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Interventions for Age-Related Macular Degeneration

Are Practice Guidelines Based on Systematic Reviews?

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Purpose: Are existing systematic reviews of interventions for age-related macular degeneration incorporated into clinical practice guidelines?

Design: High-quality systematic reviews should be used to underpin evidence-based clinical practice guidelines and clinical care. We examined the reliability of systematic reviews of interventions for age-related macular degeneration (AMD) and described the main findings of reliable reviews in relation to clinical practice guidelines.

Methods: Eligible publications were systematic reviews of the effectiveness of treatment interventions for AMD. We searched a database of systematic reviews in eyes and vision without language or date restrictions; the database was up to date as of May 6, 2014. Two authors independently screened records for eligibility and abstracted and assessed the characteristics and methods of each review. We classified reviews as reliable when they reported eligibility criteria, comprehensive searches, methodologic quality of included studies, appropriate statistical methods for meta-analysis, and conclusions based on results. We mapped treatment recommendations from the American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPPs) for AMD to systematic reviews and citations of reliable systematic reviews to support each treatment recommendation.

Results: Of 1570 systematic reviews in our database, 47 met inclusion criteria; most targeted neovascular AMD and investigated anti–vascular endothelial growth factor (VEGF) interventions, dietary supplements, or photodynamic therapy. We classified 33 (70%) reviews as reliable. The quality of reporting varied, with criteria for reliable reporting met more often by Cochrane reviews and reviews whose authors disclosed conflicts of interest. Anti-VEGF agents and photodynamic therapy were the only interventions identified as effective by reliable reviews. Of 35 treatment recommendations extracted from the PPPs, 15 could have been supported with reliable systematic reviews; however, only 1 recommendation cited a reliable intervention systematic review. No reliable systematic review was identified for 20 treatment recommendations, highlighting areas of evidence gaps.

Conclusions: For AMD, reliable systematic reviews exist for many treatment recommendations in the AAO PPPs and should be cited to support these recommendations. We also identified areas where no high-level evidence exists. Mapping clinical practice guidelines to existing systematic reviews is one way to highlight areas where evidence generation or evidence synthesis is either available or needed. *Ophthalmology 2016;■:1–14 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Age-related macular degeneration (AMD) is the leading cause of severe vision loss among people older than 65 years in industrialized countries.[1,2] This disease can be divided into 2 basic subtypes: neovascular (wet) AMD and nonneovascular (dry) AMD. Neovascular AMD is characterized by choroidal neovascularization, in which formation of abnormal blood vessels leads to subretinal and intraretinal macular edema, hemorrhage, fibrosis, or a combination thereof causing rapid central vision loss. In nonneovascular AMD, because of the gradual loss of photoreceptors and development of geographic atrophy, vision decreases slowly over many years. With no effective treatment available, patients with nonneovascular AMD are usually followed up to detect and treat complications, such as development of neovascular AMD.

For decades, laser photocoagulation was the only available treatment for neovascular AMD, yet other treatments have been the subject of research, including radiotherapy, interferon α, and photodynamic therapy; of these, photodynamic therapy received regulatory approval in April 2000.[3] More recently, treatments focusing on the neutralization of vascular endothelial growth factor (VEGF) by injecting antibodies (bevacizumab), antibody

http://dx.doi.org/10.1016/j.ophtha.2015.12.004
ISSN 0161-6420/16

fragments (ranibizumab), or fusion proteins (aflibercept) into the vitreous of the eye have become the current standard of care for neovascular AMD.[4]

Systematic reviews are summaries of the best research evidence available to address a specific question and follow explicit eligibility criteria and methods.[5] Because systematic reviews underpin evidence-based clinical practice guidelines, it is important that they are trustworthy and at low risk for bias, yet we know that this is not always the case.[6] For example, an author who has a potential conflict of interest may influence research conclusions,[7] or multiple reviews of the same topic may represent unnecessary duplication of effort and prove confusing if the review authors reach different conclusions. Some reasons for differing conclusions are understandable, for example, when the studies synthesized in systematic reviews were conducted during dissimilar periods or included different types of study designs.[8] But sometimes differing conclusions can be ascribed to the use of systematic review methods that potentially are subject to bias.[9]

The best practice for the development of clinical practice guidelines involves the integration of high-quality systematic reviews.[6] To accomplish this goal, guideline developers can elect to undertake a systematic review in house, commission a third party to conduct a systematic review, use results from previously completed systematic reviews, or implement a combination of these methods. The objectives of this study were (1) to identify all published systematic reviews in the area of eyes and vision that had examined the treatment of AMD, (2) to assess the reliability of existing reviews, and (3) to map clinical practice guideline recommendations to reliable systematic reviews to encourage the integration of reliable systematic reviews and clinical practice guideline recommendations.

Methods

Identification of Systematic Reviews of Interventions for Age-Related Macular Degeneration

The search strategies and definition used for systematic reviews have been published.[10,11] Our searches used no language or date restrictions and were up to date as of May 6, 2014. Systematic reviews eligible for this study had examined interventions for AMD; we excluded reviews concerned only with AMD etiology diagnosis, prognosis, and cost-effectiveness of treatment. Furthermore, to be eligible, reports of systematic reviews had to be full-text journal articles representing "a scientific investigation that addressed a focused question and used explicit, pre-specified scientific methods to identify, select, assess, and summarize similar but separate studies."[5,12] Systematic reviews were eligible regardless of whether meta-analyses were performed; however, we considered articles that described a meta-analysis only, without a systematic review component, to be ineligible because we could not be sure they were based on a systematic review. For eligible reviews with multiple published versions, such as updated or copublished Cochrane reviews, we included the most recent publication.

We used a 2-stage screening process to identify eligible systematic reviews. First, 2 individuals independently screened the titles and abstracts of all 1570 reviews listed in our database of systematic reviews in eyes and vision as of May 6, 2014. Next, for all records classified as potentially relevant, 2 individuals independently reviewed each full-text report for eligibility. We resolved discrepancies at each stage through discussion.

Assessment of Systematic Reviews of Interventions for Age-Related Macular Degeneration

For each eligible systematic review, 2 individuals independently abstracted data from the review onto an electronic data collection form developed, pilot tested, and maintained in the Systematic Review Data Repository.[13] This form was adapted from components of the Critical Appraisal Skills Programme,[14] the Assessment of Multiple Systematic Reviews,[15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16]; we have used the form in other studies.[9,17] We extracted data related to review objectives, populations, interventions, outcomes, methods (e.g., eligibility criteria for selection of studies for the systematic review, search strategies for eligible studies, assessment of risk of bias in included studies), results, conclusions, and financial support. When a meta-analysis was conducted, we also abstracted data on the statistical methods used. We resolved any discrepancy in data abstraction through discussion.

Based on previously published criteria[9] and standard systematic review methodology,[5,6,14–16] we classified reviews as reliable when they reported (1) defined criteria for selection of studies, (2) comprehensive searches for eligible studies, (3) assessment of risk of bias in included studies, (4) appropriate statistical methods for meta-analysis, and (5) agreement between the results and conclusions. We considered searches to be comprehensive when 3 or more bibliographic databases were searched, at least 1 method of other searching was used (e.g., handsearching conference abstracts, identifying ongoing trials, screening reference lists of included studies), and search results were not limited to English language only.[5] When 1 or more of these criteria were not met, we classified reviews as being unreliable.

We conducted descriptive analyses of review characteristics and estimated proportions of reliable reviews. We conducted a prespecified subgroup analysis by whether the systematic review was a Cochrane review. Furthermore, we explored characteristics of systematic reviews when more than 1 addressed the same research question.

Mapping Clinical Practice Guideline Recommendations to Systematic Review Evidence

We extracted treatment recommendations from the 2015 American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPPs) on management of AMD.[18] We included only recommendations related to the effectiveness of treatment interventions (i.e., recommendations related to diagnosis and follow-up were excluded) and recorded the section of the AAO PPP where we found each recommendation.

We mapped the treatment recommendations to systematic reviews identified by our study and assessed whether reliable systematic reviews were available to address each treatment recommendation and, if so, whether they were cited by the AAO PPP. We also assessed whether sources of evidence were provided with each treatment recommendation and, when provided, categorized each cited reference as a systematic review, randomized controlled trial, or other study type.