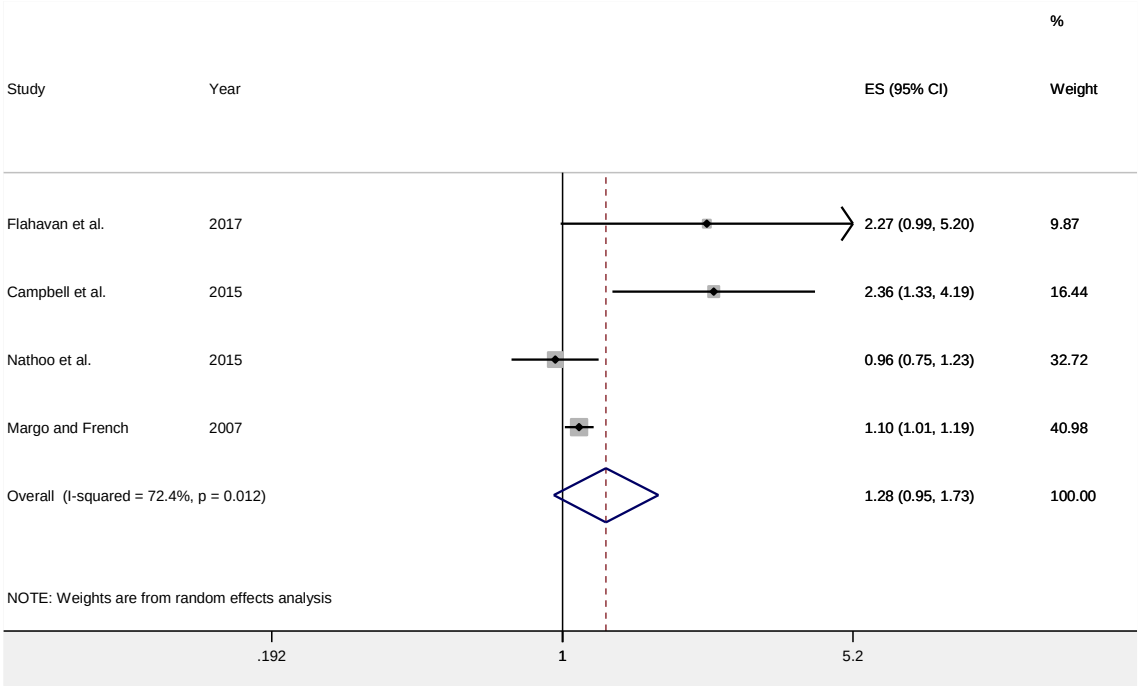

Figure 6.3 *- ORs and 95% CIs for definitive and possible cases of NAION associated with PDE5 inhibitors.*

Case reports

In the total of case reports, the administration of PDE5 inhibitors always precedes an event of NAION. A regular administration (≥ 2 months) of PDE5 inhibitors was observed in 24 (48%) case reports, whereas a recent administration was identified in 22 (44%) case reports. From the cases where a regular administration was reported, four patients admitted to double or triple the dose of PDE5 inhibitors[w20,w21,w24,w28,w30]. In general, the doses administered to each patient were within the approved. The majority of the cases reported the development of NAION in one eye (right eye = 22; 44%; left eye = 17; 34%). The results of case reports are described in Table 5.2.

Spontaneous reports

"Optic ischaemic neuropathy", including NAION, was most reported with sildenafil (n=496), followed by tadalafil (n=79) and vardenafil (n=33).

Risk of bias analysis

The full description of the methodological quality assessment was described in Appendix – Table 4.

The methodological quality was assessed as good for three observational studies and fair for one observational study. The study of Margo and French (2007) failed to report clearly the objective of the study[w4]. In the four observational studies, the patients were not blind to the exposure, neither the people who measure the outcomes. There was not randomization in any of the studies. The sample size was not estimated in any of the studies.

For all case reports, a questionnaire was answered (Appendix – Table 4). The exposure precedes the outcome. In some cases, the exposure was prolonged (≤ 2 months). For one case report[w24], the dose was over those described in the Summary of Product Characteristics. The majority of patients had risk factors to develop NAION. Insufficient or unclear data on discontinuation and rechallenge was observed in the majority of case reports. In general, there are other factors that can explain the development of NAION.

6.5. Discussion

Principal findings

Spontaneous reports were reported describing the development of NAION associated with PDE5 inhibitors exposure. Based on this data, in 2005, three regulatory agencies (European Medicines Agency (EMA), Food and Drug Administration (FDA), and Health Canada) issued a safety alert, warning healthcare professionals and consumers to be aware of visual changes related with sildenafil, tadalafil and vardenafil intake. The sections of the product label "Contraindications", "Warnings and Precautions", "Adverse reactions" and "Patient Counselling Information" were also updated (Penedones et al. 2015).

The association between the use of PDE5 inhibitors and the development of NAION is not yet established (Koksal et al, 2005; Huang and Lie, 2013; Shamloul and Ghanem, 2013; Liu et al, 2018). Several physiopathological hypotheses were studied. PDE5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION (Koksal et al, 2005; Liu et al, 2018). PDE5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation (Koksal et al, 2005; Liu et al, 2018). PDE6 enzyme is present in ocular blood vessels and have an important function in phototransduction. It is thought that PDE5 inhibitors also act on PDE6, being responsible for changes in colour perception (Koksal et al, 2005; Ferguson and Carson, 2013). A pharmacological rationale can explain the development of NAION after PDE5 inhibitors exposure.

In this review, in order to study such association, experimental and observational evidence was searched. We did not find experimental evidence studying this association. Nevertheless, four observational studies, along with 50 case reports and 608 spontaneous reports were identified.

According to the evidence found in this review, the cases occurred mostly in men exposed to sildenafil for the treatment of erectile dysfunction. NAION generally occurs in one eye after a regular PDE5 inhibitor exposure. The majority of the patients had other risk factors to develop NAION, such as hypertension. The results of the meta-analysis suggest that PDE5 inhibitors do not increase the risk of NAION development.

PDE5 inhibitors are the first line treatment for erectile dysfunction (Huang and Lie, 2013). Sildenafil was the first drug approved in this therapeutic indication and has been in the market for five years before tadalafil marketing approval (Frederik et al, 2014). Its

utilization was largely publicized (Frederik et al, 2014). Therefore, the majority of the cases reported the utilization of sildenafil. The main risk factors for developing NAION described in the case reports were anomalies on optic nerve, vascular diseases and/or tobacco use. Some of these vascular diseases and tobacco use are also risk factors for erectile dysfunction (Selvin et al, 2007). Due to the small number of case reports describing the association between the development of NAION and PDE5 inhibitors exposure, and the several confounding factors, the results of this systematic review and meta-analysis should be interpreted cautiously.

Comparison with other research

Twenty-two reviews were identified in the search performed to this systematic review and meta-analysis. Of those, 12 (50%) reviewed specifically the association between PDE5 inhibitors exposure and the risk of NAION. The present systematic review and meta-analysis has included more observational studies and case reports; however, the results of the previous published reviews were similar to those found in this systematic review.

One systematic review also performed a meta-analysis with observational studies (Liu et al, 2018). An association between PDE5 inhibitors use and the development of NAION was also not found (Liu et al, 2018). This review only included observational studies, excluding other type of observational data, such as case and series of case reports and spontaneous reports. This review included the four observational studies identified in our work along with the observational study by French and Margo (2008) which evaluated the association of PDE5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION (French and Margo, 2008). The study concluded that there was no increase in risk of NAION in men taking a PDE5 inhibitor with organic nitrates or an alfa-blocker compared with men taking PDE5 inhibitor alone (French and Margo, 2008). This observational study was not included in the present systematic review since the aim of this study was to determine if the risk of developing NAION is increased with the co-medication of organic nitrate or alfa-blockers.

Other reviews also collect case reports describing the development of NAION after PDE5 inhibitors administration (Danesh-Meyer and Levin, 2007; Thurtell and Tomsak, 2008; Laties, 2009; Azzouni and Abu samra, 2011; Yafi et al, 2018). Limitations on the type of evidence found, on the information described in each case report, and on the small number of case reports suggested that there are lack of evidence to support the

association between PDE5 inhibitors use and the development of NAION (Danesh-Meyer and Levin, 2007; Thurtell and Tomsak, 2008; Laties, 2009; Azzouni and Abu samra, 2011; Yafi et al, 2018). However, some reviews noted that despite the benefit-risk relation was not affected, some precautions should be considered in the prescription of a PDE5 inhibitor, namely to patients with risk factors for the development of NAION, such as vascular diseases and anomalies in the optic nerve (Thurtell and Tomsak, 2008; Yafi et al, 2018).

Another article analysed the spontaneous reporting to the FDA of NAION associated with sildenafil, tadalafil and vardenafil. The first spontaneous report was reported in 1999 to sildenafil, one year after its marketing authorization. Since then, an increase in spontaneous reports were observed after FDA published the safety alert with cases describing such association. A more detailed and completed cases of NAION after PDE5 inhibitors intake was obtained through spontaneous reports systems (Pomeranz, 2016).

Strengths and weaknesses of the research

A key strength of this systematic review and meta-analysis is the combination of the published available evidence on clinical practice, including several types of evidence. Observational studies, case reports, and spontaneous reports are important tools in pharmacovigilance since they are useful to detect rare and/or long-term adverse reactions.

A protocol of this work was not previously published. Some sources of information are not available in our university (such as TRIP and Scopus databases) and they need the payment of a fee to access and perform searches.

No experimental evidence was found studying the association between PDE5 inhibitors use and NAION.

There are few observational studies evaluating this association. These studies have serious risk of bias and some limitations. Observational designs are likely to be subject of bias. There was different designs and methodologies across the included observational studies. Such differences are usually associated with increased heterogeneity (Strom, 2006). Nevertheless, case-crossover was the study design more properly used. In this design, each subject is his own control and is possible to estimate the risk of acute adverse events associated with intermittent drug exposures (Strom, 2006). Therefore, the results should be interpreted cautiously. The checklist used to assess the methodological quality is one of the checklists proposed by the CRD guidance for undertaking reviews in health

care to assess non-randomized controlled trials (Centre for Reviews and Dissemination, 2009). However, this checklist may not provide detailed information on the insufficiencies of the studies. For instance, all the observational studies included are subject to exposure misclassification. PDE5 inhibitors are, generally, used periodically, data on exposure can be subject of exposure misclassification bias and/or recall bias. This bias and the low study power to detect the adverse drug reaction, may have led to the wide confidence intervals in the effect sizes for all studies. Three studies reported the presence of risk factors to develop NAION than PDE5 inhibitors. However, this data was not clear and, consequently, it was not possible to perform a sensitivity analysis to evaluate other confounding factors. Two observational studies used data from clinical databases, and the other two observational studies were conducted in centres in US and Europe: one study applied a questionnaire to patients, and the other study did not specify the data source. Since all studies were conducted in US, including data from clinical national databases or from clinical centres, there is a possibility that the data from some subjects were used in more than one study. In addition, two observational studies were financed by the manufacturers of sildenafil and tadalafil[w1,w2]. The conflict of interests should be taken in consideration when interpreting the results of these studies.

A meta-analysis was conducted as recommended by the CRD guidance for undertaking reviews in health care (Centre for Reviews and Dissemination, 2009). The quantitative synthesis of data from studies allows increasing sample size and statistical power to assess the risk of rare events, in particular (Centre for Reviews and Dissemination, 2009). However, a meta-analysis of observational studies should be designed to explore eventual sources of heterogeneity among the risk estimates rather than produce definitive conclusions on risk association (Berlin, 1995). In this systematic review, one of the observational studies identified an association between PDE5 inhibitors exposure and the development of NAION[w2]. However, the sample size of this study[w2] is low when compared with the case-control and the retrospective cohort studies, both including data from above 1 million individuals[w3,w4]. Moreover, both case-crossover studies[w1,w2] had low weight (8.58% and 11.13%) on the overall risk estimate of the meta-analysis, as opposed to the case-control[w3] and the retrospective cohort[w4] studies (34.46% and 45.82%, respectively), both estimating non-statistically significant risks and, therefore, considerably influencing the results. Thus, the result of the meta-analysis should be interpreted with caution due to the previously described limitations of the included

studies, once the overall risk estimate, although non-statistically significant, is associated with between-studies heterogeneity.

The results of this meta-analysis were stratified according to different study designs. It was not possible to perform further sensitivity analyses to understand the influence of additional risk factors on the risk estimate, since this information was not clearly reported in the four observational studies.

Case reports, as a type of observational evidence, are also subject of bias. The information reported may not be complete and correct, leading to a selective reporting and publication bias. Despite of their less strength compared with observational studies, case reports are a useful tool to detect rare adverse drug reactions and generate safety signals.

The VigiBase database was developed and is maintained by the World Health Organisation (WHO). The VigiBase detain information on spontaneous reported to the WHO Program for International Drug Monitoring from 120-member countries (WHO, 2018). The data provided by this database may not be completed and doesn't represent all worldwide data. The data available on spontaneous reports was scarce, such as the therapeutic indication, patients' past medical history and risk factors, or case's causality assessment. Further, it was not possible to calculate incidences of NAION because no data of the exposed patients to each PDE5 inhibitor was measured.

6.6. Conclusion

According to the findings, the treatment with PDE5 inhibitors was not found to be associated with an increased risk of non-arteritic anterior ischemic optic neuropathy. Yet, further research should be conducted in order to understand the influence of additional risk factors in the development of this condition.

6.7. References

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6.8. Appendix

Appendix - **Table I** - Search strategy

MEDLINE

Search	Equation
#1	"Phosphodiesterase 5 Inhibitors/adverse effects"[Mesh]
#2	"Phosphodiesterase 5 Inhibitors/poisoning"[Mesh]
#3	"Phosphodiesterase 5 Inhibitors/toxicity"[Mesh]
#4	phosphodiesterase type 5 inhibitors
#5	PDE5A inhibitors
#6	PDE5 inhibitors
#7	PDEIs
#8	avanafil
#9	lodenafil
#10	mirodenafil
#11	sildenafil
#12	tadalafil
#13	udenafil
#14	vardenafil
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	"Optic Neuropathy, Ischemic/chemically induced"[Mesh]
#17	non-arteritic anterior ischemic optic neuropathy
#18	non arteritic anterior ischemic optic neuropathy
#19	NAION
#20	#16 OR #17 OR #18 OR #19
#21	#15 AND #20

EMBASE

Search	Equation
#1	'phosphodiesterase V inhibitor'/exp
#2	phosphodiesterase type 5 inhibitors
#3	PDE5A inhibitors
#4	PDE5 inhibitors
#5	PDEIs
#6	avanafil
#7	lodenafil
#8	mirodenafil
#9	sildenafil
#10	tadalafil
#11	udenafil
#12	vardenafil
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	'ischemic optic neuropathy'/exp
#15	non-arteritic anterior ischemic optic neuropathy
#16	non arteritic anterior ischemic optic neuropathy
#17	NAION
#18	#14 OR #15 OR #16 OR #17
#19	#13 AND #18

Toxline

Search	Equation
#1	Phosphodiesterase 5 Inhibitors adverse effects* [mh]
#2	Phosphodiesterase 5 Inhibitors poisoning* [mh]
#3	Phosphodiesterase 5 Inhibitors toxicity* [mh]
#4	phosphodiesterase type 5 inhibitors
#5	PDE5A inhibitors
#6	PDE5 inhibitors
#7	PDEIs
#8	avanafil
#9	lodenafil
#10	mirodenafil
#11	sildenafil
#12	tadalafil
#13	udenafil
#14	vardenafil
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 (Phosphodiesterase 5 Inhibitors adverse effects* [mh] OR Phosphodiesterase 5 Inhibitors poisoning* [mh] OR Phosphodiesterase 5 Inhibitors toxicity* [mh] OR phosphodiesterase type 5 inhibitors OR PDE5A inhibitors OR PDE5 inhibitors OR PDEIs OR avanafil OR lodenafil OR mirodenafil OR sildenafil OR tadalafil OR udenafil OR vardenafil')
#16	Optic Neuropathy Ischemic chemically induced* [mh]
#17	non-arteritic anterior ischemic optic neuropathy
#18	non arteritic anterior ischemic optic neuropathy
#19	NAION
#20	#16 OR #17 OR #18 OR #19 (Optic Neuropathy Ischemic chemically induced* [mh] OR non-arteritic anterior ischemic optic neuropathy OR non arteritic anterior ischemic optic neuropathy OR NAION)
#21	#15 AND #20

VigiAccess

Search	Equation
#1	avanafil
#2	lodenafil
#3	mirodenafil
#5	sildenafil
#5	tadalafil
#6	vardenafil
#7	udenafil

Appendix **- Table 2 -** List of included and excluded studies

Included studies

w1. Flahavan EM, Li H, Gupte-Singh K, et al (2017). Prospective Case-crossover Study Investigating the Possible Association Between Nonarteritic Anterior Ischemic Optic Neuropathy and Phosphodiesterase Type 5 Inhibitor Exposure. Urology; 105:76-83.

w2. Campbell UB, Walker AM, Gaffney M, et al (2015). Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. J Sex Med; 12(1):139-51.

w3. Nathoo NA, Etminan M, Mikelberg FS (2015). Association between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol; 35(1):12-5.

w4. Margo CE, French DD (2007). Ischemic optic neuropathy in male veterans prescribed phosphodiesterase-5 inhibitors. Am J Ophthalmol; 143(3):538-9.

w5. Dehghani A, Alemzadeh-Ansari MH, Masjedi M, et al (2018). Anterior Ischemic Optic Neuropathy in a Patient with Erectile Dysfunction: Tadalafil as an Offending Medication. Journal of Research in Pharmacy Practice; 7(3):164-7.

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w7. Karimi S, Esfandiari H, Nikkhah H, et al (2017). Bilateral simultaneous nonarteritic anterior ischemic optic neuropathy associated with the use of sildenafil: A case report. Razavi International Journal of Medicine; 5(1).

w8. Coca MN, Morgan ML, Gupta P, et al (2016). Bilateral posterior ischemic optic neuropathy associated with the use of Sildenafil for pulmonary hypertension. Can J Ophthalmol; 51(3):e96-9.

w9. Zheng L, Miller KM, Kotlyar E, Garrick R (2016). Sildenafil-induced nonarteritic anterior ischemic optic neuropathy in a patient with pulmonary hypertension. Journal of Neuro-Ophthalmology; 36(3):348-9.

w10. Atilgan ÜC, Şendül S.Y, Güven D (2014). Nonarteritic anterior ischemic optic neuropathy in a young male patient taking sildenafil citrate. Retina-Vitreus; 22:2 (149-152)

w11. Gaffuri M, Cristofaletti A, Mansoldo C, Biban P (2014). Acute onset of bilateral visual loss during sildenafil therapy in a young infant with congenital heart disease. BMJ Case Rep; 2014.

w12. Galvez-Ruiz A, Arishi N (2013). Sequential, non-arteritic anterior ischemic optic neuropathy in patients taking sildenafil: a report of ten cases. Saudi J Ophthalmol; 27(4):241-6.

w13. Kim IG, Kim DY (2012). Anterior ischemic optic neuropathy associated with udenafil. Korean J Ophthalmol; 26(3):235-8.

w14. Tarantini A, Faraoni A, Menchini F, Lanzetta P (2012). Bilateral simultaneous nonarteritic anterior ischemic optic neuropathy after ingestion of sildenafil for erectile dysfunction. Case Rep Med; 2012:747658.

w15. El-Domyati MM, El-Fakahany HM, Morad KE (2009). Nonarteritic ischaemic optic neuropathy (NAION) after 36 h of intake of sildenafil citrate: first Egyptian case. Andrologia; 41(5):319-21.

w16. Felekis T, Asproudis I, Katsanos K, Tsianos E (2011). A case of nonarteritic anterior ischemic optic neuropathy of a male with family history of the disease after receiving sildenafil. Clin Ophthalmol; 5:1443-5.

w17. Ghanem AG (2011). A case of recurrent transient monocular visual loss after receiving sildenafil. Case Rep Ophthalmol Med; 2011:645089.

w18. Moschos MM, Margetis I (2011). Bilateral simultaneous anterior ischemic optic neuropathy associated with sildenafil. Case Rep Ophthalmol; 2(2):262-5.

w19. Prat NM, Sanchez-Dalmau BF, Foroozan R (2011). Not just for men. Surv Ophthalmol; 56(2):173-7.

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Appendix - **Table 3** - VigiBase results

[up to November 19, 2018]

Drug	**ADR (N)**	**Eye disorders (PT)**		
avanafil	581	18	Ocular hyperaemia (4) Vision blurred (4) Visual impairment (3) Blindness (2) Retinal detachment (2) Amaurosis fugax (1) Eye allergy (1) Eye discharge (1)	Eye disorder (1) Eye irritation (1) Eye swelling (1) Foreign body sensation in eyes (1) Ocular discomfort (1) Papilloedema (1) Periorbital oedema (1)
lodenafil	1	0	-	
mirodenafil	287	26	Ocular hyperaemia (22) Vision blurred (4) Eye pain (2) Eyelid oedema (2)	Abnormal sensation in eye (1) Eye discharge (1) Orbital oedema (1) Visual impairment (1)
sildenafil	49559	4467	Visual impairment (991) Vision blurred (701) Optic ischaemic neuropathy (496) Blindness (475) Cyanopsia (353) Ocular hyperaemia (334) Blindness unilateral (240) Visual acuity reduced (236) Chromatopsia (178) Eye pain (167) Cataract (160) Photophobia (148) Eye disorder (142) Eye haemorrhage (100) Diplopia (94) Blindness transient (89) Glaucoma (88) Macular degeneration (79) Photopsia (75) Retinal haemorrhage (69) Retinal detachment (65) Retinal vein occlusion (55) Lacrimation increased (53) Vitreous floaters (49) Papilloedema (46) Asthenopia (43) Retinal disorder (38) Optic nerve disorder (37)	Eye allergy (4) Eye oedema (4) Eyelid disorder (4) Pupil fixed (4) Retinal exudates (4) Retinal vascular thrombosis (4) Xerophthalmia (4) Amblyopia (3) Cataract subcapsular (3) Extraocular muscle disorder (3) Foreign body sensation in eyes (3) Lenticular opacities (3) Open angle glaucoma (3) Pupils unequal (3) Retinal ischaemia (3) Retinal toxicity (3) Ulcerative keratitis (3) Amaurosis (2) Blepharospasm (2) Choroidal infarction (2) Choroidal neovascularisation (2) Dark circles under eyes (2) Deposit eye (2) Diabetic blindness (2) Excessive eye blinking (2) Lacrimation decreased (2) Lens dislocation (2) Lens disorder (2) Miosis (2)

Drug	ADR (N)	Eye disorders (PT)		
			Chorioretinopathy (36) Retinal vein thrombosis (36) Visual brightness (36) Retinal artery occlusion (35) Abnormal sensation in eye (34) Eye swelling (34) Eye irritation (33) Optic atrophy (32) Eyelid oedema (30) Dry eye (29) Vitreous detachment (26) Ocular vascular disorder (22) Retinal tear (21) Macular oedema (20) Optic neuropathy (18) Eye movement disorder (17) Eye pruritus (16) Pupillary reflex impaired (16) Chloropsia (15) Dyschromatopsia (15) Maculopathy (15) Periorbital oedema (15) Retinal vascular disorder (15) Diabetic retinopathy (14) Mydriasis (14) Retinopathy (14) Metamorphopsia (13) Optic disc disorder (13) Conjunctival haemorrhage (12) Eyelid ptosis (12) Vitreous haemorrhage (12) Xanthopsia (12) Eye discharge (10) Retinal vascular occlusion (10) Halo vision (9) Night blindness (9) Ocular discomfort (9) Optic disc haemorrhage (9) Retinal artery thrombosis (9) Amaurosis fugax (8) Eye inflammation (8) Myopia (8) Ocular hypertension (8) Optic nerve infarction (8) Retinal oedema (8)	Neovascular age-related macular degeneration (2) Normal tension glaucoma (2) Ophthalmoplegia (2) Optic disc vascular disorder (2) Optic nerve sheath haemorrhage (2) Periorbital swelling (2) Pinguecula (2) Retinal infarction (2) Scleral discolouration (2) Scleral haemorrhage (2) Scleral hyperaemia (2) Uveitis (2) Age-related macular degeneration (1) Anterior chamber disorder (1) Arcus lipoides (1) Arteriosclerotic retinopathy (1) Astigmatism (1) Blindness cortical (1) Chalazion (1) Chorioretinal disorder (1) Chorioretinal scar (1) Choroidal detachment (1) Choroiditis (1) Conjunctival bleb (1) Conjunctival oedema (1) Conjunctivitis allergic (1) Corneal deposits (1) Corneal oedema (1) Corneal opacity (1) Cystoid macular oedema (1) Diabetic eye disease (1) Dry age-related macular degeneration (1) Erythema of eyelid (1) Eye colour change (1) Eye degenerative disorder (1) Eyelid function disorder (1) Eyelids pruritus (1) Gaze palsy (1) Glare (1) Glaucomatous optic disc atrophy (1) Hypoaesthesia eye (1) Iridocyclitis (1)

Drug	ADR (N)	Eye disorders (PT)		
			Conjunctival hyperaemia (7) Erythropsia (7) Lacrimation disorder (7) Vitreous disorder (7) Accommodation disorder (6) Colour blindness acquired (6) Corneal disorder (6) Exophthalmos (6) Lacrimal disorder (6) Retinal degeneration (6) Retinopathy hypertensive (6) Retinopathy of prematurity (6) Sudden visual loss (6) Altered visual depth perception (5) Angle closure glaucoma (5) Hypermetropia (5) Iritis (5) Macular hole (5) Orbital oedema (5) Pupillary disorder (5) Retinal scar (5) Scintillating scotoma (5) Strabismus (5) Blepharitis (4) Cataract nuclear (4)	Iris adhesions (1) Iris transillumination defect (1) Macular detachment (1) Macular fibrosis (1) Macular ischaemia (1) Macular scar (1) Optic disc drusen (1) Optic nerve cupping (1) Orbital cyst (1) Pigment dispersion syndrome (1) Polypoidal choroidal vasculopathy (1) Retinal aneurysm (1) Retinal artery embolism (1) Retinal artery stenosis (1) Retinal depigmentation (1) Retinal deposits (1) Retinal drusen (1) Retinal dystrophy (1) Retinal neovascularisation (1) Retinal pallor (1) Retinal pigment epitheliopathy (1) Retinal vasculitis (1) Retinoschisis (1) Scleral disorder (1) Scleritis (1) Swelling of eyelid (1)
tadalafil	22728	1652	Vision blurred (438) Visual impairment (273) Ocular hyperaemia (163) Blindness (110) Eye pain (91) Optic ischaemic neuropathy (79) Visual acuity reduced (70) Blindness unilateral (53) Eye disorder (50) Eye swelling (46) Cataract (44) Blindness transient (40) Diplopia (39) Eyelid oedema (39) Eye irritation (38) Cyanopsia (36) Dry eye (34) Lacrimation increased (34) Eye haemorrhage (25)	Presbyopia (3) Retinal exudates (3) Retinal vascular disorder (3) Amaurosis (2) Angle closure glaucoma (2) Blepharitis (2) Blepharospasm (2) Cataract nuclear (2) Chloropsia (2) Choroidal haemorrhage (2) Dyschromatopsia (2) Eye inflammation (2) Eyelid disorder (2) Iris disorder (2) Iritis (2) Macular hole (2) Optic nerve sheath haemorrhage (2) Retinal artery embolism (2) Retinal oedema (2)

Drug	ADR (N)	Eye disorders (PT)		
			Photophobia (25)	Sudden visual loss (2)
			Vitreous floaters (24)	Vitreous haemorrhage (2)
			Retinal detachment (23)	Age-related macular degeneration (1)
			Abnormal sensation in eye (22)	Amblyopia (1)
			Glaucoma (22)	Anterior chamber cell (1)
			Photopsia (19)	Arteriosclerotic retinopathy (1)
			Retinal vein occlusion (19)	Cataract subcapsular (1)
			Eye pruritus (16)	Chalazion (1)
			Macular degeneration (16)	Chorioretinal disorder (1)
			Papilloedema (14)	Choroidal neovascularisation (1)
			Asthenopia (13)	Corneal scar (1)
			Chromatopsia (13)	Dacryostenosis acquired (1)
			Optic neuropathy (13)	Detachment of retinal pigment epithelium (1)
			Conjunctival hyperaemia (11)	Diabetic eye disease (1)
			Ocular discomfort (11)	Erythropsia (1)
			Colour blindness acquired (10)	Extraocular muscle paresis (1)
			Optic nerve disorder (10)	Eye allergy (1)
			Conjunctival haemorrhage (9)	Eye haematoma (1)
			Macular oedema (9)	Eyelid ptosis (1)
			Periorbital oedema (9)	Eyelid vascular disorder (1)
			Retinal haemorrhage (9)	Halo vision (1)
			Vitreous detachment (9)	Hypoaesthesia eye (1)
			Accommodation disorder (8)	Iris neovascularisation (1)
			Retinal tear (8)	Keratitis (1)
			Pupillary reflex impaired (7)	Lacrimation disorder (1)
			Swelling of eyelid (7)	Lenticular opacities (1)
			Chorioretinopathy (6)	Macular detachment (1)
			Exophthalmos (6)	Macular ischaemia (1)
			Eye oedema (6)	Metamorphopsia (1)
			Maculopathy (6)	Ocular ischaemic syndrome (1)
			Optic atrophy (6)	Ocular myasthenia (1)
			Retinal vein thrombosis (6)	Ocular rosacea (1)
			Visual brightness (6)	Optic disc haemorrhage (1)
			Amaurosis fugax (5)	Optic nerve cupping (1)
			Eye discharge (5)	Optic nerve infarction (1)
			Retinal artery occlusion (5)	Periorbital swelling (1)
			Retinopathy (5)	Pinguecula (1)
			Altered visual depth perception (4)	Retinal aneurysm (1)
			Astigmatism (4)	Retinal aneurysm rupture (1)
			Diabetic retinopathy (4)	Retinal deposits (1)
			Eye movement disorder (4)	Retinal drusen (1)
			Foreign body sensation in eyes (4)	Retinal infarction (1)
			Mydriasis (4)	Retinal neovascularisation (1)
				Retinal pigment epitheliopathy (1)
				Scintillating scotoma (1)

Drug	ADR (N)	Eye disorders (PT)		
			Night blindness (4) Ocular hypertension (4) Ocular vascular disorder (4) Orbital oedema (4) Retinal disorder (4) Retinal ischaemia (4) Retinal vascular occlusion (4) Erythema of eyelid (3) Myopia (3) Optic disc disorder (3)	Scleral oedema (1) Strabismus (1) Uveitis (1) Visual acuity reduced transiently (1) Vitreous degeneration (1) Xanthopsia (1) Xerophthalmia (1)
vardenafil	6227	494	Vision blurred (104) Visual impairment (90) Ocular hyperaemia (51) Cyanopsia (39) Blindness unilateral (35) Optic ischaemic neuropathy (33) Visual acuity reduced (31) Blindness (28) Blindness transient (27) Eye pain (24) Photophobia (22) Photopsia (19) Eye disorder (18) Lacrimation increased (18) Chromatopsia (14) Retinal detachment (11) Diplopia (10) Macular degeneration (10) Vitreous floaters (10) Abnormal sensation in eye (9) Cataract (8) Eye irritation (8) Visual brightness (8) Eye haemorrhage (7) Glaucoma (7) Vitreous detachment (7) Retinal vein occlusion (6) Ocular discomfort (5) Retinal artery occlusion (5) Amaurosis fugax (4) Chloropsia (4) Dry eye (4) Retinal haemorrhage (4) Retinal oedema (4) Asthenopia (3) Eye movement disorder (3)	Eye pruritus (2) Eye swelling (2) Foreign body sensation in eyes (2) Glare (2) Halo vision (2) Optic atrophy (2) Optic nerve infarction (2) Optic neuropathy (2) Papilloedema (2) Retinal ischaemia (2) Retinal tear (2) Retinal vein thrombosis (2) Vitreous haemorrhage (2) Altered visual depth perception (1) Amaurosis (1) Amblyopia (1) Arteriosclerotic retinopathy (1) Astigmatism (1) Blepharitis (1) Cataract nuclear (1) Chorioretinal disorder (1) Choroidal detachment (1) Corneal thinning (1) Eye oedema (1) Eyelid ptosis (1) Hypermetropia (1) Intraocular haematoma (1) Iritis (1) Lacrimation disorder (1) Macular oedema (1) Myopia (1) Night blindness (1) Ocular dysmetria (1) Ocular vascular disorder (1) Open angle glaucoma (1) Optic disc disorder (1)

Drug	ADR (N)	Eye disorders (PT)		
			Eyelid oedema (3) Metamorphopsia (3) Mydriasis (3) Optic nerve disorder (3) Pupillary reflex impaired (3) Retinopathy (3) Accommodation disorder (2) Chorioretinopathy (2) Colour blindness acquired (2) Conjunctival haemorrhage (2) Exophthalmos (2) Eye discharge (2)	Optic nerve sheath haemorrhage (1) Periorbital oedema (1) Presbyopia (1) Retinal dystrophy (1) Retinal exudates (1) Retinal infarction (1) Retinal vascular thrombosis (1) Scintillating scotoma (1) Scleral discolouration (1) Uveitis (1) Xanthopsia (1)
udenafil	406	35	Eye pain (11) Ocular hyperaemia (8) Conjunctival hyperaemia (6) Vision blurred (5)	Orbital oedema (2) Visual impairment (2) Eye haemorrhage (1)

ADR, Adverse Drug Reaction; PT, Preferred Term (according to MedDRA terminology)

Appendix - **Table 4** - Methodological Quality assessment of observational studies and case reports.

For observational studies, the checklist proposed by Downs and Black was used. Studies' methodological quality was assessed as good, fair, or poor when the total score was ≥20, from 15 to 19, and ≤14, respectively. When more than one reference was found for the same study, the methodological quality evaluation was based on the total set of information. The case reports were evaluated according to the questions elaborated on the Chapter 4 of the CRD's guidance for undertaking reviews in health care.

[ordered by date]

Dehghani et al, 2018	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure was constant (20 mg twice weekly for 8 years). Response to repeat exposure: The patient took tadalafil for 8 years. There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Vargas-Sánchez et al, 2018	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: The initial visual acuity was not recovered. Dose-response relationship: The information is not clear. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: The information is not clear.

Karimi et al, 2018	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: Three months later the patient presents a pale disk in both eyes. Dose-response relationship: Insufficient data (patient start using sildenafil 20 days before the attack). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient data.

Flahavan et al, 2017	
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1
3. Are the characteristics of the patients included in the study clearly described?	1
4. Are the interventions of interest clearly described?	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2
6. Are the main findings of the study clearly described?	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	1
9. Have the characteristics of patients lost to follow-up been described?	1
10. Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1
External validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1
Internal validity - bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0
16. If any of the results of the study were based on "data dredging", was this made clear?	1
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0
18. Were the statistical tests used to assess the main outcomes appropriate?	1
19. Was compliance with the intervention/s reliable?	1
20. Were the main outcome measures used accurate (valid and reliable)?	1
Internal validity – confounding (selection bias)	

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1
23. Were study subjects randomized to intervention groups?	0
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1
26. Were losses of patients to follow-up taken into account?	1
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0
Total	22

Coca et al, 2016	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to ION, such as pulmonary hypertension. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure was constant (20 mg 3 times daily for 3 years). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Zheng et al, 2016	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to NAION, such as pulmonary hypertension and arterial hypertension. Response to discontinuation: At discharge from hospital, the visual field defect was improved. Dose-response relationship: The exposure was constant (10 mg 3 times daily for 7 years). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Campbell et al, 2015	
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1
3. Are the characteristics of the patients included in the study clearly described?	1
4. Are the interventions of interest clearly described?	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2
6. Are the main findings of the study clearly described?	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	1
9. Have the characteristics of patients lost to follow-up been described?	1
10. Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1
External validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1
Internal validity - bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0
16. If any of the results of the study were based on "data dredging", was this made clear?	1
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0
18. Were the statistical tests used to assess the main outcomes appropriate?	1
19. Was compliance with the intervention/s reliable?	1
20. Were the main outcome measures used accurate (valid and reliable)?	1
Internal validity – confounding (selection bias)	
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1
23. Were study subjects randomized to intervention groups?	0
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1
26. Were losses of patients to follow-up taken into account?	1
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0
Total	22

Nathoo et al, 2015	
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1
3. Are the characteristics of the patients included in the study clearly described?	1
4. Are the interventions of interest clearly described?	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2
6. Are the main findings of the study clearly described?	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	1
9. Have the characteristics of patients lost to follow-up been described?	1
10. Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1
External validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1
Internal validity - bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0
16. If any of the results of the study were based on "data dredging", was this made clear?	1
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0
18. Were the statistical tests used to assess the main outcomes appropriate?	1
19. Was compliance with the intervention/s reliable?	1
20. Were the main outcome measures used accurate (valid and reliable)?	1
Internal validity – confounding (selection bias)	
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1
23. Were study subjects randomized to intervention groups?	0
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1
26. Were losses of patients to follow-up taken into account?	1
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0
Total	22

Atilgan et al, 2014	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to NAION, such as small optic cup/ optic disc ratio. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (dose and frequency unknown; for 3 years). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient data.

Gaffuri et al, 2014	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to ION, such as pulmonary hypertension, increased systemic blood pressure and Glenn operation. Response to discontinuation: At 1-year follow-up, visual defects maintain. Dose-response relationship: The exposure was constant (0.2 mg/kg 3 times daily for 4 weeks). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Galvez-Ruiz and Arishi, 2013	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patients have other risk factors to NAION, such as diabetes mellitus, hypertension, ischemic heart disease, dyslipidaemia and hypercholesterolemia. Response to discontinuation: Insufficient data. Some of the patients did not discontinue the drug. Dose-response relationship: The exposure varied according to the different cases reported. In general, the exposure was regular. Response to repeat exposure: Nine patients reported a second episode of NAION after rechallenge. One patient has no sufficient data. Presence of toxic concentrations: No.

Kim and Kim, 2012	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as smoking. Response to discontinuation: At 1-month follow-up, the patient's BCVA improved, and fundoscopy revealed a slightly pale disc. Dose-response relationship: The patient was exposed once. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Tarantini et al, 2012	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as diabetes mellitus. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The patient was exposed three days consecutively to 50 mg of sildenafil. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

El-Domyati et al, 2011	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (patient start using sildenafil 50 mg, 36 hours before the attack). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Felekis et al, 2011	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to NAION, such as mild hypercholesterolemia and family history (father) of bilateral attacks of NAION. Response to discontinuation: At 1-year follow-up, visual acuity improved to 8/10, and optic disk atrophy without any changes. Dose-response relationship: The exposure was constant (once a week for 6 months). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient information.

Ghanem, 2011	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: At six-month follow-up, visual acuity improved to 8/10, the optic disk swelling has disappeared, and the optic disk was pale. Dose-response relationship: The exposure was constant (once a week for 4 months; dose unknown). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient data.

Moschos and Margetis, 2011	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: At three-weeks follow-up, the visual acuity was 1.0 in both eyes, the visual field in the OS was normal, while in OD the visual field defect remained. At three-month follow-up, the parameters remained equal. Dose-response relationship: The exposure was constant (50 mg 4-5 times per month for 8 months). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Prat et al, 2011	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to NAION, such as pulmonary hypertension, aortic valve replacement, arterial hypertension, atrial fibrillation and peripheral vascular disease. Response to discontinuation: The patient died with concomitant diseases. Dose-response relationship: Insufficient data (drug's start time was unclear; 50 mg 3 times daily). Response to repeat exposure: The patient died with concomitant diseases. Presence of toxic concentrations: No.

Pepin and Pitha-Rowe, 2008	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as essential hypertension. Response to discontinuation: The patient took sildenafil more two times. Dose-response relationship: The exposure was constant for 5 years (25 mg sporadically). In the night before the attack, the patient took 100 mg of sildenafil. Response to repeat exposure: Two more episodes of NAION occurred 24 hours after taking sildenafil. Presence of toxic concentrations: No.

Su et al, 2008	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to ION, such as hypertension, hyperlipidaemia, and stroke. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure was constant for 7 weeks (patient took one capsule once a day or every other day), but 36 hours before the attack, the patient took 3 capsules. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Gedik et al, 2007	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome Lack of alternative causes: The patient has other risk factors to NAION, such as hypotension and small cup-to-disc ratio. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (patient start using sildenafil 100mg in the night before the attack). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Margo and French, 2007	
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	0
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1
3. Are the characteristics of the patients included in the study clearly described?	1
4. Are the interventions of interest clearly described?	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	0
6. Are the main findings of the study clearly described?	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	1
9. Have the characteristics of patients lost to follow-up been described?	1
10. Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1
External validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1
Internal validity - bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0
16. If any of the results of the study were based on "data dredging", was this made clear?	1
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0
18. Were the statistical tests used to assess the main outcomes appropriate?	1
19. Was compliance with the intervention/s reliable?	1
20. Were the main outcome measures used accurate (valid and reliable)?	1
Internal validity – confounding (selection bias)	

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1
23. Were study subjects randomized to intervention groups?	0
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0
26. Were losses of patients to follow-up taken into account?	1
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0
Total	18

Sivaswamy and Vanstavern, 2007	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: The patient discontinued the treatment. Follow-up information was not provided. Dose-response relationship: The exposure was constant (10 mg 3 times daily for 15 months). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Akash et al, 2005	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: The patient discontinued the treatment. Follow-up information was not provided. Dose-response relationship: The exposure was constant for weeks (100 mg 2-3 times weekly). Few hours before the attack, the patient took 200 mg. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Overdose.

Bollinger and Lee, 2005	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as hypercholesterolemia. Response to discontinuation: The patient took the drug five times. Dose-response relationship: The patient experienced symptoms 4 times (in five administrations), 2 hours after taking 20 mg of tadalafil. Response to repeat exposure: The patient experienced symptoms 5 times (in five administrations). Presence of toxic concentrations: No.

Escaravage et al, 2005	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data. The patient took 20 mg 45 hours before the attack. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Peter et al, 2005	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The patient took 20 mg of tadalafil 7 days consecutively. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Pomeranz and Bhavsar, 2005	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patients have other risk factors to NAION, such as hypertension, elevated lipids, diabetes mellitus, retinal detachment and hypoplastic optic neuropathy. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure varied according to the different cases reported. In three cases, the patients took sildenafil for the first time few hours before the attack. In one case, the dose was doubled in the night before the attack. Response to repeat exposure: There's no information about rechallenge after the episode of NAION. Presence of toxic concentrations: No.

Gruhn and Fedelini, 2004	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome Lack of alternative causes: The patient has other risk factor to NAION, such as vague right eye visual disturbance (in the day before). Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (patient start using sildenafil 50 mg 18 hours before the attack). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Sinha et al, 2004	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as vague right eye visual disturbance (in the day before). Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure was not clear. The patient doubled the dose of sildenafil (100 mg) on the night before the attack. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Boshier et al, 2002	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factors to NAION, such as hypertension, elevated lipids, smoking, coronary artery disease and myocardial infarction. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Data on drug's dose and frequency of administration was not available. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations:

Dheer et al, 2002	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has no other risk factors to NAION. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (drug's dose and frequency of administration was unclear). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient data.

Pomeranz et al, 2002	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patients have other risk factors to NAION, such as elevated lipids, diabetes mellitus, NAION on fellow eye, smoking and coronary artery disease. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: The exposure varied according to the different cases reported. In general, the exposure occurred few hours before the attack. In two cases, the drug's dose was unknown. Response to repeat exposure: There's no information about rechallenge after the episode of NAION. Presence of toxic concentrations: Insufficient data.

Cunningham and Smith, 2001	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: It is unknow if the patient has other risk factors to NAION. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Data on drug's dose and frequency of administration was not clear. Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: Insufficient data.

Egan and Pomeranz, 2000	
Risk of bias *(according to chapter 4 of CRD's guidance)*	
Bias	Author's judgement
How was the adverse effect(s) attributed to the intervention?	Temporal relationship: The exposure precedes the outcome. Lack of alternative causes: The patient has other risk factor to NAION, such as smoking. Response to discontinuation: There's no information about discontinuation. Dose-response relationship: Insufficient data (patient start using sildenafil 50 mg 36 hours before the attack). Response to repeat exposure: There's no information about rechallenge after this episode of NAION. Presence of toxic concentrations: No.

Chapter 7 - Risk of non-arteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis

This systematic review and meta-analysis were conducted in accordance with the "Cochrane Handbook for Systematic Reviews of Interventions" (Higgins and Green, 2011).

7.1. Abstract

Background: The phosphodiesterase type 5 (PDE5) inhibitors are approved for the treatment of erectile dysfunction, signs and symptoms of benign prostatic hyperplasia and pulmonary arterial hypertension. The PDE5 inhibitors are well tolerated and most of their adverse reactions are adjacent to their vascular role. The development of nonarteritic anterior ischaemic optic neuropathy (NAION), presented as sudden and with vision loss, has been described to PDE5 inhibitors.

Objectives: To assess the risk of NAION associated with PDE5 inhibitors exposure. A systematic review is carried out based on pre- and post-marketing data.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform, and VigiBase. We did not use any date or language restrictions in the electronic search. We last searched the electronic databases on November 19, 2018. We also searched reference lists of articles.

Selection criteria: We included randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports in which the risk of NAION was assessed with PDE5 inhibitors.

Data collection and analysis: We used standard methodological procedures of The Cochrane Collaboration for study selection, data extraction, and risk of bias assessment. Two review authors independently screened records, abstracted data, and assessed risk of bias of included studies; we resolved discrepancies by discussion and consensus.

Main results: Four observational studies, 3 series of cases, 30 case reports, and 608 spontaneous reports were identified. Three observational studies were retrospective. All observational studies evaluated males treated for erectile dysfunction. Treatment with PDE5 inhibitors are not associated with an increased risk of NAION (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I2 = 62.6%). The methodological quality was assessed as good for three observational studies and fair for one observational study. Among case reports, 12

(23%) patients did not have risk factors to develop NAION. Hypertension (n=16; 31%) was the most described risk factor. Forty (77%) patients were treated for erectile dysfunction. Sildenafil was the PDE5 inhibitor most reported (n=47; 90%). A regular administration of PDE5 inhibitors was observed in 25 (48%) case reports. All case reports were assessed as higher risk of bias.

Authors' conclusions: A plausible biological mechanism can explain the development of NAION associated with PDE5 inhibitors exposure. Several case reports were published in the last years. A close monitoring of the prescription of these drugs may be of great value in clinical practice.

7.2. Introduction

Description of the condition

Ischaemic optic neuropathies are the main cause of acute optic nerve injury in Caucasian patients aged 50 years or older. Depending on the affected nerve, they can be divided into anterior or posterior ischaemic optic neuropathy. Ischaemic optic neuropathies can also be classified, according to aetiology, into arteritic or non-arteritic. In 85% of the cases, the ischaemic optic neuropathy is a nonarteritic anterior ischaemic optic neuropathy (NAION) (Kerr et al, 2009; Luneau et al, 2008; Mathews, 2005; Peeler and Cestari, 2016).

The pathophysiology of NAION remains unknown. The hypothesis most accepted is that NAION results from small vessel disease, such as an occlusion, of the short posterior ciliary arteries, which supplied the optic nerve head, resulting in hypoperfusion and infarction of the anterior optic nerve (Kerr et al, 2009; Luneau et al, 2008; Peeler and Cestari, 2016).

Several factors increase the risk of developing NAION (Kerr et al, 2009; Luneau et al, 2008; Mathews, 2005; Peeler and Cestari, 2016). Anomalies in optic nerve anatomy such as optic nerve head drusen and small cup-to-disc ratio or absence of the cup, were a clear risk factor, with 97% of the patients with anomalies susceptible to develop NAION (Peeler and Cestari, 2016). Increased age and genetic predisposition were also a risk factor (Kerr et al, 2009; Luneau et al, 2008; Mathews, 2005; Peeler and Cestari, 2016). Underlying systemic diseases, such as hypertension, episodic hypotension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnoea, and blood loss, have been evaluated as potential risk factor to develop NAION (Kerr et

al, 2009; Luneau et al, 2008; Mathews, 2005; Peeler and Cestari, 2016). Other evaluated risk factors included prolonged surgical procedures, cataract surgery, and medication, such as amiodarone, interferon-α, nasal decongestants, several vasopressors or vasoconstricting drugs, and PDE5 inhibitors (Kerr et al, 2009; Luneau et al, 2008; Peeler and Cestari, 2016).

The diagnosis of NAION is essentially clinical. No specific diagnostic procedures are mandatory to confirm the diagnosis (Kerr et al, 2009). NAION is, generally, presented as sudden, painless, and associated with any pattern of visual field loss (Kerr et al, 2009; Luneau et al, 2008; Mathews, 2005; Peeler and Cestari, 2016). Patients may present decreased visual acuity, reduced colour vision, visual field defect, or flame-shaped haemorrhages (Kerr et al, 2009). Few patients, almost 10%, reported pain and headache. This can help distinguish NAION from optic neuritis (Kerr et al, 2009; Peeler and Cestari, 2016). In the fellow eye, small or absent physiological cup may also happen (Luneau et al, 2005; Peeler and Cestari, 2016).

Despite NAION high incidence, most patients demonstrated spontaneous improvement weeks after symptoms onset (Kerr et al, 2009; Peeler and Cestari, 2016). There is no treatment for this condition. Several procedures, such as optic nerve decompression surgery, and medicines, as systemic corticosteroids, anticoagulants, antiplatelet drugs, diphenylhydantoin, levodopa, brimonidine, oestrogen, and citicoline, were assessed, but the results were not satisfactory (Kerr et al, 2009; Mathews, 2005).

Description of the intervention

The PDE5 inhibitors are a drug class mainly approved for the treatment of erectile dysfunction. Avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil are examples of selective PDE5 inhibitors. Some of PDE5 inhibitors were also approved for the treatment of signs and symptoms of benign prostatic hyperplasia (tadalafil) and pulmonary arterial hypertension (sildenafil and tadalafil) (Huang and Lie, 2013). Sildenafil was the first PDE5 inhibitor introduced in the market, in 1998. Since then, PDE5 inhibitors are the most prescribed medicines for the treatment of erectile dysfunction (Frederick et al, 2014).

Erectile dysfunction is defined as the inability to achieve or maintain an erection able to satisfactory sexual performance (Shamloul et al, 2013). Psychologic, vascular, neurologic, endocrinal, drug-induced, and lifestyle factors can be related to the erectile dysfunction (Ferguson and Carson, 2013; Frederick et al, 2014; Koksal et al, 2005; Rew

and Heidelbaugh, 2016). Its pathogenesis is well known. After sexual stimulation, nitric oxide (NO) is one of the mediators of the penile smooth muscle relaxation (Ferguson and Carson, 2013). Cholinergic and non-noradrenergic, non-cholinergic fibres and the endothelium, from nerve terminals and endothelial cells in the corpus cavernosum, release NO (Huang and Lie, 2013; Shamloul and Ghanem, 2013). NO activate soluble guanylate cyclase (sGC) producing cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP) (Huang and Lie, 2013; Shamloul and Ghanem, 2013). The increased concentration of cGMP decreases intracellular calcium and lead to smooth muscle relaxation in the corpus cavernosum and increased blood flow to the penis (Ferguson and Carson, 2013; Huang and Lie, 2013; Shamloul and Ghanem, 2013). PDE5 enzyme, found in the smooth muscle of the corpus cavernosum, stimulate hydrolysis of cGMP into GMP, decreasing the concentration of cGMP and NO cascade and, consequently, the erection. PDE5 inhibitors bind to PDE5 enzymes, avoiding cGMP hydrolysis (Huang and Lie, 2013; Shamloul and Ghanem, 2013). Therefore, it potentiates NO cascade and concentration of cGMP in the smooth muscle cells in corpus cavernosum, resulting in muscle relaxation, increased blood flow and prolonged erection (Ferguson and Carson, 2013; Huang and Lie, 2013; Shamloul and Ghanem, 2013).

The same mechanism of action is observed for the treatment of pulmonary arterial hypertension and signs and symptoms of benign prostatic hyperplasia (Barnes et al, 2017; Gacci et al, 2016; Giuliano et al, 2013; Montani et al, 2009). For pulmonary arterial hypertension, PDE5 inhibitors by increasing the concentration of cGMP, decrease intracellular calcium and increase phosphorylation of myosin, leading to decreasing hypertrophy and hyperplasia and increasing vasodilation. Therefore, a reverse pulmonary artery remodelling and a reduced pulmonary vascular tone are achieved (Barnes et al, 2017; Montani et al, 2009). In the treatment of signs and symptoms of benign prostatic hyperplasia, PDE5 inhibitors play a role in the micturition and prostate functioning. PDE5 inhibitors, through NO/cGMP cascade, regulate the smooth muscle tone, present in the human urinary bladder, prostate and urethra, increase the blood supply, which leads to vasodilation, and modulate the afferent nerve activity, responsible for the regulation of micturition reflex (Gacci et al, 2016; Giuliano et al, 2013).

The PDE5 inhibitors are well tolerated and most of their adverse reactions are adjacent to their vascular role (Ferguson and Carson, 2013). Patients taking nitrate compounds should not use PDE5 inhibitors, since it can result in a sudden hypotension

(Ferguson and Carson, 2013). Headache, flushing, nasal congestion, and dyspepsia are the most common adverse reactions associated with PDE5 inhibitors (Ferguson and Carson, 2013; Huang and Lie, 2013; Shamloul and Ghanem, 2013). In addition, tadalafil was also related with myalgia and back pain (Huang and Lie, 2013; Shamloul and Ghanem, 2013). Some serious and rare adverse reactions have been described to PDE5 inhibitors, such as priapism (painful erections) (Shamloul and Ghanem, 2013). Sudden hearing loss was also reported with PDE5 inhibitors. Despite this association was not established, patients were advised to discontinue the PDE5 inhibitors, if they experienced hearing impairment (Huang and Lie, 2013; Shamloul and Ghanem, 2013). Patients using PDE5 inhibitors also experienced visual abnormalities, such as changes in colour perception, blurred vision and NAION. Particular attention should be taken to patients who share risk factors to develop NAION and erectile dysfunction (Huang and Lie, 2013; Shamloul and Ghanem, 2013).

How the intervention might work

The association between the use of PDE5 inhibitors and the development of NAION remains unknown (Huang and Lie, 2013; Kokal et al, 2005; Liu et al, 2018; Shamloul and Ghanem, 2013). Several hypotheses were studied but the results were not significant (Koksal et al, 2005; Liu et al, 2018). PDE5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION (Koksal et al, 2005; Liu et al, 2018). PDE5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation (Koksal et al, 2005; Liu et al, 2018). PDE6 enzyme is present in ocular blood vessels and have an important function in phototransduction. It is thought that PDE5 inhibitors also act on PDE6, being responsible for changes in colour perception (Ferguson and Carson, 2013; Koksal et al, 2005).

Why it is important to do this research

NAION causes a serious visual disability with sudden vision. PDE5 inhibitors are the first line treatment for erectile dysfunction, which is a common medical condition. In addition, PDE5 inhibitors could be used for the treatment of pulmonary arterial hypertension and signs and symptoms of benign prostatic hyperplasia. Several studies assessed the association between PDE5 inhibitors intake and the development of NAION. A systematic review and meta-analysis can combine all available evidence and provide a

more precise result, helpful to healthcare professionals, patients and, also, regulatory authorities.

Objective

To assess the risk of NAION associated with PDE5 inhibitors exposure. A systematic review is carried out based on pre- and post-marketing data.

7.3. Methods

Criteria for considering studies in this review

- Type of studies: Randomized controlled trials (RCT), cohort studies, case-control studies, case reports or series of cases and spontaneous reports. All longitudinal studies need to report incidences. Case reports or series of cases could also be described in editorials, letters, commentaries, and abstracts from congresses;
- Type of participants: Patients for whom a PDE5 inhibitor is indicated in one of the three approved therapeutic indications;
- Type of interventions: PDE5 inhibitors (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil) comparing with placebo, active treatment or no treatment;
- Type of outcome measures: Development of NAION.

Search methods for identification of studies

- Electronic searches: A literature search was performed at Cochrane Controlled Register of Trials (CENTRAL) (https://www.cochranelibrary.com/central), MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed/), and EMBASE (https://www.embase.com/) databases. The databases were searched since its inception until November 19, 2018. Search terms comprised the drug name [including the pharmacotherapeutic class, international non-proprietary name (INN) and brand name] and ophthalmic adverse drug reaction term. A combination of thesaurus terms and free terms were used. No filters were applied to the literature search. The literature search and search strategy for each bibliographic database are listed in Appendix - Table 1;
- Searching other resources: In addition, Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform, and VigiBase were also searched to identify all studies with available results. The reference list of all identified articles was also searched for additional studies.

Data collection

- Selection of studies: Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. Disagreement was resolved by discussion and consensus.
- Data extraction and management: The following data were extracted from each study: reference; country; study design; population (number and demographic data); intervention (and comparator); number of individuals with the ophthalmic adverse drug reaction; risk factor; and medical history. Data was extracted from each included study by two researchers independently.
- Assessment of risk of bias: Included studies were independently assessed for bias according to the methods described in Chapter 13.5 and Chapter 14.6 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

Measures of treatment effect

Data analysis followed the guidelines set out in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). Studies must have provided risk estimates [relative risk (RR), odds ratio (OR), or hazard ratio (HR)] for patients treated with the suspected drug compared with a control group; or data allowing calculation of such risk estimates. A minimum of three studies was needed in order to carry out a meta-analysis.

Data synthesis

Data from case and spontaneous reports were analysed using descriptive statistics. A meta-analysis was conducted to analyse data from observational studies. Statistical analyses were conducted with Stata version 13.

The meta-analyses were conducted based on the DerSimonian and Laird random-effects model, which was used to pool ORs with their 95% confidence intervals (CIs) (DerSimonian and Laird, 1986). This model was chosen since the validity of tests of heterogeneity can be limited with a small number of component studies and it is more conservative than a fixed-effect model in the presence of between-studies heterogeneity. The effect size estimates available for the shortest time intervals between PDE5 inhibitors exposure and NAION were used. The analysis was conducted by study design and only included the cases of definitive NAION (excluding those as possible NAION).

Investigation of heterogeneity

The I^2 statistic test was used to assess for heterogeneity between studies, where an I^2 estimate >50% was considered indicative of substantial heterogeneity.

Sensitivity analysis

A sensitive analysis was conducted to estimate the global risk including both definitive and possible cases of NAION.

7.4. Results

Description of studies

Results of the search

A total of 295 potentially relevant records were yielded from literature search (MEDLINE, EMBASE and CENTRAL). Additionally, 462 records were identified through other resources (Google Scholar, Web of Science, Open Grey, International Clinical Trials Register Platform). Two potential articles were identified through reference lists of reviews. Based on above inclusion criteria, 87 records were selected for full-text further inclusion. A final sample of 37 references covering 4 observational studies, 3 series of cases reports and 30 case reports met the inclusion criteria. The selection of references is shown in Figure 1. The references of the included and excluded studies are listed in the Appendix – Table 2. The results of the VigiBase search for NAION events were described below

Missing data

The authors of two articles were contacted to grant access of their articles. None of the authors replied. No more efforts were made in order to obtain further data.

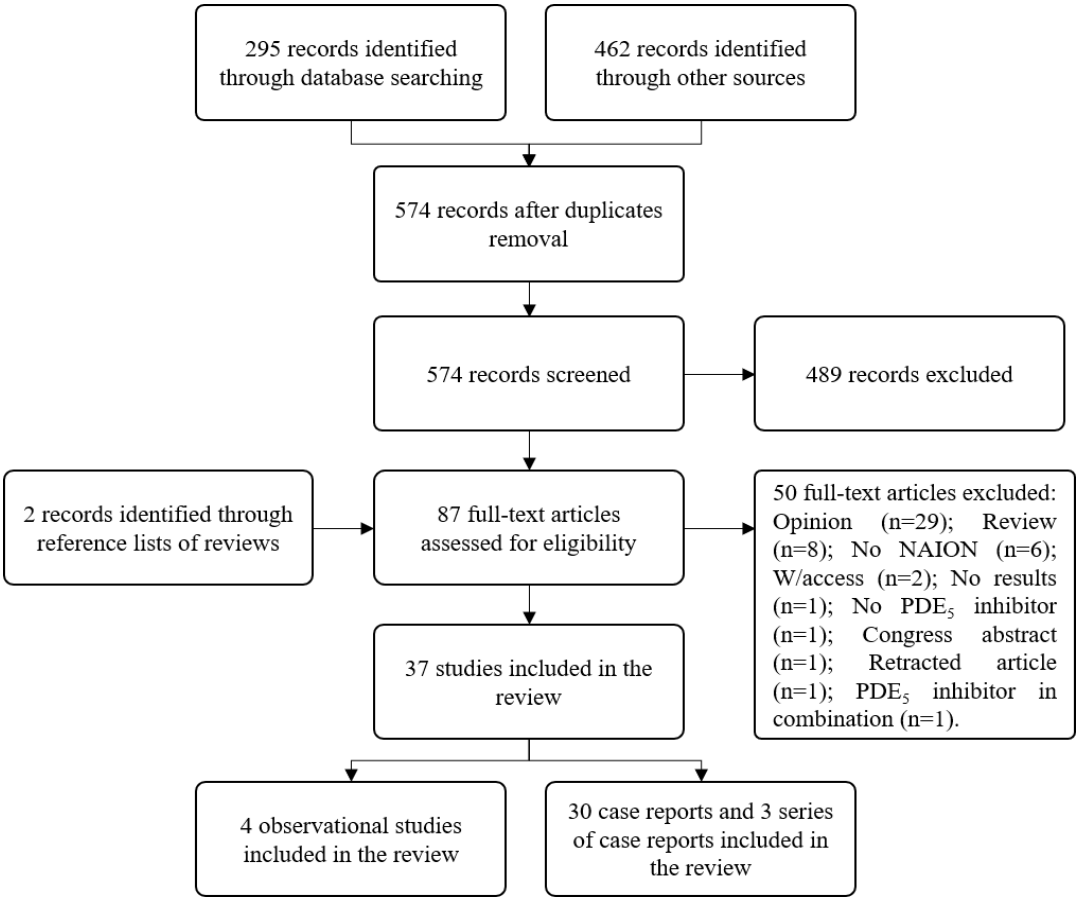

Figure 7.1 – *Study flow diagram.*

Included studies

Studies

No clinical trials were identified. Four observational studies evaluating the association of PDE_5 inhibitors with NAION were identified.[w1-w4] Three studies were retrospective.[w2-w4] One observational study used the case-control design[w3] and two studies were case-crossover[w1,w2]. Two studies included patients from United States (US) in their evaluations[w2,w4].

Three series of case reports comprising 22 case reports along with 30 case reports describing the development of NAION when the patient was exposed to a PDE5 inhibitor were identified. Twenty case reports were from US. A single publication reported 10 case reports from Saudi Arabia.[w13]

In VigiBase, 689 spontaneous reports of "Eye disorders" were identified (Appendix - Table 3).

Participants

All observational studies evaluated males treated for erectile dysfunction. Their mean age was 64.1 years old. A total of 5,396,708 men were included in the 4 studies. 480,700 were exposed to a PDE5 inhibitor and 4,915,781 men were the comparator. From the total of participants, 114 men were their own control in case-crossover studies. Risk factors to develop NAION and medical history were recorded in three studies.

A total of 52 patients exposed to a PDE5 inhibitor with NAION were described in the literature. Forty-seven (90%) patients were men. The average age of the patients were 52.9 years old (min= 7 months; max= 76). Twelve (23%) patients had not risk factors to develop NAION. Hypertension (n=16; 31%), diabetes mellitus (n=12; 23%) and dyslipidaemia (n=11; 21%) were the most described risk factors.

Interventions

All observational studies evaluated the use of PDE5 inhibitors for the treatment of erectile dysfunction. In two studies, the PDE5 inhibitors were specified to vardenafil, tadalafil and sildenafil.[w1,w3]

Forty (77%) case reports described patients treated for erectile dysfunction, and five (10%) case reports described patients treated for pulmonary arterial hypertension. Sildenafil was the PDE5 inhibitor most reported (n=47; 90%) in case reports, followed by tadalafil (n=4; 8%) and udenafil (n=1; 2%).

Type of outcome measures

All studies reported the risk of developing NAION with PDE5 inhibitors exposure. In case reports, the unit of analysis was each case report.

Excluded studies

Fifty articles did not meet the inclusion criteria for this review. The majority of the articles were opinions, including editorials and commentaries. Two articles were not available. One record, registered on ClinicalTrials.gov, did not present results. One congress abstract was excluded since a full and complete article was later published (Campbell et al, 2015)[w2]. One observational study was retracted and was not include in this systematic review. One observational study was excluded since it evaluates the risk of NAION associated with PDE5 inhibitors plus a nitrate with PDE5 inhibitors plus α-blockers. The references of all excluded articles are listed in the Appendix – Table 2.

Risk of bias in included studies

All case reports were assessed for bias (Appendix - Table 4). Despite a plausible biological mechanism can explain the development of NAION associated with PDE5 inhibitors exposure, the results of the observational studies evaluating the risk of such association were not significant. Therefore, none of the case reports have a good predictive value and causality, and cannot be used to demonstrate such association.

The risk of bias of each observational study was also assessed (Table 7.1). The results are as the follows.

Bias due to confounding

One observational study was assessed as having critical risk of bias.[w4] No one of the confounders were controlled. The other three studies were assessed as serious risk of bias.[w1-w3]

Bias in selection of the participants into the study

In three studies, the selection process was strongly related with the intervention and the outcome.[w1,w2,w4] In the other study, the selection process only depended on outcome.[w3]

Bias in classification of interventions

All studies were assessed as low risk of bias. The intervention was well defined at the start of the study.

Bias due to deviations from intended interventions

All studies were assessed as low risk of bias. As observational studies, all deviations in study reflected the usual practice.

Bias due to missing data

All studies were assessed as low risk of bias. Data from the studies were complete.

Bias in measurement of outcomes

All studies were assessed as low risk of bias. The methods of assessment were comparable across intervention groups.

Bias in selection of the reported result

The studies did not provide sufficient information to evaluate this risk of bias.

Table 7.1 - *Risk of bias summary: authors' judgements for each included study.*

	Flahavan et al, 2017[w1]	**Campbell et al, 2015[w2]**	**Nathoo et al, 2015[w3]**	**Margo and French, 2007[w4]**
Bias due to confounding	Serious	Serious	Serious	Critical
Bias in selection of the participants into the study	Critical	Critical	Moderate	Critical
Bias in classification of interventions	Low	Low	Low	Low
Bias due to deviations from intended interventions	Low	Low	Low	Low
Bias due to missing data	Low	Low	Low	Low
Bias in measurement of outcomes	Low	Low	Low	Low
Bias in selection of the reported result	NI	NI	NI	NI

NI: No information.

Effects of interventions

Observational studies

Treatment with PDE5 inhibitors are not associated with an increased risk of NAION (OR 1.16; 95% CI 0.89, 1.52, p = 0.046; I^2 = 62.6%) (Figure 7.2; Table 7.2).

Two case-crossover studies evaluated the association of intermittent use of PDE5 inhibitors and development of NAION.[w1,w2] Both studies examined the risk of NAION associated with PDE_5 inhibitors exposure within 5 half-lives compared with a more prior time period.[w1,w2] The results showed that there is an increased risk of NAION within five half-lives of PDE5 inhibitors use (OR 2.20; 95% CI 1.29, 3.76; p = 0.922; I^2 = 0%) (Figure 7.2; Table 7.2). [w1,w2]

Nathoo et al (2015), a retrospective nested case-control study, compared the risk of NAION in individuals exposed to PDE5 inhibitors to controls.[w3] The results were not statistically significant and concluded that there is not any association between PDE5 inhibitors exposure and NAION (OR 0.96 95% CI 0.75, 1.23) (Figure 7.2; Table 7.2).[w3] An identical result was achieved by Margo and French (2007) (OR 1.02; 95% CI 0.92, 1.13) (Figure 7.2; Table 7.2).[w4]

Table 7.2 – *Observational studies summary.*

Reference	Study design	Population			Cases (N)	Control (N)	Interventions	ADR Cases (N)	ADR Control (N)	Measure	95% CI	Risk factor
		Sex	Age (y)	N								
Flahavan et al, 2017 (NCT01131104)[w1]	Prospective case-crossover study	Male	61.5	279	24	24	Tadalafil, vardenafil, sildenafil	11	13	Rate ratio 2.27	0.99–5.20	Tobacco use; alcohol consumption; recreational / illicit drug use
Campbell et al, 2015[w2]	Retrospective case-crossover study	Male	61.1	673	D: 43 D + P: 64	248 374	PDE_5 inhibitor	43 64	- -	Odds ratio 2.15 2.36	1.06–4.35 1.33–4.19	No risk-factors described
Nathoo et al, 2015[w3]	Retrospective nested case-control study	Male	69.8	1,238,399	1,109	1,237,290	Tadalafil, vardenafil, sildenafil	6.8%	7.4%	Adjusted rate ratio 0.96	0.75–1.23	Diabetes mellitus, hypertension, stroke, myocardial infarction, statins
Margo and French, 2007[w4]	Retrospective cohort study	Male	64	4,157,357	479,489	3,677,868	PDE_5 inhibitor	D: 442 D+P: 670	- -	Risk ratio 1.02 1.10	0.92–1.13 1.01-1.19	No risk-factors described

PDE_5 – phosphodiesterase type 5; D: Definitive cases; D + P: Definitive and Possible cases.

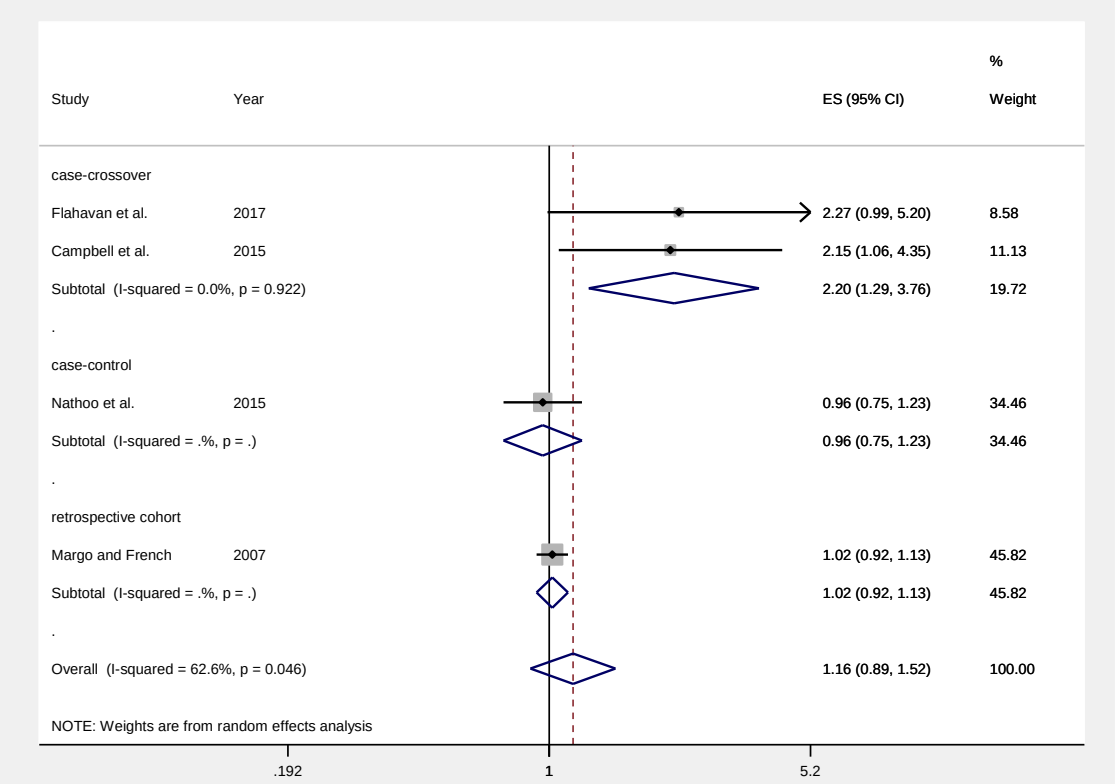

Figure 7.2 - *ORs and 95% CIs for definitive cases of NAION associated with PDE5 inhibitors.*

Sensitive analysis

The risk of NAION changed when the analysis included both definitive and possible cases of NAION (OR 1.28; 95% CI 0.95, 1.73; p = 0.012; I^2 = 72.4%) (Figure 7.3).

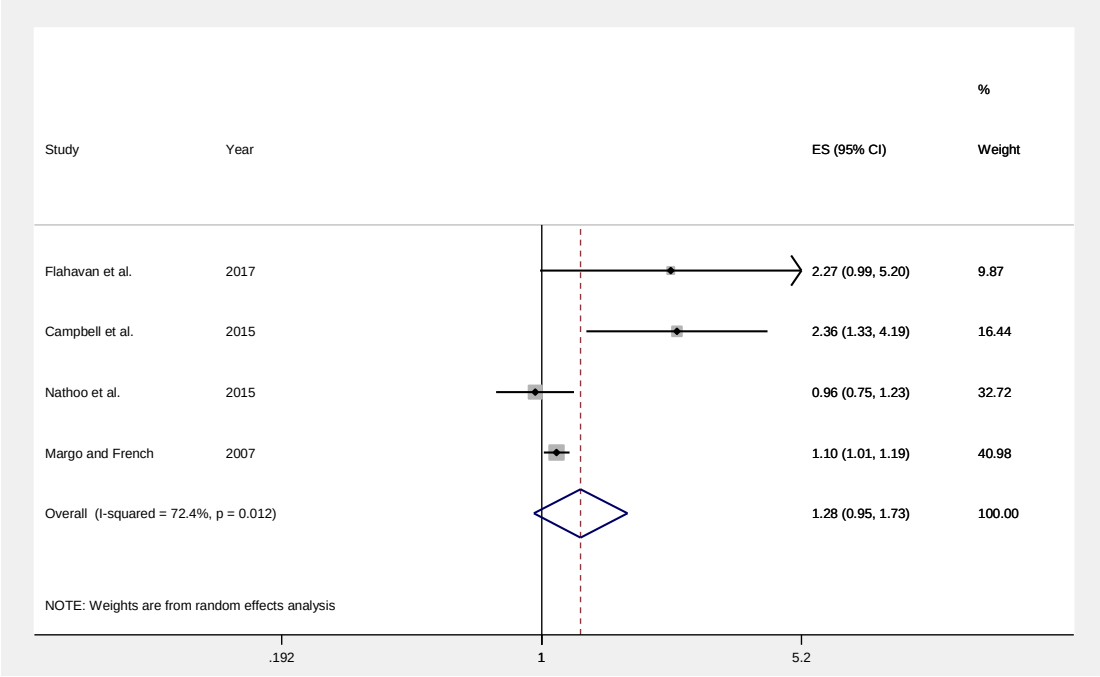

Figure 7.3 - *ORs and 95% CIs for definitive and possible cases of NAION associated with PDE5 inhibitors.*

Table 7.3 – *Characteristics and results of case reports.*

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose*	Therapeutic indication
Dehghani et al, 2018[w5]	Iran	1	42	Male	None	OD	Tadalafil	20 mg twice weekly for 8 years	Erectile dysfunction
Neufeld and Warner, 2018[w6]	US	1	66	Male	Hypertension and hypercholesterolemia	OU	Sildenafil	Last 7 years, in the first attack (OS) the patient doubled the dose of sildenafil; in the second attack (OD) the patient took sildenafil two consecutive days	Erectile dysfunction
Vargas-Sánchez et al, 2018[w7]	Spain	1	58	Male	Post-traumatic cervical myelopathy and spastic tetra paresis	OU	Sildenafil	Not clear	Erectile dysfunction
Karimi et al, 2017[w8]	Iran	1	65	Male	None	OU	Sildenafil	20 days before the attack	Erectile dysfunction
Coca et al, 2016[£ w9]	US	1	39	Female	Not clear	OU	Sildenafil	20 mg 3 times daily for 3 years	Pulmonary hypertension
Zheng et al, 2016[w10]	Australia	1	56	Female	Arterial hypertension	OS	Sildenafil	10 mg 3 times daily for 7 years	Pulmonary hypertension
Atilgan et al, 2014[w11]	Turkey	1	35	Male	Small optic cup/optic disc ratio	Not know	Sildenafil	Last 3 years	Erectile dysfunction
Gaffuri et al, 2014[£ w12]	Italy	1	7 months	Female	Systemic blood pressure was persistently found at upper normal levels for age and Glenn operation	OU	Sildenafil	0.2 mg/kg 3 times daily for 4 weeks	Pulmonary hypertension
Galvez-Ruiz and Arishi, 2013[w13]	Saudi Arabia	10	52	Male	Diabetes mellitus	OD	Sildenafil	100 mg routinely (>2–3 times per month) for 1 year	Not clear
			50	Male	Diabetes mellitus and ischaemic heart disease	OS	Sildenafil	Routinely for 1 year	Not clear
			52	Male	Diabetes mellitus	OS	Sildenafil	He had used Sildenafil regularly for approximately two years (2–3 times per week)	Not clear
			41	Male	Diabetes mellitus	OS	Sildenafil	Regularly (>2–3 times per week)	Erectile dysfunction
			45	Male	Diabetes mellitus	OS	Sildenafil	Regularly (>2–3 times per week) for 6 months	Erectile dysfunction
			38	Male	Diabetes mellitus and dyslipidaemia	OU	Sildenafil	Daily	Not clear
			56	Male	Hypertension and hypercholesterolemia	OD	Sildenafil	Regularly (>2–3 times per week) for 6– 8 months before	Erectile dysfunction
			51	Male	Diabetes mellitus and dyslipidaemia	OD	Sildenafil	Intake in the days before to the attack	Erectile dysfunction
			52	Male	Diabetes mellitus and hypertension	OD	Sildenafil	Regularly (>2–3 times per week) for over 1 year	Erectile dysfunction
			70	Male	Diabetes mellitus and dyslipidaemia	OD	Sildenafil	Regularly for several months (>2–3 months)	Erectile dysfunction

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose*	Therapeutic indication
Kim and Kim, 2012[β w14]	South Korea	1	54	Male	Smoking	OD	Udenafil	100 mg the night before the attack	Erectile dysfunction
Tarantini et al, 2012[w15]	Italy	1	60	Male	Diabetes mellitus	OU	Sildenafil	50 mg in 3 consecutive days before the attack	Erectile dysfunction
El-Domyati et al, 2011[w16]	Egypt	1	48	Male	None	OD	Sildenafil	50 mg 36 hours before the attack	Improve sexual performance
Felekis et al, 2011[w17]	Greece	1	51	Male	Mild hypercholesterolemia and family history (father) with OU attacks of NAION	OD	Sildenafil	Once a week in the previous 6 months	Erectile dysfunction
Ghanem, 2011[w18]	Egypt	1	53	Male	None	OS	Sildenafil	Once a week in the previous 4 months	Erectile dysfunction
Moschos and Margetis, 2011[w19]	Greece	1	55	Male	None	OU	Sildenafil	50 mg, 4–5 times a month in the previous 8 months	Erectile dysfunction
Prat et al, 2011[w20]	Spain	1	63	Female	Aortic valve replacement 8 years ago, atrial fibrillation, arterial hypertension, peripheral vascular disease resulting in amputation of her right toe 2 months before	OS	Sildenafil	50 mg 3 times daily	Pulmonary hypertension
Shen and Gurka, 2011[w21]	US	1	60	Male	Coronary artery disease, ischaemic dilated cardiomyopathy, hyperlipidaemia and recent cardiovascular surgery including CABG	OU	Sildenafil	Unclear	After cardiovascular surgery
Pepin and Pitha-Rowe, 2008[w22]	US	1	63	Male	Essential hypertension	OS	Sildenafil	25 mg sporadically for the last 5 years; in the night before to the attack the patient took 100 mg	Erectile dysfunction
Su et al, 2008[w23]	Singapore	1	76	Male	Hypertension, hyperlipidaemia, and stroke	OU	Sildenafil	1 capsule once a day or 1 capsule every other day. 36 hours before the attack, patient took 3 capsules (96.66 mg)	Erectile dysfunction
Gedik et al, 2007[w24]	Turkey	1	36	Male	Hypotension and small cup-to-disc ratio	OU	Sildenafil	100 mg for the first time on the night before to the attack	Not clear
Sivaswamy and Vanstavern, 2007[w25]	US	1	6	Female	None	OS	Sildenafil	11 mg three times daily for 15 months	Pulmonary hypertension
Akash et al, 2005[w26]	UK	1	54	Male	None	OS	Sildenafil	200 mg few hours before the attack; 100 mg 2–3 times a week over a few months	Erectile dysfunction
Bollinger and Lee, 2005[w27]	US	1	67	Male	Hypercholesterolemia	OD	Tadalafil	20 mg 2 hours before the attack	Erectile dysfunction
Escaravage et al, 2005[w28]	US	1	59	Male	None	OS	Tadalafil	20 mg 45 hours before the attack	Erectile dysfunction
Peter et al, 2005[w29]	UK	1	59	Male	None	OS	Tadalafil	20 mg 7 days consecutively	Erectile dysfunction
Pomeranz and Bhavsar, 2005[w30]	US	7	59	Male	Hypertension and elevated lipids	OU	Sildenafil	25 mg sporadically, the patient took one dose in the night before the attack	Erectile dysfunction

Reference	Country	N	Age (y)	Sex	Risk factors	Eyes affected	Drug	Dose*	Therapeutic indication
			58	Male	Hypertension and elevated lipids	OD	Sildenafil	50 mg 1 hour before to the attack	Erectile dysfunction
			67	Male	Hypertension	OD	Sildenafil	Intermittently for 5 weeks, 50 mg in the night before the attack	Erectile dysfunction
			50	Male	Hypertension and hypoplastic optic neuropathy	OS	Sildenafil	50 mg for two consecutive nights, 100 mg in the night before the attack	Erectile dysfunction
			69	Male	Hypertension and retinal detachment on left eye	OS	Sildenafil	50 mg per week in the last 3 months	Erectile dysfunction
			66	Male	Hypertension, diabetes mellitus, elevated lipids and retinal detachment on left eye	OD	Sildenafil	24-36 hours before to the attack	Erectile dysfunction
			60	Male	Hypertension and elevated lipids	OD	Sildenafil	Next morning	Erectile dysfunction
Gruhn and Fledelius, 2004[w31]	Denmark	1	69	Male	Vague right eye visual disturbance (in the day before)	OD	Sildenafil	50 mg 18 hours before the attack	Erectile dysfunction
Sinha et al, 2004 β [w32]	UK	1	31	Male	Smoking, disc-at-risk	OD	Sildenafil	The patient doubled the dose to100 mg in the night before the attack	Erectile dysfunction
Boshier et al, 2002[w33]	UK	1	61	Male	Hypertension, elevated lipids, smoking, coronary artery disease and myocardial infarction	OD	Sildenafil	Not clear	Erectile dysfunction
Dheer et al, 2002[w34]	India	1	48	Male	None	OS	Sildenafil	90 minutes before the attack	Erectile dysfunction
Pomeranz et al, 2002[w35]	US	5	52	Male	None	OS	Sildenafil	50 mg 30 minutes before the attack	Erectile dysfunction
			69	Male	Elevated lipids	OD	Sildenafil	45 minutes before the attack	Erectile dysfunction
			42	Male	None	OD	Sildenafil	Next morning	Erectile dysfunction
			62	Male	NAION on left eye	OD	Sildenafil	50 mg per week in the last 15 months	Erectile dysfunction
			59	Male	Diabetes mellitus, smoking and coronary artery disease	OD	Sildenafil	50 mg several hours before the attack	Erectile dysfunction
Cunningham and Smith, 2001[β w36]	US	1	42	Male	Not clear	OD	Sildenafil	Not clear	Erectile dysfunction
Egan and Pomeranz, 2000[α w37]	US	1	52	Male	Smoking	OS	Sildenafil	50 mg 36 hours before the attack	Erectile dysfunction

* As described in the case report. α ION (ischaemic optic neuropathy); β AION (anterior ischaemic optic neuropathy); £ PION (posterior optic neuropathy). OD: *Oculus dextrus* (right eye); OS: *Oculus sinister* (left eye); OU: *Oculus uterque* (both eyes).

Case reports

In the total of case reports, the administration of PDE5 inhibitors always precedes an event of NAION. A regular administration (≥ 2 months) of PDE5 inhibitors was observed in 25 (48%) case reports, whereas a recent administration was identified in 22 (42%) case reports. From the cases where a regular administration was reported, five patients admitted to double or triple the dose of PDE5 inhibitors.[w6,w21,w22,w26,w30] In general, the doses administered to each patient were within the approved. Most of the cases reported the development of NAION in one eye (right eye = 22; 42%; left eye = 17; 33%). The characteristics and results of case reports are described in Table 7.3.

Spontaneous reports

"Optic ischaemic neuropathy", including NAION, was most reported with sildenafil (n=496), followed by tadalafil (n=79) and vardenafil (n=33) (Table 7.4).

Table 7.4 – *Spontaneous reports of PDE5 inhibitors registered in VigiBase.*

PDE_5 inhibitor	**ADR (n)**	**SOC *Eye disorders***	**PT *Optic ischaemic neuropathy***
Avanafil	581	18	0
Lodenafil	1	0	0
Mirodenafil	287	26	0
Sildenafil	49,559	4,467	496
Tadalafil	22,728	1,652	79
Vardenafil	6227	494	33
Udenafil	406	35	0

PDE_5 – phosphodiesterase type 5; ADR – adverse drug reaction; SOC – system organ class (1st level of MedDRA terminology); PT – preferred term (4th level of MedDRA terminology).

7.5. Discussion

Summary of main results

Some observational studies studied the association of PDE5 inhibitors exposure and the development of NAION. However, their results were not statistically significant, even when compared the intermittent exposure of PDE5 inhibitors with exposure in a more previous time.

Several case reports described the development of NAION when the patient was taking a PDE5 inhibitor. The cases occurred mostly in men exposed to sildenafil for the treatment of erectile dysfunction. Almost 75% of patients had risk factors to develop NAION. In most cases, the PDE5 inhibitor exposure was regular. NAION generally occurs in one eye.

Overall completeness and applicability of evidence

This review included four observational studies. All of them have serious methodological issues, namely in assuring methods to avoid bias due to confounders, for example, determining the influence of risk factors to develop NAION or co-medications. Another critical issue was the selection of the participants into the study. In the included observational studies, the participants were selected according to the outcome and exposure, this is, the population was chosen according to the specific and pre-established aim leading to a risk of bias in the selection of participants. In the majority of the observational studies, the confounders were not controllable, since the population chosen was representative of the clinical practice.

The case reports also describe the events occurred in clinical practice. In general, the included case reports were well-described. However, some aspects, such as causality, result in higher risk in using this information to corroborate an association between PDE5 inhibitors use and NAION.

The data available on spontaneous reports was scarce, such as the therapeutic indication, patients' past medical history and risk factors, or case's causality assessment. Further, it was not possible to calculate incidences of NAION because no data of the exposed patients to each PDE5 inhibitor was measured.

Despite the methodological problems observed on the available evidence, in 2005, the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) issued a safety alert based on spontaneous reports. The sections of the product label "Contraindications", "Warnings and Precautions", "Adverse reactions" and "Patient Counselling Information" were updated (Penedones et al, 2015).

Potential biases in the review process

A protocol of this review was not previously published. The methodological quality level of the included evidence is low. Observational studies, case reports, and spontaneous reports are important tools in pharmacovigilance since they are useful to detect rare and/or long-term adverse reactions. However, observational designs are more likely to be subject of bias. The study search, study selection and study extraction process were systematic and independent, that should minimize bias.

Some sources of information are not available in our university (such as TRIP and Scopus databases) and they need the payment of a fee to access and perform searches.

The International Clinical Trials Register Platform and VigiBase are databases, developed and maintained by the World Health Organisation (WHO). The International Clinical Trials Register Platform contains trials registries from several worldwide data providers, such as ClinicalTrials.gov and EU Clinical Trials Register (World Health Organisation, 2018a). The VigiBase detain information reported to the WHO Programme for International Drug Monitoring from 120-member countries (World Health Organisation, 2018b). The data provided by these two databases may not be completed and doesn't represent all worldwide data.

There was different designs and methodologies across the included observational studies. Such differences are usually associated with increased heterogeneity (Alves et al, 2014). Therefore, the results should be interpreted cautiously. Nevertheless, case-crossover was the study design more properly used. In this design, each subject is his own control and is possible to estimate the risk of acute adverse events associated with intermittent drug exposures (Strom, 2006).

Agreements and disagreements with other studies or reviews

Twenty-two reviews were identified in the search performed to this review. Of those, 12 (50%) reviewed specifically the association between PDE5 inhibitors exposure and the risk of NAION. Three systematic reviews identified some case reports and observational studies. Despite the present systematic review has included more studies and case reports, the results of the previous published reviews were similar to those found in this systematic review.

One systematic review also performed a meta-analysis with observational studies (Liu et al, 2018). No association between PDE5 inhibitors use and the development of NAION was found (Liu et al, 2018). This review included the observational study by French and Margo (2008) which evaluated the association of PDE5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION (French and Margo, 2008). The study concluded that there was no increase in risk of NAION in men taking a PDE5 inhibitor with organic nitrates or an alfa-blocker compared with men taking PDE5 inhibitor alone (French and Margo, 2008). This observational study was not included in the present systematic review since it does not allow to measure the risk of PDE5 inhibitors alone.

One article analysed the spontaneous reporting to the FDA of NAION associated with sildenafil, tadalafil and vardenafil. The first spontaneous report was reported in 1999 to sildenafil, one year after its marketing authorization. Since then, an increase in

spontaneous reports were observed after FDA published the safety alert with cases describing such association. A more detailed and completed cases of NAION after PDE5 inhibitors intake was obtained through spontaneous reports systems (Pomeranz, 2016).

7.6. Conclusions

Implications for research and practice

There are few studies evaluating the association between PDE5 inhibitors use and NAION. These studies have serious risk of bias and several limitations. New large and comparative studies evaluating such association are needed.

Despite the available evidence was scarce, a plausible mechanism can explain the development of NAION resultant from PDE5 inhibitors use. Additionally, several case reports and spontaneous reports have been published in literature. Some of them resulted in the generation of a safety alert from regulatory authorities, such as EMA and FDA.

A close monitoring of the prescription of PDE5 inhibitors may be of great value in clinical practice. The anticipated identification of patients with risk factors and co-morbidities could result in better outcomes, such as prevention of NAION or suspension of the PDE5 inhibitor.

7.7. References

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7.8. Appendix

Appendix - **Table 1** - Search strategy

CENTRAL

Search	Equation
#1	"Phosphodiesterase 5 Inhibitors/adverse effects"[Mesh]
#2	"Phosphodiesterase 5 Inhibitors/poisoning"[Mesh]
#3	"Phosphodiesterase 5 Inhibitors/toxicity"[Mesh]
#4	phosphodiesterase type 5 inhibitors
#5	PDE5A inhibitors
#6	PDE5 inhibitors
#7	PDEIs
#8	avanafil
#9	lodenafil
#10	mirodenafil
#11	sildenafil
#12	tadalafil
#13	udenafil
#14	vardenafil
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	"Optic Neuropathy, Ischemic/chemically induced"[Mesh]
#17	non-arteritic anterior ischemic optic neuropathy
#18	non arteritic anterior ischemic optic neuropathy
#19	NAION
#20	#16 OR #17 OR #18 OR #19
#21	#15 AND #20

MEDLINE

Search	Equation
#1	"Phosphodiesterase 5 Inhibitors/adverse effects"[Mesh]
#2	"Phosphodiesterase 5 Inhibitors/poisoning"[Mesh]
#3	"Phosphodiesterase 5 Inhibitors/toxicity"[Mesh]
#4	phosphodiesterase type 5 inhibitors
#5	PDE5A inhibitors
#6	PDE5 inhibitors
#7	PDEIs
#8	avanafil
#9	lodenafil
#10	mirodenafil
#11	sildenafil
#12	tadalafil
#13	udenafil
#14	vardenafil
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	"Optic Neuropathy, Ischemic/chemically induced"[Mesh]
#17	non-arteritic anterior ischemic optic neuropathy
#18	non arteritic anterior ischemic optic neuropathy
#19	NAION
#20	#16 OR #17 OR #18 OR #19
#21	#15 AND #20

EMBASE

Search	Equation
#1	'phosphodiesterase V inhibitor'/exp
#2	phosphodiesterase type 5 inhibitors
#3	PDE5A inhibitors
#4	PDE5 inhibitors
#5	PDEIs
#6	avanafil
#7	lodenafil
#8	mirodenafil
#9	sildenafil
#10	tadalafil
#11	udenafil
#12	vardenafil
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	'ischemic optic neuropathy'/exp
#15	non-arteritic anterior ischemic optic neuropathy
#16	non arteritic anterior ischemic optic neuropathy
#17	NAION
#18	#14 OR #15 OR #16 OR #17
#19	#13 AND #18

Web of Science

Search	***Equation***
#1	TS=(Phosphodiesterase 5 Inhibitors)
#2	TS=(phosphodiesterase type 5 inhibitors)
#3	TS=(PDE5A inhibitors)
#4	TS=(PDE5 inhibitors)
#5	TS=(PDEIs)
#6	TS=(avanafil)
#7	TS=(lodenafil)
#8	TS=(mirodenafil)
#9	TS=(sildenafil)
#10	TS=(tadalafil)
#11	TS=(udenafil)
#12	TS=(vardenafil)
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	TS=(ischemic optic neuropathy)
#15	TS=(non-arteritic anterior ischemic optic neuropathy)
#16	TS=(non arteritic anterior ischemic optic neuropathy)
#17	TS=(NAION)
#18	#14 OR #15 OR #16 OR #17
#19	#13 AND #18

Google Scholar

Search	Equation
#1	"Phosphodiesterase 5 Inhibitors" "ischemic optic neuropathy"

Open Grey

Search	Equation
#1	Phosphodiesterase 5 Inhibitors
#2	Phosphodiesterase 5 Inhibitor
#3	phosphodiesterase type 5 inhibitors
#5	avanafil
#5	lodenafil
#6	mirodenafil
#7	sildenafil
#8	tadalafil
#9	udenafil
#10	vardenafil
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	non-arteritic anterior ischemic optic neuropathy
#13	non arteritic anterior ischemic optic neuropathy
#14	NAION
#15	#12 OR #13 OR #14
#16	#11 AND #15

International Clinical Trials Register Platform:

non-arteritic anterior ischemic optic neuropathy = Condition AND avanafil OR lodenafil OR mirodenafil OR sildenafil OR tadalafil OR udenafil OR vardenafil = Intervention

VigiAccess

Search	Equation
#1	avanafil
#2	lodenafil
#3	mirodenafil
#5	sildenafil
#5	tadalafil
#6	vardenafil
#7	udenafil

Appendix - **Table 2** – List of included and excluded studies

Included studies

w1. Flahavan EM, Li H, Gupte-Singh K, et al (2017). Prospective Case-crossover Study Investigating the Possible Association Between Nonarteritic Anterior Ischemic Optic Neuropathy and Phosphodiesterase Type 5 Inhibitor Exposure. Urology; 105:76-83.

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w3. Nathoo NA, Etminan M, Mikelberg FS (2015). Association between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol; 35(1):12-5.

w4. Margo CE, French DD (2007). Ischemic optic neuropathy in male veterans prescribed phosphodiesterase-5 inhibitors. Am J Ophthalmol; 143(3):538-9.

w5. Dehghani A, Alemzadeh-Ansari MH, Masjedi M, et al (2018). Anterior Ischemic Optic Neuropathy in a Patient with Erectile Dysfunction: Tadalafil as an Offending Medication. Journal of Research in Pharmacy Practice; 7(3):164-7.

w6. Neufeld A, Warner J (2018). Case of Bilateral Sequential Nonarteritic Ischemic Optic Neuropathy After Rechallenge With Sildenafil. Journal of Neuro-Ophthalmology; 38(1):123-4.

w7. Vargas-Sánchez J, Góngora-Rodríguez R, Soriano-Gil R, et al (2018). Bilateral and simultaneous nonarteritic anterior ischemic optic neuropathy related to sildenafil intake. Ophthalmic Research; 60(2):122.

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w10. Zheng L, Miller KM, Kotlyar E, Garrick R (2016). Sildenafil-induced nonarteritic anterior ischemic optic neuropathy in a patient with pulmonary hypertension. Journal of Neuro-Ophthalmology; 36(3):348-9.

w11. Atilgan ÜC, Şendül S.Y, Güven D (2014). Nonarteritic anterior ischemic optic neuropathy in a young male patient taking sildenafil citrate. Retina-Vitreus; 22:2 (149-152)

w12. Gaffuri M, Cristofaletti A, Mansoldo C, Biban P (2014). Acute onset of bilateral visual loss during sildenafil therapy in a young infant with congenital heart disease. BMJ Case Rep; 2014.

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w18. Ghanem AG (2011). A case of recurrent transient monocular visual loss after receiving sildenafil. Case Rep Ophthalmol Med; 645089.

w19. Moschos MM, Margetis I (2011). Bilateral simultaneous anterior ischemic optic neuropathy associated with sildenafil. Case Rep Ophthalmol; 2(2):262-5.

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W/Access

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Appendix - **Table 3** - VigiBase results

[up to November 19, 2018]

Drug	**ADR (N)**	**Eye disorders (PT)**		
avanafil	581	18	Ocular hyperaemia (4) Vision blurred (4) Visual impairment (3) Blindness (2) Retinal detachment (2) Amaurosis fugax (1) Eye allergy (1) Eye discharge (1)	Eye disorder (1) Eye irritation (1) Eye swelling (1) Foreign body sensation in eyes (1) Ocular discomfort (1) Papilloedema (1) Periorbital oedema (1)
lodenafil	1	0	-	
mirodenafil	287	26	Ocular hyperaemia (22) Vision blurred (4) Eye pain (2) Eyelid oedema (2)	Abnormal sensation in eye (1) Eye discharge (1) Orbital oedema (1) Visual impairment (1)
sildenafil	49559	4467	Visual impairment (991) Vision blurred (701) Optic ischaemic neuropathy (496) Blindness (475) Cyanopsia (353) Ocular hyperaemia (334) Blindness unilateral (240) Visual acuity reduced (236) Chromatopsia (178) Eye pain (167) Cataract (160)	Eye allergy (4) Eye oedema (4) Eyelid disorder (4) Pupil fixed (4) Retinal exudates (4) Retinal vascular thrombosis (4) Xerophthalmia (4) Amblyopia (3) Cataract subcapsular (3) Extraocular muscle disorder (3) Foreign body sensation in eyes (3)

Drug	ADR (N)	Eye disorders (PT)		
			Photophobia (148)	Lenticular opacities (3)
			Eye disorder (142)	Open angle glaucoma (3)
			Eye haemorrhage (100)	Pupils unequal (3)
			Diplopia (94)	Retinal ischaemia (3)
			Blindness transient (89)	Retinal toxicity (3)
			Glaucoma (88)	Ulcerative keratitis (3)
			Macular degeneration (79)	Amaurosis (2)
			Photopsia (75)	Blepharospasm (2)
			Retinal haemorrhage (69)	Choroidal infarction (2)
			Retinal detachment (65)	Choroidal neovascularisation (2)
			Retinal vein occlusion (55)	Dark circles under eyes (2)
			Lacrimation increased (53)	Deposit eye (2)
			Vitreous floaters (49)	Diabetic blindness (2)
			Papilloedema (46)	Excessive eye blinking (2)
			Asthenopia (43)	Lacrimation decreased (2)
			Retinal disorder (38)	Lens dislocation (2)
			Optic nerve disorder (37)	Lens disorder (2)
			Chorioretinopathy (36)	Miosis (2)
			Retinal vein thrombosis (36)	Neovascular age-related macular degeneration (2)
			Visual brightness (36)	Normal tension glaucoma (2)
			Retinal artery occlusion (35)	Ophthalmoplegia (2)
			Abnormal sensation in eye (34)	Optic disc vascular disorder (2)
			Eye swelling (34)	Optic nerve sheath haemorrhage (2)
			Eye irritation (33)	Periorbital swelling (2)
			Optic atrophy (32)	Pinguecula (2)
			Eyelid oedema (30)	Retinal infarction (2)
			Dry eye (29)	Scleral discolouration (2)
			Vitreous detachment (26)	Scleral haemorrhage (2)
			Ocular vascular disorder (22)	Scleral hyperaemia (2)
			Retinal tear (21)	Uveitis (2)
			Macular oedema (20)	Age-related macular degeneration (1)
			Optic neuropathy (18)	Anterior chamber disorder (1)
			Eye movement disorder (17)	Arcus lipoides (1)
			Eye pruritus (16)	Arteriosclerotic retinopathy (1)
			Pupillary reflex impaired (16)	Astigmatism (1)
			Chloropsia (15)	Blindness cortical (1)
			Dyschromatopsia (15)	Chalazion (1)
			Maculopathy (15)	Chorioretinal disorder (1)
			Periorbital oedema (15)	Chorioretinal scar (1)
			Retinal vascular disorder (15)	Choroidal detachment (1)
			Diabetic retinopathy (14)	Choroiditis (1)
			Mydriasis (14)	Conjunctival bleb (1)
			Retinopathy (14)	Conjunctival oedema (1)
			Metamorphopsia (13)	Conjunctivitis allergic (1)
			Optic disc disorder (13)	

Drug	ADR (N)	Eye disorders (PT)		
			Conjunctival haemorrhage (12) Eyelid ptosis (12) Vitreous haemorrhage (12) Xanthopsia (12) Eye discharge (10) Retinal vascular occlusion (10) Halo vision (9) Night blindness (9) Ocular discomfort (9) Optic disc haemorrhage (9) Retinal artery thrombosis (9) Amaurosis fugax (8) Eye inflammation (8) Myopia (8) Ocular hypertension (8) Optic nerve infarction (8) Retinal oedema (8) Conjunctival hyperaemia (7) Erythropsia (7) Lacrimation disorder (7) Vitreous disorder (7) Accommodation disorder (6) Colour blindness acquired (6) Corneal disorder (6) Exophthalmos (6) Lacrimal disorder (6) Retinal degeneration (6) Retinopathy hypertensive (6) Retinopathy of prematurity (6) Sudden visual loss (6) Altered visual depth perception (5) Angle closure glaucoma (5) Hypermetropia (5) Iritis (5) Macular hole (5) Orbital oedema (5) Pupillary disorder (5) Retinal scar (5) Scintillating scotoma (5) Strabismus (5) Blepharitis (4) Cataract nuclear (4)	Corneal deposits (1) Corneal oedema (1) Corneal opacity (1) Cystoid macular oedema (1) Diabetic eye disease (1) Dry age-related macular degeneration (1) Erythema of eyelid (1) Eye colour change (1) Eye degenerative disorder (1) Eyelid function disorder (1) Eyelids pruritus (1) Gaze palsy (1) Glare (1) Glaucomatous optic disc atrophy (1) Hypoaesthesia eye (1) Iridocyclitis (1) Iris adhesions (1) Iris transillumination defect (1) Macular detachment (1) Macular fibrosis (1) Macular ischaemia (1) Macular scar (1) Optic disc drusen (1) Optic nerve cupping (1) Orbital cyst (1) Pigment dispersion syndrome (1) Polypoidal choroidal vasculopathy (1) Retinal aneurysm (1) Retinal artery embolism (1) Retinal artery stenosis (1) Retinal depigmentation (1) Retinal deposits (1) Retinal drusen (1) Retinal dystrophy (1) Retinal neovascularisation (1) Retinal pallor (1) Retinal pigment epitheliopathy (1) Retinal vasculitis (1) Retinoschisis (1) Scleral disorder (1) Scleritis (1) Swelling of eyelid (1)
tadalafil	22728	1652	Vision blurred (438) Visual impairment (273)	Presbyopia (3) Retinal exudates (3)

Drug	ADR (N)	Eye disorders (PT)		
			Ocular hyperaemia (163)	Retinal vascular disorder (3)
			Blindness (110)	Amaurosis (2)
			Eye pain (91)	Angle closure glaucoma (2)
			Optic ischaemic neuropathy (79)	Blepharitis (2)
			Visual acuity reduced (70)	Blepharospasm (2)
			Blindness unilateral (53)	Cataract nuclear (2)
			Eye disorder (50)	Chloropsia (2)
			Eye swelling (46)	Choroidal haemorrhage (2)
			Cataract (44)	Dyschromatopsia (2)
			Blindness transient (40)	Eye inflammation (2)
			Diplopia (39)	Eyelid disorder (2)
			Eyelid oedema (39)	Iris disorder (2)
			Eye irritation (38)	Iritis (2)
			Cyanopsia (36)	Macular hole (2)
			Dry eye (34)	Optic nerve sheath haemorrhage (2)
			Lacrimation increased (34)	Retinal artery embolism (2)
			Eye haemorrhage (25)	Retinal oedema (2)
			Photophobia (25)	Sudden visual loss (2)
			Vitreous floaters (24)	Vitreous haemorrhage (2)
			Retinal detachment (23)	Age-related macular degeneration (1)
			Abnormal sensation in eye (22)	Amblyopia (1)
			Glaucoma (22)	Anterior chamber cell (1)
			Photopsia (19)	Arteriosclerotic retinopathy (1)
			Retinal vein occlusion (19)	Cataract subcapsular (1)
			Eye pruritus (16)	Chalazion (1)
			Macular degeneration (16)	Chorioretinal disorder (1)
			Papilloedema (14)	Choroidal neovascularisation (1)
			Asthenopia (13)	Corneal scar (1)
			Chromatopsia (13)	Dacryostenosis acquired (1)
			Optic neuropathy (13)	Detachment of retinal pigment epithelium (1)
			Conjunctival hyperaemia (11)	Diabetic eye disease (1)
			Ocular discomfort (11)	Erythropsia (1)
			Colour blindness acquired (10)	Extraocular muscle paresis (1)
			Optic nerve disorder (10)	Eye allergy (1)
			Conjunctival haemorrhage (9)	Eye haematoma (1)
			Macular oedema (9)	Eyelid ptosis (1)
			Periorbital oedema (9)	Eyelid vascular disorder (1)
			Retinal haemorrhage (9)	Halo vision (1)
			Vitreous detachment (9)	Hypoaesthesia eye (1)
			Accommodation disorder (8)	Iris neovascularisation (1)
			Retinal tear (8)	Keratitis (1)
			Pupillary reflex impaired (7)	Lacrimation disorder (1)
			Swelling of eyelid (7)	Lenticular opacities (1)
			Chorioretinopathy (6)	Macular detachment (1)

Drug	ADR (N)	Eye disorders (PT)		
			Exophthalmos (6) Eye oedema (6) Maculopathy (6) Optic atrophy (6) Retinal vein thrombosis (6) Visual brightness (6) Amaurosis fugax (5) Eye discharge (5) Retinal artery occlusion (5) Retinopathy (5) Altered visual depth perception (4) Astigmatism (4) Diabetic retinopathy (4) Eye movement disorder (4) Foreign body sensation in eyes (4) Mydriasis (4) Night blindness (4) Ocular hypertension (4) Ocular vascular disorder (4) Orbital oedema (4) Retinal disorder (4) Retinal ischaemia (4) Retinal vascular occlusion (4) Erythema of eyelid (3) Myopia (3) Optic disc disorder (3)	Macular ischaemia (1) Metamorphopsia (1) Ocular ischaemic syndrome (1) Ocular myasthenia (1) Ocular rosacea (1) Optic disc haemorrhage (1) Optic nerve cupping (1) Optic nerve infarction (1) Periorbital swelling (1) Pinguecula (1) Retinal aneurysm (1) Retinal aneurysm rupture (1) Retinal deposits (1) Retinal drusen (1) Retinal infarction (1) Retinal neovascularisation (1) Retinal pigment epitheliopathy (1) Scintillating scotoma (1) Scleral oedema (1) Strabismus (1) Uveitis (1) Visual acuity reduced transiently (1) Vitreous degeneration (1) Xanthopsia (1) Xerophthalmia (1)
vardenafil	6227	494	Vision blurred (104) Visual impairment (90) Ocular hyperaemia (51) Cyanopsia (39) Blindness unilateral (35) Optic ischaemic neuropathy (33) Visual acuity reduced (31) Blindness (28) Blindness transient (27) Eye pain (24) Photophobia (22) Photopsia (19) Eye disorder (18) Lacrimation increased (18) Chromatopsia (14) Retinal detachment (11) Diplopia (10) Macular degeneration (10)	Eye pruritus (2) Eye swelling (2) Foreign body sensation in eyes (2) Glare (2) Halo vision (2) Optic atrophy (2) Optic nerve infarction (2) Optic neuropathy (2) Papilloedema (2) Retinal ischaemia (2) Retinal tear (2) Retinal vein thrombosis (2) Vitreous haemorrhage (2) Altered visual depth perception (1) Amaurosis (1) Amblyopia (1) Arteriosclerotic retinopathy (1) Astigmatism (1)

Drug	ADR (N)	Eye disorders (PT)		
			Vitreous floaters (10) Abnormal sensation in eye (9) Cataract (8) Eye irritation (8) Visual brightness (8) Eye haemorrhage (7) Glaucoma (7) Vitreous detachment (7) Retinal vein occlusion (6) Ocular discomfort (5) Retinal artery occlusion (5) Amaurosis fugax (4) Chloropsia (4) Dry eye (4) Retinal haemorrhage (4) Retinal oedema (4) Asthenopia (3) Eye movement disorder (3) Eyelid oedema (3) Metamorphopsia (3) Mydriasis (3) Optic nerve disorder (3) Pupillary reflex impaired (3) Retinopathy (3) Accommodation disorder (2) Chorioretinopathy (2) Colour blindness acquired (2) Conjunctival haemorrhage (2) Exophthalmos (2) Eye discharge (2)	Blepharitis (1) Cataract nuclear (1) Chorioretinal disorder (1) Choroidal detachment (1) Corneal thinning (1) Eye oedema (1) Eyelid ptosis (1) Hypermetropia (1) Intraocular haematoma (1) Iritis (1) Lacrimation disorder (1) Macular oedema (1) Myopia (1) Night blindness (1) Ocular dysmetria (1) Ocular vascular disorder (1) Open angle glaucoma (1) Optic disc disorder (1) Optic nerve sheath haemorrhage (1) Periorbital oedema (1) Presbyopia (1) Retinal dystrophy (1) Retinal exudates (1) Retinal infarction (1) Retinal vascular thrombosis (1) Scintillating scotoma (1) Scleral discolouration (1) Uveitis (1) Xanthopsia (1)
udenafil	406	35	Eye pain (11) Ocular hyperaemia (8) Conjunctival hyperaemia (6) Vision blurred (5)	Orbital oedema (2) Visual impairment (2) Eye haemorrhage (1)

ADR, Adverse Drug Reaction; PT, Preferred Term (according to MedDRA terminology)

Appendix - **Table 4** - Methodological Quality assessment of observational studies and case reports.

Dehghani et al, 2018		
Methods	Study design: case report Population: 1 man Country: Iran	
Participants	Case: 1 man, 42 years old	
Interventions	Tadalafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no risk factors	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published in the literature and

		reported to regulatory authorities, respectively. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (20 mg twice weekly for 8 years). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Neufeld and Warner, 2018			
Methods	Study design: case report Population: 1 man Country: US		
Participants	Case: 1 man, 66 years old		
Interventions	Sildenafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	Risk factors: hypertension and hypercholesterolemia		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals

		exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as hypertension and hypercholesterolemia. Temporal sequence: The exposure precedes the outcome. Dose response: The patient took sildenafil for seven years. In the night before the first attack of NAION, the patient doubled the dose of sildenafil. Before the second attack of NAION, the patient took sildenafil for two consecutive days. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase

intervention to the adverse event?		concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Vargas-Sánchez et al, 2018			
Methods	Study design: case report Population: 1 man Country: Spain		
Participants	Case: 1 man, 58 years old		
Interventions	Sildenafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	Medical history: post-traumatic cervical myelopathy and spastic tetra paresis		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker

		compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The information is not clear. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, and sequence of exposure-outcome were described. Information on drug's dose was not clear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Karimi et al, 2018	
Methods	Study design: case report Population: 1 man Country: Iran
Participants	Case: 1 man, 65 years old
Interventions	Sildenafil (for erectile dysfunction)
Outcomes	NAION
Notes	The patient has no risk factors
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*	

Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (patient start using sildenafil 20 days before the attack). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias).

		Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Flahavan et al, 2017		
Methods	Study design: prospective case-crossover study Period time: 05 May 2010 - 15 December 2015 Population: patients with suspected NAION from 41 ophthalmology and neuro-ophthalmology sites Country: US	
Participants	Cases: male subjects ≥18 years old who experienced abrupt visual loss in one eye (<1 day or visual loss noted upon awakening) and presented for an initial visit to an ophthalmologist within 45 days of onset of NAION symptoms that resulted in a diagnosis of suspected NAION Exclusion criteria: previous history of NAION, arteritis (anywhere in the body) or clinical or diagnostic testing evidence of temporal arteritis, glaucoma in either one or both eyes, and multiple sclerosis or evidence of optic neuritis; and ongoing dementia or other memory impairment	
Interventions	Sildenafil, vardenafil, or tadalafil (for erectile dysfunction)	
Outcomes	Rate ratio of NAION	
Notes	The primary analysis used person-time method over 30 days exposure period. The secondary analysis used person-time method over 1-year exposure period.	
Risk of bias (across domains): Critical risk of bias		
Bias	Author's judgement	Support for judgement
Bias due to confounding	Serious risk of bias	At least one known important domain was not appropriately measure, or not controlled for.
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N	-
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	-	-

1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	"The primary statistical analysis used the person-time method. The risk estimate, expressed as a Mantel-Haenszel rate ratio (RR), compared PDE5i exposure in the 30 days before IDO by exposed case definition (ie, PDE5i-exposed within the hazard period). An RR with a lower 95% confidence limit >1.0 suggested an increased risk of NAION with the use of PDE5i. Sensitivity analyses were conducted: (1) defining exposure only on PDE5i-reported dosing days and (2) defining exposure based on PDE5i effect period, imputing unknown PDE5i medications as tadalafil and (3) then as sildenafil or vardenafil. The secondary person-time analysis compared PDE5i exposure in the 12 months before IDO. Sensitivity analyses (1) defined exposure based on PDE5i-reported dosing days and (2) based on PDE5i-reported effect period with imputation of PDE5i use as subject's monthly average if the data on PDE5i use was reported for ≥6 months. The matched-interval method was a pre-specified secondary statistical analysis, including subjects with intermittent PDE5i use in the 42 days prior to IDO, using a hazard period preceding IDO and 4 matched control periods in the 4 weeks preceding IDO; the intervals were matched on the day of the week of IDO (Supplementary Figure 1). This approach was used to examine the impact of pre-specified time-variant risk factors: acute myocardial infarction, transient ischemic attack, ischemic stroke, hemorrhage, and use of phentermine, interferon-α, sumatriptan, beta-blocker eye drops, or nasal decongestants."
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y	"The primary statistical analysis used the person-time method. The risk estimate, expressed as a Mantel-Haenszel rate ratio (RR), compared PDE5i exposure in the 30 days before IDO by exposed case definition (ie, PDE5i-exposed within the hazard period). An RR with a lower 95% confidence limit >1.0 suggested an increased risk of NAION with the use of PDE5i. Sensitivity analyses were conducted: (1) defining exposure only on PDE5i-reported dosing days and (2) defining exposure based on PDE5i effect period, imputing unknown PDE5i medications as tadalafil and (3) then as sildenafil or vardenafil. The secondary person-time analysis compared PDE5i exposure in the 12 months before IDO. Sensitivity analyses (1) defined exposure based on PDE5i-reported dosing days and (2) based on PDE5i-reported effect period with imputation of PDE5i use as subject's monthly average if the data on PDE5i use was reported for ≥6 months. The matched-interval method was a pre-specified secondary statistical analysis, including subjects

		with intermittent PDE5i use in the 42 days prior to IDO, using a hazard period preceding IDO and 4 matched control periods in the 4 weeks preceding IDO; the intervals were matched on the day of the week of IDO (Supplementary Figure 1). This approach was used to examine the impact of pre-specified time-variant risk factors: acute myocardial infarction, transient ischemic attack, ischemic stroke, hemorrhage, and use of phentermine, interferon-α, sumatriptan, beta-blocker eye drops, or nasal decongestants."
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	N	-
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	-	-
1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
Bias in selection of participants into the study	Critical risk of bias	Selection into the study was very strongly related to intervention and outcome, and this could not be adjusted for in the analysis.
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y	"Only subjects with adjudication-confirmed NAION and intermittent PDE5i use (ie, non-chronic PDE5i users who reported taking at least 1 dose of PDE5i on known date(s) during the specified study period [30 days, 42 days, or 12 months] prior to IDO of NAION) were retained in the analysis populations."
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Y	"Only subjects with adjudication-confirmed NAION and intermittent PDE5i use (ie, non-chronic PDE5i users who reported taking at least 1 dose of PDE5i on known date(s) during the specified study period [30 days, 42 days, or 12 months] prior to IDO of NAION) were retained in the analysis populations."
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Y	"Only subjects with adjudication-confirmed NAION and intermittent PDE5i use (ie, non-chronic PDE5i users who reported taking at least 1 dose of PDE5i on known date(s) during the specified study period [30 days, 42 days, or 12 months] prior to IDO of NAION) were retained in the analysis populations."
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y	"Only subjects with adjudication-confirmed NAION and intermittent PDE5i use (ie, non-chronic PDE5i users who reported taking at least 1 dose of PDE5i on known date(s) during the specified study period [30 days, 42 days, or 12 months] prior to IDO of NAION) were retained in the analysis populations."
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to	Y	Case-crossover study

correct for the presence of selection biases?		
Bias in classification of interventions	Low risk of bias	Intervention status is well defined; and intervention definition is based solely on information collected at the time of intervention.
3.1 Were intervention groups clearly defined?	Y	"As part of a structured interview on PDE5i use, subjects were asked to recall specific days and the type of PDE5i taken (tadalafil, sildenafil, or vardenafil) on a day-by-day basis for the 42 days prior to IDO and on a monthly basis (average monthly PDE5i use) for the 12 months prior to IDO."
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y	"As part of a structured interview on PDE5i use, subjects were asked to recall specific days and the type of PDE5i taken (tadalafil, sildenafil, or vardenafil) on a day-by-day basis for the 42 days prior to IDO and on a monthly basis (average monthly PDE5i use) for the 12 months prior to IDO."
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N	"As part of a structured interview on PDE5i use, subjects were asked to recall specific days and the type of PDE5i taken (tadalafil, sildenafil, or vardenafil) on a day-by-day basis for the 42 days prior to IDO and on a monthly basis (average monthly PDE5i use) for the 12 months prior to IDO."
Bias due to deviations from intended interventions	Low risk of bias	Any deviations from intended intervention reflected usual practice.
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	N	-
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	-	-
4.3. Were important co-interventions balanced across intervention groups?	-	-
4.4. Was the intervention implemented successfully for most participants?	-	-
4.5. Did study participants adhere to the assigned intervention regimen?	-	-
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-
Bias due to missing data	Low risk of bias	Data were reasonably complete.
5.1 Were outcome data available for all, or nearly all, participants?	Y	
5.2 Were participants excluded due to missing data on intervention status?	N	-

5.3 Were participants excluded due to missing data on other variables needed for the analysis?	N	-
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	-	-
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Y	"… only men with adjudication-confirmed NAION were included in the analysis sets."
Bias in measurement of outcomes	Low risk of bias	The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants or the outcome assessors were unaware of the intervention received by study participants; and any error in measuring the outcome is unrelated to intervention status.
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	"An independent adjudication committee comprised of 3 neuro-ophthalmologists, masked to PDE5i treatment, reviewed all cases of physician-confirmed NAION based on standard diagnostic practices at each institution."
6.2 Were outcome assessors aware of the intervention received by study participants?	N	"An independent adjudication committee comprised of 3 neuro-ophthalmologists, masked to PDE5i treatment, reviewed all cases of physician-confirmed NAION based on standard diagnostic practices at each institution."
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	"At the single study visit, informed consent was signed, and study data were collected from enrolled subjects…"
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	-
Bias in selection of the reported result	No information	There is too little information to make a judgement.
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	NI	-
7.2 ... multiple analyses of the intervention-outcome relationship?	NI	-
7.3 ... different subgroups?	NI	-

Coca et al, 2016	
Methods	Study design: case report Population: 1 woman Country: US
Participants	Case: 1 woman, 39 years old
Interventions	Sildenafil (for pulmonary hypertension)
Outcomes	PION

Notes	Medical history: bronchopulmonary dysplasia secondary to prematurity, secondary pulmonary hypertension, kyphoscoliosis, pectus defect status post-surgery as an infant, severe obstructive and restrictive lung disease, and malignant fibrous histiocytoma of the right gluteal musculature status post-surgery, and radiation 7 years before already in remission	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and ION is not well established. The patient has other risk factor to ION, such as pulmonary hypertension. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (20 mg 3 times daily for 3 years).

		Experimental evidence: The association between PDE_5 inhibitors and ION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of ION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of ION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. Data on risk factors were unclear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and ION may overweight the risk in the benefit-risk ratio.

Zheng et al, 2016		
Methods	Study design: case report Population: 1 woman Country: Australia	
Participants	Case: 1 woman, 56 years old	
Interventions	Sildenafil (for pulmonary hypertension)	
Outcomes	NAION	
Notes	Risk factors: arterial hypertension Medical history: systemic lupus erythematous, which was treated with long-term low-dose corticosteroids; complications of lupus included glomerulonephritis and pulmonary hypertension with left ventricular failure	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other

		observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as pulmonary hypertension and arterial hypertension. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (10 mg 3 times daily for 7 years). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published. Analogy:
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations,

		drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Campbell et al, 2015		
Methods	Study design: retrospective case-crossover study Period time: October 2008 – October 2012 Population: patients with suspected NAION from 102 ophthalmology sites Country: US and Europe (UK, France, Germany, Italy, Spain)	
Participants	Cases: male patients aged ≥ 45 years; had experienced an abrupt visual change in one eye on an identifiable date; had an afferent pupillary defect in the affected eye; presented to the participating centre within 3 weeks of NAION symptom onset; had no pain consistent with an arteritic or inflammatory process or with optic neuritis; had no other cause that explained the acute vision loss (e.g. injury, inflammation, and retinopathy); had no history of optic neuropathy in the affected eye or optic neuritis in either eye; had not used a PDE_5 inhibitor on a daily basis for treatment of pulmonary arterial hypertension; was able to complete a telephone interview and provide informed consent; and was not participating in another study within 60 days of the presenting visit.	
Interventions	PDE_5 inhibitor (for erectile dysfunction)	
Outcomes	NAION	
Notes	The primary analysis used person-time method over 30 days exposure period. The secondary analysis used person-time method over 8-week exposure period.	
Risk of bias (across domains): critical risk of bias		
Bias	Author's judgement	Support for judgement
Bias due to confounding	Serious risk of bias	At least one known important domain was not appropriately measure, or not controlled for.
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N	-
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	-	-
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	"Sensitivity analyses were performed to assess the impact of the middle-day-rule used in the primary analysis when subjects reported a range of dates for a single instance of PDE5i use. […] The number and percentage of case and control windows exposed to each PDE5i product were calculated. We performed subgroup analyses defined by characteristics with adequate cell sizes, which included age group (<65 years vs. ≥65 years), hypertension (ever vs. never diagnosed), hyperlipidemia (ever vs. never diagnosed), and smoking (ever vs. never). In addition, we performed subgroup analyses by concomitant medication use for those medication classes that represented a biologically plausible interaction with PDE5i

		and for which there were relatively equal proportions of users and nonusers of the concomitant medication. These included medications acting on the renin–angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aliskiren) and aspirin."
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y	"Sensitivity analyses were performed to assess the impact of the middle-day-rule used in the primary analysis when subjects reported a range of dates for a single instance of PDE5i use. […] The number and percentage of case and control windows exposed to each PDE5i product were calculated. We performed subgroup analyses defined by characteristics with adequate cell sizes, which included age group (<65 years vs. ≥65 years), hypertension (ever vs. never diagnosed), hyperlipidemia (ever vs. never diagnosed), and smoking (ever vs. never). In addition, we performed subgroup analyses by concomitant medication use for those medication classes that represented a biologically plausible interaction with PDE5i and for which there were relatively equal proportions of users and nonusers of the concomitant medication. These included medications acting on the renin–angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aliskiren) and aspirin."
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	N	-
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	-	-
1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
Bias in selection of participants into the study	Critical risk of bias	Selection into the study was very strongly related to intervention and outcome, and this could not be adjusted for in the analysis.
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y	"Participating ophthalmologists identified potential NAION cases as they presented to their sites. Following provision of informed consent, patients were enrolled into the study. Site staff administered a brief "screening" interview to determine whether PDE5i and other medications taken as needed were used during the 2-month period prior to NAION symptom onset."
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Y	"Participating ophthalmologists identified potential NAION cases as they presented to their sites. Following provision of informed consent, patients were enrolled into the study.

		Site staff administered a brief "screening" interview to determine whether PDE5i and other medications taken as needed were used during the 2-month period prior to NAION symptom onset."
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Y	"Participating ophthalmologists identified potential NAION cases as they presented to their sites. Following provision of informed consent, patients were enrolled into the study. Site staff administered a brief "screening" interview to determine whether PDE5i and other medications taken as needed were used during the 2-month period prior to NAION symptom onset."
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y	
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y	Case-crossover study
Bias in classification of interventions	Low risk of bias	Intervention status is well defined; and intervention definition is based solely on information collected at the time of intervention.
3.1 Were intervention groups clearly defined?	Y	"For each of the 81 subjects reporting use of a PDE5i during the 60 days prior to symptom onset, the site assembled and submitted the subject's clinical and laboratory information for adjudication. Twenty-five unexposed subjects were randomly selected over the course of the enrolment period for adjudication as well, so that the adjudicators would not be aware whether a given subject had used a PDE5i."
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y	"For each of the 81 subjects reporting use of a PDE5i during the 60 days prior to symptom onset, the site assembled and submitted the subject's clinical and laboratory information for adjudication. Twenty-five unexposed subjects were randomly selected over the course of the enrolment period for adjudication as well, so that the adjudicators would not be aware whether a given subject had used a PDE5i."
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N	"For each of the 81 subjects reporting use of a PDE5i during the 60 days prior to symptom onset, the site assembled and submitted the subject's clinical and laboratory information for adjudication. Twenty-five unexposed subjects were randomly selected over the course of the enrolment period for adjudication as well, so that the adjudicators would not be aware whether a given subject had used a PDE5i."
Bias due to deviations from intended interventions	Low risk of bias	Any deviations from intended intervention reflected usual practice.
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	N	-

4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	-	-
4.3. Were important co-interventions balanced across intervention groups?	-	-
4.4. Was the intervention implemented successfully for most participants?	-	-
4.5. Did study participants adhere to the assigned intervention regimen?	-	-
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-
Bias due to missing data	Low risk of bias	Data were reasonably complete.
5.1 Were outcome data available for all, or nearly all, participants?	Y	
5.2 Were participants excluded due to missing data on intervention status?	N	-
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	N	-
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	-	-
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NI	-
Bias in measurement of outcomes	Low risk of bias	The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants; and any error in measuring the outcome is unrelated to intervention status.
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	-
6.2 Were outcome assessors aware of the intervention received by study participants?	Y	-
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	Case-crossover study.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	-

Bias in selection of the reported result	No information	There is too little information to make a judgement.
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	NI	-
7.2 ... multiple analyses of the intervention-outcome relationship?	NI	-
7.3 ... different subgroups?	NI	-

Nathoo et al, 2015		
Methods	Study design: retrospective nested case-control study Database: IMS Lifelink Period time: 2000-2011 Population: 1 million men were randomly selected Country: Canada	
Participants	Cases: men with ICD-9 diagnosis of NAION (ICD-9 code 377.41) Controls: no history of NAION and matched to the cases by age, calendar time, and index date of the case Exclusion criteria: history or subsequent diagnosis of polymyalgia rheumatica and giant cell arteritis	
Interventions	Sildenafil, vardenafil, or tadalafil (for erectile dysfunction)	
Outcomes	Risk ratio of NAION	
Notes	A conditional logistic regression model was created to adjust for the following covariates: diabetes, statins, hypertension, myocardial infarction, and stroke.	
Risk of bias (across domains): serious risk of bias		
Bias	Author's judgement	Support for judgement
Bias due to confounding	Serious risk of bias	At least one known important domain was not appropriately measure, or not controlled for.
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N	-
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	-	-
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	"We further stratified our analysis to the type of a PDE-5 inhibitor where a user was defined as a subject who had received at least 1 prescription of either sildenafil, vardenafil, or tadalafil within 1 year of the index date. A conditional logistic regression model was created to adjust for the following covariates: diabetes, statins, hypertension, myocardial infarction, and stroke. Adjusted rate ratios were computed with non-users of PDE-5 inhibitors (in the year before the index date) as the control group."
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by	Y	"We further stratified our analysis to the type of a PDE-5 inhibitor where a user was defined as a subject who had received at least 1 prescription of either sildenafil, vardenafil, or

the variables available in this study?		tadalafil within 1 year of the index date. A conditional logistic regression model was created to adjust for the following covariates: diabetes, statins, hypertension, myocardial infarction, and stroke. Adjusted rate ratios were computed with non-users of PDE-5 inhibitors (in the year before the index date) as the control group."
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	N	-
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	-	-
1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
Bias in selection of participants into the study	Moderate risk of bias	Selection into the study may have been related to intervention and outcome; and the authors used appropriate methods to adjust for the selection bias.
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y	"Cases were defined as those with the first ICD-9 diagnosis of NAION (ICD-9 code 377.41)."
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	N	-
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Y	"Cases were defined as those with the first ICD-9 diagnosis of NAION (ICD-9 code 377.41)."
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y	-
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y	Case-control study.
Bias in classification of interventions	Low risk of bias	Intervention status is well defined; and intervention definition is based solely on information collected at the time of the intervention.
3.1 Were intervention groups clearly defined?	Y	"Cases were defined as those with the first ICD-9 diagnosis of NAION (ICD-9 code 377.41). […] For each case, all eligible controls with no history of NAION were identified and matched to the cases by age, calendar time, and index date of the case."

3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y	Methods
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N	-
Bias due to deviations from intended interventions	Low risk of bias	Any deviations from intended intervention reflected usual practice.
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	N	-
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	-	-
4.3. Were important co-interventions balanced across intervention groups?	-	-
4.4. Was the intervention implemented successfully for most participants?	-	-
4.5. Did study participants adhere to the assigned intervention regimen?	-	-
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-
Bias due to missing data	Low risk of bias	Data were reasonably complete.
5.1 Were outcome data available for all, or nearly all, participants?	Y	
5.2 Were participants excluded due to missing data on intervention status?	N	-
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	N	-
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	-	-
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NI	-
Bias in measurement of outcomes	Low risk of bias	The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants; and any error in measuring

		the outcome is unrelated to intervention status.
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	-
6.2 Were outcome assessors aware of the intervention received by study participants?	Y	-
6.3 Were the methods of outcome assessment comparable across intervention groups?	NI	-
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	-
Bias in selection of the reported result	No information	There is too little information to make a judgement.
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	NI	-
7.2 ... multiple analyses of the intervention-outcome relationship?	NI	-
7.3 ... different subgroups?	NI	-

Atilgan et al, 2014		
Methods	Study design: case report Population: 1 man Country: Turkey	
Participants	Case: 1 man, 35 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factor: small optic cup/optic disc ratio	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-

		lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as small optic cup/ optic disc ratio. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (dose and frequency unknown; for 3 years). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Higher risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, and sequence of exposure-outcome were described. Data on drug's dose and frequency of administration, and eye(s) affected unknown.
Are there any potential problems from using data from the reports, which might outweigh the	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and

perceived benefit of being comprehensive?		NAION may overweight the risk in the benefit-risk ratio.

Gaffuri et al, 2014		
Methods	Study design: case report Population: 1 child Country: Italy	
Participants	Case: 1 child, female, 7 months old	
Interventions	Sildenafil (for pulmonary hypertension)	
Outcomes	PION	
Notes	Risk factor: systemic blood pressure was persistently found at upper normal levels for age and Glenn operation Medical history: congenital heart disease	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant.

		Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and ION is not well established. The patient has other risk factors to ION, such as pulmonary hypertension, increased systemic blood pressure and Glenn operation. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (0.2 mg/kg 3 times daily for 4 weeks). Experimental evidence: The association between PDE_5 inhibitors and ION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of ION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of ION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and ION may overweight the risk in the benefit-risk ratio.

Galvez-Ruiz and Arishi, 2013		
Methods	Study design: retrospective review of case reports Population: 10 men; mean age of 50.7 years (range, 38 years and 70 years) Country: Saudi Arabia	
Participants	Cases: 10 men with several episodes of NAION	
Interventions	Sildenafil	
Outcomes	NAION	
Notes	Risk factors: diabetes mellitus, hypertension, ischaemic heart disease, dyslipidaemia and hypercholesterolemia	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the

		development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patients have other risk factors to NAION, such as diabetes mellitus, hypertension, ischaemic heart disease, dyslipidaemia and hypercholesterolemia. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure varied according to the different cases reported. In general, the exposure was regular. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase

intervention to the adverse event?		concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	In general, data on patients, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. In four case reports, drug's therapeutic indication was not clear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this series of case reports to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Kim and Kim, 2012		
Methods	Study design: case report Population: 1 man Country: South Korea	
Participants	Case: 1 man, 54 years old	
Interventions	Udenafil (for erectile dysfunction)	
Outcomes	AION	
Notes	Risk factors: smoking	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker

		compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as smoking. Temporal sequence: The exposure precedes the outcome. Dose response: The patient was exposed once. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Tarantini et al, 2012	
Methods	Study design: case report Population: 1 man Country: Italy
Participants	Case: 1 man, 60 years old
Interventions	Sildenafil (for erectile dysfunction)
Outcomes	NAION
Notes	Risk factors: diabetes mellitus
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*	

Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as diabetes mellitus. Temporal sequence: The exposure precedes the outcome. Dose response: The patient was exposed three days consecutively to 50 mg of sildenafil. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias).

		Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

El-Domyati et al, 2011		
Methods	Study design: case report Population: 1 man Country: Egypt	
Participants	Case: 1 man, 48 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no medical history or risk factors	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a

		more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (patient start using sildenafil 50 mg, 36 hours before the attack). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Felekis et al, 2011	
Methods	Study design: case report

	Population: 1 man Country: Greece	
Participants	Case: 1 man, 51 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factors: mild hypercholesterolemia and family history (father) of bilateral attacks of NAION	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as mild hypercholesterolemia and family history (father) of bilateral attacks of NAION. Temporal sequence: The exposure precedes the outcome.

		Dose response: The exposure was constant (once a week for 6 months). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Ghanem, 2011			
Methods	Study design: case report Population: 1 man Country: Egypt		
Participants	Case: 1 man, 53 years old		
Interventions	Sildenafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	The patient has no medical history or risk factors		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009.

		Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (once a week for 4 months; dose unknown). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, and sequence of exposure-outcome were described. Data on drug's dose was unknown.
Are there any potential problems from using data from the reports,	Higher risk	Consistent with the results of the available evidence, using this case report to assume an

which might outweigh the perceived benefit of being comprehensive?		association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Moschos and Margetis, 2011		
Methods	Study design: case report Population: 1 man Country: Greece	
Participants	Case: 1 man, 55 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no medical history or risk factors	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published.

		Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant (50 mg 4-5 times per month for 8 months). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Prat et al, 2011		
Methods	Study design: case report Population: 1 woman Country: Spain	
Participants	Case: 1 woman, 63 years old	
Interventions	Sildenafil (for pulmonary hypertension)	
Outcomes	NAION	
Notes	Risk factors: aortic valve replacement 8 years ago, arterial hypertension, atrial fibrillation, peripheral vascular disease resulting in amputation of her right toe 2 months before Medical history: hypothyroidism, chronic renal failure, and cadaveric kidney transplant 10 years ago with graft failure 3 years ago	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and

		the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as pulmonary hypertension, aortic valve replacement, arterial hypertension, atrial fibrillation and peripheral vascular disease. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (drug's start time was unclear; 50 mg 3 times daily). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase

intervention to the adverse event?		concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, and sequence of exposure-outcome were described. Data on drug's start date was unclear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Shen and Gurka, 2011		
Methods	Study design: case report Population: 1 man Country: US	
Participants	Case: 1 man, 60 years old	
Interventions	Sildenafil (for pulmonary hypertension)	
Outcomes	NAION	
Notes	Risk factors: coronary artery disease, ischaemic dilated cardiomyopathy, hyperlipidaemia and recent cardiovascular surgery including CABG	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of

		NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as coronary artery disease, ischaemic dilated cardiomyopathy, hyperlipidaemia and recent cardiovascular surgery including CABG. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (data on drug's dose and frequency of administration unknown). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Higher risk	Data on patient, medical history and risk factors, and sequence of exposure-outcome were described. Data on clinical symptoms and examination, and drug's dose and frequency of administration was unknown.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Pepin and Pitha-Rowe, 2008	
Methods	Study design: case report Population: 1 Caucasian man Country: US

Participants	Case: 1 man, 63 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factors: essential hypertension Medical history: prostatectomy for prostate cancer The patient re-challenged sildenafil 100 mg twice in the 14 days after the first attack, NAION reappears.	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as essential hypertension. Temporal sequence: The exposure precedes the outcome.

		Dose response: The exposure was constant for 5 years (25 mg sporadically). In the night before the attack, the patient took 100 mg of sildenafil. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Su et al, 2008		
Methods	Study design: case report Population: 1 man Country: Singapore	
Participants	Case: 1 man, 76 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	PION	
Notes	Risk factors: hypertension, hyperlipidaemia, and stroke The patient took a Chinese health supplement containing sildenafil	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose

		study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and ION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and ION is not well established. The patient has other risk factors to ION, such as hypertension, hyperlipidaemia, and stroke. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant for 7 weeks (patient took one capsule once a day or every other day), but 36 hours before the attack, the patient took 3 capsules. Experimental evidence: The association between PDE_5 inhibitors and ION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of ION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of ION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]

Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and ION may overweight the risk in the benefit-risk ratio.

Margo and French, 2007			
Methods	Study design: retrospective cohort study Database: Veterans Health Administration Decision Support Systems and Veterans Health Administration National Patient Care Database Period time: Fiscal years 2004 and 2005 Population: Users of PDE_5 inhibitors with ICD-9 diagnosis of NAION Country: US		
Participants	Cases: men veterans aged ≥ 50 years old with ICD-9 diagnosis of NAION (ICD-9 code 377.41) and a second group of possible NAION (optic neuritis, other ICD-9 code 377.39, optic neuritis, unspecified ICD-9 code 377.30, and optic papillitis ICD-9 code 377.31) Exclusion criteria: history of a previous diagnosis of optic nerve disease, temporal arteritis or polymyalgia rheumatica		
Interventions	PDE_5 inhibitor		
Outcomes	Risk ratio of NAION		
Notes	-		
Risk of bias: (across domains): Critical risk of bias			
Bias		Author's judgement	Support for judgement
Bias due to confounding		Critical risk of bias	Confounding inherently not controllable.
1.1 Is there potential for confounding of the effect of intervention in this study?		Y	
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?		N	-
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?		-	-
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		N	-
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		-	-
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		N	-
1.7. Did the authors use an appropriate analysis method that controlled for all the important		-	-

confounding domains and for time-varying confounding?		
1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
Bias in selection of participants into the study	Critical risk of bias	Selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y	"Exposure to the PDE-5 inhibitors was cross-referenced to newly diagnosed cases of ischemic optic neuropathy during a two-year interval…"
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Y	"Exposure to the PDE-5 inhibitors was cross-referenced to newly diagnosed cases of ischemic optic neuropathy during a two-year interval…"
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Y	"Exposure to the PDE-5 inhibitors was cross-referenced to newly diagnosed cases of ischemic optic neuropathy during a two-year interval…"
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y	"Exposure to the PDE-5 inhibitors was cross-referenced to newly diagnosed cases of ischemic optic neuropathy during a two-year interval…"
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N	-
Bias in classification of interventions	Low risk of bias	Intervention status is well defined; and intervention definition is based solely on information collected at the time of intervention.
3.1 Were intervention groups clearly defined?	Y	"Relative risks were calculated as the ratio of the two-year incidence of NION according to exposure status to PDE-5 inhibitors. Event rates of NION were based on a single diagnosis of ischemic optic neuropathy per patient."
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y	"Relative risks were calculated as the ratio of the two-year incidence of NION according to exposure status to PDE-5 inhibitors. Event rates of NION were based on a single diagnosis of ischemic optic neuropathy per patient."
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N	"Relative risks were calculated as the ratio of the two-year incidence of NION according to exposure status to PDE-5 inhibitors. Event rates of NION were based on a single diagnosis of ischemic optic neuropathy per patient."
Bias due to deviations from intended interventions	Low risk of bias	Any deviations from intended intervention reflected usual practice.
4.1. Were there deviations from the intended intervention beyond	N	-

what would be expected in usual practice?		
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	-	-
4.3. Were important co-interventions balanced across intervention groups?	-	-
4.4. Was the intervention implemented successfully for most participants?	-	-
4.5. Did study participants adhere to the assigned intervention regimen?	-	-
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-
Bias due to missing data	Low risk of bias	Data were reasonably complete.
5.1 Were outcome data available for all, or nearly all, participants?	Y	
5.2 Were participants excluded due to missing data on intervention status?	N	-
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	NI	-
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	-	-
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NI	-
Bias in measurement of outcomes	Low risk of bias	The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants; and any error in measuring the outcome is unrelated to intervention status.
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	
6.2 Were outcome assessors aware of the intervention received by study participants?	Y	-
6.3 Were the methods of outcome assessment comparable across intervention groups?	NI	-

6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	-
Bias in selection of the reported result	No information	There is too little information to make a judgement.
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	NI	-
7.2 ... multiple analyses of the intervention-outcome relationship?	NI	-
7.3 ... different subgroups?	NI	-

Gedik et al, 2007		
Methods	Study design: case report Population: 1 man Country: Turkey	
Participants	Case: 1 man, 36 years old	
Interventions	Sildenafil (therapeutic indication not clear)	
Outcomes	NAION	
Notes	Risk factors: hypotension and small cup-to-disc ratio Medical history: haemodialysis for chronic renal failure Along with NAION, it was identified cilioretinal artery occlusion, and central retinal vein occlusion The patient re-challenged sildenafil 100 mg. In the next morning, the patient presented darkened superior visual field in his right eye	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study

		concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as hypotension and small cup-to-disc ratio. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (patient start using sildenafil 100mg in the night before the attack). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. Data on drug's therapeutic indication was not clear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Sivaswamy and Vanstavern, 2007	
Methods	Study design: case report Population: 1 child Country: US

Participants	Case: 1 child, female, 6 years old	
Interventions	Sildenafil (for pulmonary hypertension)	
Outcomes	NAION	
Notes	The patient has no risk factors Medical history: surgery for repair of a coarctation of the aorta at age 2 years and mitral-valve replacement and pacemaker placement at age 4 years	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome.

		Dose response: The exposure was constant (10 mg 3 times daily for 15 months). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Akash et al, 2005		
Methods	Study design: case report Population: 1 Caucasian man Country: UK	
Participants	Case: 1 man, 54 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no medical history or risk factors	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009.

		Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was constant for weeks (100 mg 2-3 times weekly). Few hours before the attack, the patient took 200 mg. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.

Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Bollinger and Lee, 2005		
Methods	Study design: case report Population: 1 man Country: US	
Participants	Case: 1 man, 67 years old	
Interventions	Tadalafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factor: hypercholesterolemia The patient re-challenged tadalafil 20 mg and symptoms of NAION reappear.	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.

		Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as hypercholesterolemia. Temporal sequence: The exposure precedes the outcome. Dose response: The patient experienced symptoms 4 times (in five administrations), 2 hours after taking 20 mg of tadalafil. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Escaravage et al, 2005			
Methods	Study design: case report Population: 1 man Country: US		
Participants	Case: 1 man, 59 years old		
Interventions	Tadalafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	Medical history: prostate cancer, laparoscopic prostatectomy and depression		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al

		(2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data. The patient took 20 mg 45 hours before the attack. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors

		may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Peter et al, 2005		
Methods	Study design: case report Population: 1 man Country: UK	
Participants	Case: 1 man, 59 years old	
Interventions	Tadalafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no risk factors Medical history: radical prostatectomy for adenocarcinoma of the prostate	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone.

		Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: The patient took 20 mg of tadalafil 7 days consecutively. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Pomeranz and Bhavsar, 2005	
Methods	Study design: review of case reports Population: 7 men; age range: 50-69 years old Country: US
Participants	Case: 7 men
Interventions	Sildenafil (for erectile dysfunction)
Outcomes	NAION
Notes	Risk factors: hypertension, elevated lipids, diabetes mellitus, retinal detachment and hypoplastic optic neuropathy
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*	

Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patients have other risk factors to NAION, such as hypertension, elevated lipids, diabetes mellitus, retinal detachment and hypoplastic optic neuropathy. Temporal sequence: The exposure precedes the outcome. Dose response: The exposure varied according to the different cases reported. In three cases, the patients took sildenafil for the first time few hours before the attack. In one case, the dose was doubled in the night before the attack.

		Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. In one case report, drug's dose and frequency of administration was unknown.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this series of case reports to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Gruhn and Fedelini, 2004			
Methods	Study design: case report Population: 1 man Country: Denmark		
Participants	Case: 1 man, 69 years old		
Interventions	Sildenafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	Risk factors: vague right eye visual disturbance (in the day before)		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of

		NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as vague right eye visual disturbance (in the day before). Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (patient start using sildenafil 50 mg 18 hours before the attack). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.

Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Sinha et al, 2004		
Methods	Study design: case report Population: 1 man Country: UK	
Participants	Case: 1 man, 61 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	AION	
Notes	Risk factors: smoking, disc-at-risk	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.

		Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as vague right eye visual disturbance (in the day before). Temporal sequence: The exposure precedes the outcome. Dose response: The exposure was not clear. The patient doubled the dose of sildenafil (100 mg) on the night before the attack. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. Data on drug's frequency of administration was not clear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Boshier et al, 2002		
Methods	Study design: case report Population: 1 man Country: UK	
Participants	Case: 1 man, 61 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factors: hypertension, elevated lipids, smoking, coronary artery disease and myocardial infarction	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively.

		Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factors to NAION, such as hypertension, elevated lipids, smoking, coronary artery disease and myocardial infarction. Temporal sequence: The exposure precedes the outcome. Dose response: Data on drug's dose and frequency of administration was not available. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.

Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Higher risk	Data on patient, medical history and risk factors were described. Data on clinical symptoms and examinations, drug and sequence exposure-outcome were not provided.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Dheer et al, 2002		
Methods	Study design: case report Population: 1 man Country: India	
Participants	Case: 1 man, 48 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	The patient has no risk factors	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study

		concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. However, the patient has no other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (drug's dose and frequency of administration was unclear). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, and sequence of exposure-outcome were described. Data on drug's dose and frequency of administration was unclear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Pomeranz et al, 2002	
Methods	Study design: review of case reports Population: 5 men; age range: 42-69 years old Country: US
Participants	Case: 5 men

Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	Risk factors: elevated lipids, diabetes mellitus, NAION on fellow eye, smoking and coronary artery disease	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patients have other risk factors to NAION, such as elevated lipids, diabetes mellitus, NAION on fellow eye, smoking and coronary artery disease. Temporal sequence: The exposure precedes the outcome.

		Dose response: The exposure varied according to the different cases reported. In general, the exposure occurred few hours before the attack. In two cases, the drug's dose was unknown. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described. In two cases, the drug's dose was unknown.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this series of case reports to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Cunningham and Smith, 2001		
Methods	Study design: case report Population: 1 man Country: US	
Participants	Case: 1 man, 42 years old	
Interventions	Sildenafil (for erectile dysfunction)	
Outcomes	NAION	
Notes	-	
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*		
Bias	Author's judgement	Support for judgement
Do the reports have good predictive value?	Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was

		observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. It is unknow if the patient has other risk factors to NAION. Temporal sequence: The exposure precedes the outcome. Dose response: Data on drug's dose and frequency of administration was not clear. Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]

Do the reports provide enough information to allow detailed appraisal of the evidence?	Higher risk	Data on patient, clinical symptoms and examinations were described. Data on medical history and risk factors, drug's dose and frequency of administration and sequence exposure-outcome were unclear.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Egan and Pomeranz, 2000			
Methods	Study design: case report Population: 1 man Country: US		
Participants	Case: 1 man, 52 years old		
Interventions	Sildenafil (for erectile dysfunction)		
Outcomes	NAION		
Notes	Risk factors: smoking Medical history: transurethral resection for prostate cancer, Crohn disease, attention deficit (methylphenidate hydrochloride), amitriptyline		
Risk of bias *(according to chapter 14.6.3 of Cochrane Handbook)*			
Bias		Author's judgement	Support for judgement
Do the reports have good predictive value?		Higher risk	Several case and spontaneous reports, reporting a suspected association between PDE_5 inhibitors exposure and NAION, were published in the literature and reported to regulatory authorities, respectively. Some observational studies studied the association of PDE_5 inhibitors exposure and the development of NAION. Nathoo et al (2015) compared the risk of NAION in individuals exposed to PDE_5 inhibitors to controls. The results concluded that there is not any association between PDE_5 inhibitors exposure and NAION. The same result was observed by Margo and French (2007), whose study showed a non-significant risk of NAION with PDE_5 inhibitors use. Two other observational studies (Flahavan et al, 2009. Campbell et al, 2015) compared the risk of NAION between individuals with intermittent exposure of PDE_5 inhibitors (within five half-lives) with exposure in a more previous time period. The results showed that there is an increased risk of NAION within five half-lives of PDE_5 inhibitors use compared with use in a more prior time period. In addition, French et al (2008) evaluated the association of PDE_5 inhibitors plus organic nitrate or alfa-blockers and the development of NAION. The study concluded that there was no increase in risk of NAION in men dispensed a PDE_5 inhibitor with either organic nitrates or an alfa-blocker compared with men dispensed PDE_5 inhibitor alone. Despite the several case and spontaneous reports available, according to the

		observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant.
Determining causality	Higher risk	Strength: According to the observational studies, the possible association of PDE_5 inhibitors use and NAION onset was not significant. Consistency: Several case and spontaneous reports were published. Specificity: The association between PDE_5 inhibitors and NAION is not well established. The patient has other risk factor to NAION, such as smoking. Temporal sequence: The exposure precedes the outcome. Dose response: Insufficient data (patient start using sildenafil 50 mg 36 hours before the attack). Experimental evidence: The association between PDE_5 inhibitors and NAION was assessed in observational studies and reported in cases and spontaneous reports (see question one on bias). Biological plausibility: See question three on bias. Coherence: Several case reports, spontaneous reports and observational studies were published.
Is there a plausible biological mechanism linking the intervention to the adverse event?	Low risk	The association between the use of PDE_5 inhibitors and the development of NAION remains unknown. PDE_5 inhibitors increase concentration of NO, prolonging vasodilation. This led to a rapid systemic hypotension, one of the risk factors of NAION. PDE_5 inhibitors may also have a role in the perfusion of optic nerve head, causing a local deregulation. [Koksal (2005); Liu (2018)]
Do the reports provide enough information to allow detailed appraisal of the evidence?	Low risk	Data on patient, medical history and risk factors, clinical symptoms and examinations, drug and sequence of exposure-outcome were described.
Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?	Higher risk	Consistent with the results of the available evidence, using this case report to assume an association between PDE_5 inhibitors use and NAION may overweight the risk in the benefit-risk ratio.

Chapter 8 – General discussion

Systematic reviews are characterized by their rigorous and systematic methodology. They can produce evidence that can be used to take informed decisions. Regulatory authorities consider data obtained from systematic reviews in health decision process (Barbui et al, 2017). For example, a review identified four drugs withdrawn from the market due to safety concerns after systematic review evidence evaluation (Onakpoya et al, 2016). In order to being update, regulatory authorities conduct periodic evaluations to drug's safety. The European Medicines Agency (EMA) performs regular evaluations of drug's safety by evaluating the Periodic Safety Update Reports (PSUR) (EMA, 2019a) and updating the information of each drug in their European Public Assessment Report (EPAR) (EMA, 2019b). Moreover, since a systematic review pools data from several sources, a rapid detection of safety signals is possible (Barbui et al, 2019). Health professionals and consumers can also use data provided by systematic reviews in their decisions. Since a clinical decision should be supported by more than one study, systematic reviews have an important role in providing answers in clinical practice (Murad et al, 2014). They can also be used in the development of clinical practice guidelines (Davoli et al, 2015; Lindsey et al, 2016). The World Health Organisation (WHO) developed a guideline based on the results of Cochrane reviews on opioid dependence (Davoli et al, 2015). A guideline for chronic heart failure was developed based on a systematic review of pre-existing guidelines (Muth et al, 2009).

In drug's safety, systematic reviews face some issues, namely the definition of methodology to conduct and/ or to report a systematic review and how to manage data from several sources with different study designs. The aim of this thesis was to identify and characterize the available recommendations to conduct and/ or report a systematic review in drug's safety and to understand their major methodological challenges.

In the first work, a scoping review was performed to identify the available recommendations to conduct and/ or to report a systematic review in medical literature. There are several recommendations. Some of them were developed by organisations dedicated to research in systematic review methodology, such as the Cochrane Collaboration (Higgins et al, 2019), the Centre for Reviews and Dissemination of the University of York (University of York, 2009) and the Joanna Briggs Institute (Jordan et al, 2006). There are recommendations that can be applied to specific research subjects,

such as economics or safety; to clinical subjects, such as cardiology, pain or nephrology; to investigation procedures subjects, such as diagnostic or prognostic; or to other medical subjects. Nonetheless, there are more than one recommendation in each area of interest. For instance, to conduct and/ or to report a systematic review in drug's safety, there are four available recommendations. Although there is a similarity in systematic reviews methodology between the available recommendations, they differed. In literature search, different sources of information are recommended. This can influence the number of studies included in the systematic review. The same can be noted to the recommended methodological quality scales, that can differently appraise the included studies and, consequently, generate different interpretations of their results.

The results of this work are consistent with those published by a recent scoping review performed by Mueller et al (2018). This review identified the available recommendations to conduct a systematic review and meta-analysis of observational studies (Mueller et al, 2018). The review also compared the recommendations and found discrepancies in their methodology, namely on the inclusion of different observational study designs, in the used methodological quality scales and in the selection of the model for meta-analysis (Mueller et al, 2018).

Pussegoda et al (2017a) identified studies assessing the reporting and methodological quality of systematic reviews. Similarly, with the results of the first work of this thesis, a unique recommendation to report and assess the methodological quality of systematic reviews was not identified. Several recommendations were identified and some of them were developed by major research groups, such as the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) and A Measurement Tool to Assess Systematic Reviews (AMSTAR) (Pussegoda et al, 2017a). Others were developed by the authors performing the systematic review (Pussegoda et al, 2017a).

This first work has some limitations, namely those related with the literature search. Indexed terms describing methodology of systematic reviews were used to search in three bibliographic databases. These terms could not retrieve all available recommendations to conduct and/ or to report a systematic review published in the literature. Moreover, articles published in other language than English or published in Grey Literature were excluded. Therefore, some recommendations may not be included in this scoping review. Nonetheless, this review included a large sample of recommendations. As described in theoretical saturation concept, despite continuing searching and collecting,

no new data will emerge (Bloor and Wood, 2006; Mueller et al, 2018). Therefore, since this work is methodological, to identify every recommendation is not mandatory (Bloor and Wood, 2006; Mueller et al, 2018).

In the second work, the methodology of the published systematic reviews was characterised. Systematic reviews evaluating ophthalmic adverse drug reactions published in Ophthalmology journals were identified. Approximately, 40% of the systematic reviews did not follow a recommendation to conduct and/ or to report a systematic review. From those that followed a recommendation, most of the systematic reviews followed only one recommendation, the PRISMA, which is specific for the reporting of systematic reviews. Although the existence of one recommendation to conduct systematic reviews in ophthalmology and four recommendations to conduct and/or report systematic reviews in drug's safety, none of these were followed by the analysed systematic reviews. Nevertheless, the inclusion of different sources of information, that is a specific orientation when studying drug's safety, was observed among the evaluated systematic reviews. A comparison between the methodology used in the assessed systematic reviews showed differences in their elaboration and reporting. All the analysed systematic reviews structured the research hypothesis and eligibility criteria with PICO strategy, described the results in detail and presented the sources of conflict. Lower agreement in the methodology was observed in the previous publication of a protocol, explanation of the selection of studies and in the description of both included and excluded studies.

The systematic review performed by Lee et al (2017) assessed the compliance of the reporting of systematic reviews published in the five major journals in Ophthalmology with the methods described in the recommendation to report systematic reviews the PRISMA. An agreement of 56% (range 5-96%) was observed between the analysed systematic reviews and the recommendation provided by PRISMA (Lee et al, 2017). The items with higher agreement were the following: "description of rationale" (100%), "the general interpretation of results" (96%) and "the inclusion of a structured summary in the abstract" (90%) (Lee et al, 2017). The items with lower agreement were the following: "indication of review protocol and registration" (9%), "specification of risk of biases that may affect the cumulative evidence" (24%) and "description of clear objectives in the introduction" (26%) (Lee et al, 2017). These results are in line with those reported in the second work of this thesis. No further studies assessing the methodology of systematic reviews in Ophthalmology were found.

Several groups have studied the methodological quality of systematic reviews addressing drug's safety. Golder et al (2006) assessed 256 systematic reviews. Differences in the development and reporting of systematic reviews were observed (Golder et al, 2006). Only 5% of the systematic reviews reported enough data on search strategy; only 41% assessed methodological quality of the included studies; and only 48% reported any source of conflict (Golder et al, 2006). Nonetheless, 76% of the systematic reviews included data other than randomized controlled trials (RCT) (Golder et al, 2006). Other issues were related with the identification of studies and their methodological quality assessment (Golder et al, 2006). Zorzela et al (2014) also studied the quality of reporting adverse drug reactions in systematic reviews. From a sample of approximately 300 systematic reviews, the proportion of those with good reporting was 0.56 (range 0.55 – 0.57) (Zorzela et al, 2014). Besides methodological aspects of systematic reviews studying drug's safety, this review also highlight the need to report aspects, such as patient's risk factors, medical history, pharmacology history or length of follow-up, which may be important in the causality assessment by systematic reviews' readers (Zorzela et al, 2014).

Differences in systematic reviews were observed among the diverse studies assessing their methodology. Several recommendations are available to conduct and/ or to report systematic reviews. However, some reviews did not follow any of these recommendations. In the second work of this thesis, only 60% of the analysed systematic reviews follow a recommendation. Among these, differences in methodology were found. The same was observed in the works of Golder et al (2006), Page et al (2016) and Zorzela et al (2014). The three studies assessed Cochrane reviews and non-Cochrane reviews (Golder et al, 2006; Page et al, 2016; Zorzela et al, 2014). Cochrane reviews, which followed the same recommendation, showed differences in their methods and results (Golder et al, 2006; Page et al, 2016; Zorzela et al, 2014).

This second work has limitations. Since this work has a limited time of execution, a previous protocol was not published. A search literature was performed using indexed terms of journals' titles in Ophthalmology and was restricted to systematic reviews published in the last decade. Ophthalmology was used as case study in this thesis. The use of indexed terms and choice of ten years as length of follow-up helped to narrow the search literature. Since drug's safety is not yet an indexed term, we searched for all systematic reviews and screened those related with drug's safety. Nonetheless, this work

allowed to identify systematic reviews addressing drug's safety in Ophthalmology and characterize their methodology.

In the third work, an assessment of the two recommendations to conduct and/or to report a systematic review in drug's safety most commonly used was performed. The recommendations developed by the Centre for Reviews and Dissemination of University of York (Centre for Reviews and Dissemination, 2009) and the Cochrane Collaboration (Higgins and Green, 2011) were selected to conduct and report the systematic reviews. The same research hypothesis, in Ophthalmology, was identified. Important questions affecting the elaboration of systematic reviews, namely the access to information (some bibliographic databases are not available to search publicly) and the assessment of methodological quality of the included evidence (insufficient scales) were observed. These questions were found in the two systematic reviews and are the major differences between them. They could influence the identification of adverse drug reactions, due the difference in the number of identified studies. In both systematic reviews, the difference in the included studies was minimal. Only two studies, two case reports, were not included in one of the systematic reviews. Therefore, no major differences on the results of the systematic reviews were observed. Nevertheless, the evaluated ophthalmic adverse drug reaction is rare. If this adverse drug reaction occurred more frequently, the difference between the included studies could have a major impact in the results. Furthermore, if the missed studies were experimental or observational studies with incidence estimates, this could influence the results of the meta-analysis or other statistical analysis (this is, the sample size was smaller, and the risk estimates weren't statistically significant).

A study by Dretzke et al (2014) evaluated eight systematic reviews of prognosis studies assessing the same research hypothesis, by comparing their methodology. As the results of the third work of this thesis, the study by Dretzke et al (2014) identified a different number of included studies in the eight systematic reviews. Some explanations were discussed, such as the different eligibility criteria among the analysed systematic reviews or the poor-quality reporting of the primary studies, which hampers the identification of studies to include in the systematic reviews (Dretzke et al, 2014).

Another study, Low et al (2017), also assessed the results of two systematic reviews, but those were performed by two different research centres. Both systematic reviews had the same research hypothesis, methods, resources and time (Low et al, 2017).

In general, the two systematic reviews agreed; however, some discrepancies were found, namely in the approach to synthesize and analyse the data and, consequently, in the results (Low et al, 2017). The study demonstrated that different authors using the same valid methodology to conduct a systematic review could retrieve different results, due the different interpretation of the available recommendations (Low et al, 2017).

Recently, Giang et al (2019) performed a survey to evaluate the methodology used by systematic reviews' authors. They developed a questionnaire based on the literature on how to conduct a systematic review and assessed the answers of systematic reviews' authors (Giang et al, 2019). Manual search, searching in grey literature, risk of bias assessment and data extraction are some of the methods that are still not performed by systematic reviews' authors (Giang et al, 2019). Although the availability of recommendations to conduct and/ or to perform a systematic review, the compliance on following their methodology continued to be suboptimal.

This third work has limitations. Despite several recommendations are available, only two recommendations were compared. However, based in the results of the second work of this thesis, the two selected recommendations were the most used to conduct and report a systematic review in drug's safety. An exploratory analysis was performed. This do not allow a proper comparison to prove equality (or difference) between the two recommendations/ systematic reviews. A new version (6.0) of the Cochrane Handbook for Systematic Reviews of Interventions was launched in July 2019 and was available online since October 2019 (Higgins et al, 2019). At the time of submission for publication of both systematic reviews and comparison among their methodology and results, the version in force was the 5.1 version (Higgins and Green, 2011). Therefore, the results of the systematic review performed according to the Cochrane Collaboration's recommendation are in line with the previous version of this guidance. By reviewing the differences from the previous version with the updated one, no major changes were performed to the chapter related with "adverse effects" (Higgins and Thomas, 2019). However, some improvements were performed in the construction of the research hypothesis, use of PICO strategy, identification of evidence (new approaches and explanation), preparation to synthesise evidence and meta-analysis, incorporation of the new scales of methodological quality and introduction of new chapters with new perspectives in systematic review, such as equity and complex interventions (Higgins and

Thomas, 2019). Since the focus of this thesis was to study systematic review in drug's safety, the changes in this recommendation do not affect the results of this thesis.

The fourth and the fifth works consisted in the elaboration of two systematic reviews according to the recommendations developed by the Centre for Reviews and Dissemination of University of York (Centre for Reviews and Dissemination, 2009) and the Cochrane Collaboration (Higgins and Green, 2011). These systematic reviews allowed to the comparison between the two most used recommendations and supported the third work of this thesis.

These works evaluated the association of the phosphodiesterase type 5 (PDE5) inhibitors intake with the development of nonarteritic ischaemic optic neuropathy (NAION). This hypothesis was identified through spontaneous reports and supported the safety alerts issued by three regulatory agencies. The association of these drugs with this clinical event is not yet established.

The major challenges on these systematic reviews were discussed in the third work and comprised the access to data and the assessment of methodological quality of included studies. A search for experimental and observational data was performed. Both systematic reviews did not find experimental evidence on this adverse drug reaction – suspected class of drugs pair. From the observational data, the same number of observational studies (n= 4) and spontaneous reports (n= 608) were identified; however, a different number of case reports (n= 50 vs. n= 52) were retrieved. Since the search literature was not performed in the same bibliographic databases for both systematic reviews, the number of included studies differ. Moreover, the access to some databases was difficult. In most cases, the databases are not publicly accessible. The same difference was observed in the methodological quality assessment of the included studies. Different tools were suggested in accordance with the two studied recommendations to conduct and/or to report a systematic review and most of them are not adapted to assess studies on drug's safety.

By applying meta-analysis, an association between PDE5 inhibitors and NAION was not found. Similar results were obtained when comparing these results with other reviews. A difference in these reviews and those performed in this thesis is in the type of included evidence. Drug's safety profile can be characterized by experimental and observational data (Strom, 2006). Common adverse drug reactions can be identified in pre-marketing setting; however, rare adverse drug reactions are identified in post-

marketing setting mainly through case and spontaneous reports (Strom, 2006). Therefore, in our systematic reviews, we selected all types of evidence in order to better characterize and answer to the research hypothesis.

These works have limitations. A previous protocol for these systematic reviews was not performed due the limited time of this thesis. These systematic reviews studied a rare adverse drug reaction. This has influence in the identification of studies reporting this adverse drug reaction. For example, in these reviews no experimental studies and only four observational studies were found. This has implications in the risk estimative. Another important limitation is the inherent bias associated with the study design. Several types of studies were searched, each one has specific characteristics and bias. In general, the studies have lower methodological quality. Some of these limitations are discussed in the third work.

Few recommendations to conduct and/ or to report a systematic review in drug's safety were published. Most of the available recommendations are focused on the combination of sources of information of higher methodological quality, such as RCTs that have homogenous characteristics (Mueller et al, 2018). This can advent some issues, namely in the choice of bibliographic databases to search other type of studies with lower methodological quality, but with high value in pharmacovigilance (e.g. case reports, spontaneous reports, …); and in the choice of the methodological quality scales to assess different study designs (Mueller et al, 2018). Golder et al (2014) compared the search strategies of systematic reviews of adverse drug reactions with other systematic reviews. The search strategies are inefficient for any type of systematic review; however, systematic reviews of adverse drug reactions included more data from different study designs (Golder et al, 2014). The same research group studied the reporting of adverse drug reactions in systematic reviews (Golder et al, 2016). They concluded that there is underreporting of adverse drug reactions and that most adverse drug reactions are described in unpublished studies (Golder et al, 2016). Other study evaluated the methodological quality assessment of observational studies in a sample of systematic reviews (Mallen et al, 2006). It was concluded that the methodological quality assessment of observational studies is not frequent and, in most times, a prespecified methodology is not used (Mallen et al, 2006). The same results were observed in the second work of this thesis. The majority of the methodological quality assessment scales are not prepared to assess studies reporting adverse drug reactions (Faillie et al, 2017).

These challenges can induce bias in the results of systematic reviews and, consequently, affect and influence systematic review' results and quality (Pussegoda et al, 2017b). Several studies assessed the bias of including different study designs in a systematic review, namely those related with the study design, risk of bias, selective reporting, confounding and meta-analysis (Higgins et al, 2013; Norris et al, 2013; Valentine and Thompson, 2013). Recommendations to conduct and/ or to report systematic reviews in drug's safety should include adequate search strategies in varied sources of information. In this thesis, four recommendations addressing drug's safety were identified and they suggested to search in several databases; however, few systematic reviews adhered to these recommendations when performing and/ or reporting a systematic review. Moreover, the four recommendations only suggested methodological quality scales to assess RCTs, clinical trials and observational studies, such as cohort studies and case-control studies. Tools to evaluate case reports and other type of study designs are not suggested.

Several initiatives have improved the reporting of systematic reviews. In 1999, a recommendation to report meta-analysis was developed (the QUORUM: Quality Of Reporting Of Meta-analyses) (Moher et al, 2009). Afterwards, there was a need to develop recommendations on the reporting of systematic reviews. In 2009, the PRISMA statement was developed and replaced the previous statement, QUORUM (Moher et al, 2009). Currently, PRISMA is a wide scale adopted recommendation and has extensions, this is, specific recommendations, such as on harms (Zorzela et al, 2016). Other initiatives include journals recommendations on the submission of systematic reviews or on the peer review of systematic reviews (Li and Bartley, 2014; Moher, 2015). Some of them adhered to PRISMA and other still recommended the adoption of a recommendation to conduct a systematic review (Li and Bartley, 2014; Moher, 2015). This can improve systematic reviews methodological quality. Despite these initiatives, several studies demonstrated the suboptimal compliance of systematic reviews to these recommendations (Page and Moher, 2017). Page and Moher (2017) evaluated studies assessing the adherence of systematic reviews to reporting and methodological quality recommendations. From the analysed systematic reviews, 67% did not follow nine items (of 27 items) of the PRISMA, this is, one third of the steps described in this recommendation (Page and Moher, 2017).

Systematic reviews in drug's safety could benefit from a single recommendation to conduct and/ or to report a systematic review. To adopt the same methodology may

improve systematic reviews' quality. Some methodological aspects need further research. Strategies to search several sources of information to retrieve drug's safety data and access to this data should be defined. Moreover, methodological quality scales to assess observational data related with drug's safety should be developed. Finally, how to best combine data from different study designs should be improved.

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Chapter 9 – Conclusions

This thesis evaluated if the current recommendations to conduct and/ or to report a systematic review are prepared to be used in drug's safety. It aimed to identify the strengths and limitations of the available recommendations and to understand how to perform and report a systematic review by combining several types of study designs. In order to answer to these questions, this work was divided into four stages. A summary of the main findings is described below.

- There are several recommendations to conduct and/ or to report a systematic review in medical literature. To assess drug's safety, four recommendations are available. They are the "Cochrane Handbook for Systematic Reviews of Interventions", "Systematic Reviews' CRD guidance for undertaking reviews in healthcare", "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" and the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) Harms.

- A sample of systematic reviews addressing drug's safety in Ophthalmology were studied. Their methodology varied, namely in the recommendation adopted, in the search literature, in the type of study designs included, in the methodological quality assessment, and in the data analysis. Nonetheless, although none of the systematic reviews followed a specific recommendation adapted to study drug's safety, the inclusion of different study designs was observed in some systematic reviews.

- The methodology of the two most used recommendations to conduct and/ or to report a systematic review in drug's safety were compared by performing two systematic reviews. Some challenges were found. The access to the information and the methodological quality assessment scales are insufficient. These issues reflected the results of both systematic reviews. The number of included studies was different. The recommended methodological quality scales only assessed experimental and observational studies, excluding observational data such as case and spontaneous reports.

- Two systematic reviews were conducted according to the two most used recommendations. The research hypothesis was the same for both systematic reviews. Several types of evidence, such as experimental and observational, were searched. The number of included studies and their methodological quality assessment differed. Both systematic reviews did not find a statistical association between the ophthalmic adverse drug reaction and the suspected drugs.

Some challenges were found when developing this thesis. To perform and to report a systematic review in drug's safety is still a subject in research. Few research groups study the methodology of systematic reviews in drug's safety. Moreover, few scientific journals published research on systematic reviews' methodology. Nonetheless, some studies and initiatives have already been reported and complement the results of this thesis. These works were described and discussed in the previous section.

Systematic reviews methodology has become well established. Several research groups are entirely dedicated to this. However, the role of the systematic review in drug's safety is not yet well defined. There are few recommendations to conduct and/or to report a systematic review in drug's safety and their methods are still in development.

Several issues need further research. There are no strategies to search several sources of information to retrieve data on drug's safety. It is also important to understand how better combine data from different study designs. In addition, the available methodological quality scales are not prepared to evaluate study designs such as case reports, spontaneous reports or some designs of observational studies, which are important studies in drug's safety.

The methodology to report a systematic review is well characterized and defined, mostly due the role of PRISMA in developing and updating its guidelines and their adoption by most scientific journals when publishing a systematic review.

The reinforcement of the use of recommendations to conduct and/ or report a systematic review in drug's safety is still of major importance. In order to avoid bias and misleading information provided by the methodological differences identified in the available recommendations, systematic reviews in drug's safety may benefit from a single recommendation to conduct and/or to report it.