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Gaps in current knowledge and priorities for future research in dry eye

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Abstract

Purpose—Dry eye, a common, yet under-recognized and evolving field, has few recommended treatment algorithms, mostly based on expert consensus rather than robust research evidence. There are high costs associated with managing dry eye and conducting research to identify effective and safe long-term treatments. To support evidence-based management of dry eye, our purpose was to identify and prioritize important clinical research questions for future clinical research.

Methods—We translated recommendations from the American Academy of Ophthalmology's 2013 Preferred Practice Patterns for dry eye into answerable clinical research questions about treatment effectiveness. Clinicians around the world who manage patients with dry eye rated each question's importance from 0 (not important) to 10 (very important) using a two-round online Delphi survey. We considered questions as “important” if 75% of respondents assigned a rating of 6 or more in Round 2. We mapped the identified important clinical research questions to reliable systematic reviews published up to March 2016.

Results—Seventy-five clinicians from at least 21 countries completed both Delphi rounds. Among the 58 questions, 24 questions met our definition of “important”: 9/24 and 7/24 addressed topical and systemic treatments, respectively. All four questions with the highest 25th percentiles addressed topical treatments. While 6/24 “important” questions were associated with four existing reliable systematic reviews, none of these reviews came to a definitive conclusion about treatment effectiveness.

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CONFLICTS OF INTEREST

None

Conclusion—We identified gaps pertaining to treatment options for dry eye. Future clinical research on the management of dry eye should strongly consider these prioritized questions.

INTRODUCTION

Dry eye is a common ocular surface condition with prevalence around the world ranging from 7% to 33%, depending on the definition of the condition and the age of the population studied.¹ Dry eye has a significant negative impact on patient quality-of-life due to ocular discomfort and symptoms of fluctuating vision.² Estimates suggest that more than 60% of patients with severe dry eye symptoms use artificial tears, while only less than 30% use medicated drops.³ In the United States, managing dry eye costs the healthcare system \$3.8 billion annually; but when indirect costs such as reductions in productivity also are considered, the annual cost increases to \$55.4 billion.⁴

There are only a few recommended treatment algorithms for dry eye, most of which are based on expert consensus rather than robust research evidence.^{2,5,6} Expert consensus recommendations might be susceptible to personal preferences and/or biases of the guideline development committee members. Another major challenge with the state of the current evidence for dry eye treatments is that most clinical trials have focused on demonstrating improvements in short-term outcomes, as needed for regulatory approval.^{2,5} Dry eye is a chronic condition, however. Decision-makers such as clinicians and patients need reliable scientific information about the longer-term benefit and harms associated with these treatments.

Information about treatment benefit and harms is best obtained through comparative effectiveness research (i.e., randomized controlled trials (RCTs) and systematic reviews of RCTs) that addresses specific unanswered questions in a fashion that minimizes bias. Comparative effectiveness research, however, costs a considerable amount of resources and time. The scientific community needs to prioritize which research gets done first. Various approaches to prioritizing research have been examined by our group and others, involving the use of systematic reviews,^{7–10} clinical practice guidelines (CPGs),^{8,9,10,11} surveys,¹² and discussion forums.¹³ Within the field of ophthalmology, our group has developed and tested an approach for generating and prioritizing research questions using CPGs and clinical specialist-informants.^{8,9,12,14} We call this approach “E-Gap” (Evidence Gap). Thus far, we have tested it with clinicians in three eye conditions: primary open angle glaucoma,^{8,9} primary angle closure glaucoma,¹² and diabetic retinopathy.¹⁴ Other E-Gap projects are underway, for example, in age-related macular degeneration (AMD). Briefly, for each of these conditions, we extract recommendation statements related to treatment effectiveness and safety from CPG documents (Preferred Practice Patterns or PPPs) issued by the American Academy of Ophthalmology (AAO), translate those statements into answerable clinical questions, and use Delphi surveys to prioritize those clinical questions through consultation with clinicians who manage patients with that condition. Finally, we evaluate whether up-to-date, reliable systematic reviews that address the prioritized questions are available and, if not, we include the question in our list of priority topics for Cochrane systematic reviews.

Our objective in this study was to identify and prioritize important clinical research questions for future clinical research of the management of patients with dry eye.

METHODS

The seven key steps of this application of the E-Gap framework to identifying important clinical research questions for systematic reviews of dry eye are listed in Box 1. The Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health approved this study (IRB # JHSPH 2709).

Step 1: Identification of recommendation statements and relevant patient subgroups

We considered recommendations about management of patients with dry eye to be eligible for our study. We excluded statements that were recommendations about etiology, pathophysiology, diagnostic testing, or other topics unrelated to management. From the 2013 AAO PPP on dry eye,¹⁵ two individuals independently extracted all verbatim text that could be considered as containing a recommendation for the management of patients with dry eye. We resolved all differences in extracted information through discussion. For each recommendation, we also abstracted the patient subgroup(s) to which the recommendation applied, including mild dry eye, moderate dry eye, severe dry eye, evaporative dry eye, and aqueous deficient dry eye.

Step 2: Translating the 2013 PPP recommendation statements into answerable clinical research questions

We initially translated all recommendation statements into answerable clinical research questions. To ensure accuracy and completeness, one clinician (E.K.A.) reviewed the research questions, editing them as appropriate. Supplemental Digital Content Appendix 1 lists the final research questions derived from the PPP that we asked recipients to prioritize in our survey.

Step 3: Identification of survey recipients (clinicians managing patients with dry eye)

We surveyed members of the Tear Film and Ocular Surface Society (TFOS, www.tearfilm.org), an international (90-country) non-profit organization headquartered in the United States.¹⁶ TFOS's mission is threefold: to (1) "advance the research, literacy, and educational aspects of the scientific field of the tear film and ocular surface;" (2) "organize and coordinate international conferences, meetings, workshops, seminars and events to promote better understanding of the tear film and ocular surface;" and (3) "stimulate interactions among members, and attract new members with diverse disciplinary interests and expertise (e.g., basic scientists, academic clinicians and industry representatives) into the field of the tear film and ocular surface."¹⁶ Membership to TFOS is free, and membership is open to clinicians as well as non-clinicians, although most members are clinicians (Dr. David Sullivan, personal communication). TFOS maintains a list-serv with email addresses of its members, 93% of whom are based in North America or Europe.

Step 4: Round 1 of the Delphi Survey

We developed an online survey instrument using Qualtrics® (Qualtrics, Provo, Utah). In September 2016, the Executive Director of TFOS (Ms. Amy Gallant Sullivan) emailed the members of TFOS a link to the survey. We asked members whether they manage patients with dry eye, restricting participation in the survey to members who responded to that question affirmatively. We informed recipients that completing Round 1 of the survey likely would take approximately one hour. The initial email invitation was followed four weeks later by one reminder email from E.K.A. to enhance participation. We accepted responses to Round 1 up to six weeks after the first email announcement.

In Round 1 of the Delphi survey, we asked respondents three groups of questions: (1) demonstration that respondents understood the purpose of the survey; (2) respondent characteristics and email addresses; and (3) ratings of the importance of each of the 58 clinical research questions (see Supplemental Digital Content Appendix 1).

Once respondents demonstrated an understanding of the purpose of the survey, the survey tool presented each of the 58 research questions individually. As a part of each research question, recipients were instructed to: “Rate the importance of having an answer from research for the following clinical question” (see Supplemental Digital Content Appendix 2). The research question was then listed, followed by the relevant patient subgroup(s) to which the question applied. Recipients were asked to provide their rating of the question by selecting one of 11 radio buttons, ranging from 0 (“not important at all”) to 10 (“highly important”). The radio button for 5 pertained to “moderately important”. The survey respondent had the option to select the option “No judgement” and progress to the next question. Irrespective of their response to a particular research question, respondents could comment on the research question in a free-text box immediately following each question.

Step 5: Round 2 of the Delphi Survey

For Round 2 of the Delphi survey, which followed the 6-week response period for Round 1, we compiled the ratings we received for each research question in Round 1 using (1) a histogram displaying the ratings along with a summary of all ratings for that question, including the median and interquartile range; and (2) an anonymized list of any comments made by respondents to the question.

In November 2016, E.K.A. emailed all TFOS members who completed Round 1 with a link to Round 2 of the survey. This was followed four weeks later by one reminder email from E.K.A.

In Round 2 of the survey, we asked respondents to re-rate each of the 58 research questions by taking into account their own responses and those of their peers during Round 1 (i.e., the histogram, ratings summary, and anonymized comments). As in Round 1, we accepted responses to Round 2 up to 6 weeks after the first email announcement regarding Round 2. We communicated to recipients that completing Round 2 of the survey would take approximately one hour. Respondents were not compensated for their time spent on either of the two Delphi rounds.

Step 6: Identification of important research questions

Because the distributions of ratings of the importance of each research question were unlikely to be normally distributed, we analyzed the median, interquartile range, and range for each question. We constructed box plots displaying the minimum, 25th percentile, median, 75th percentile, and maximum of the ratings for each question in Round 2. Based on prior work of our research group,^{12,14} we considered as “important” all questions to which at least 75% of respondents assigned a rating of 6 or higher. Similarly, we considered as “moderately important” all questions to which at least 75% of respondents assigned a rating of 5 or higher.

Step 7: Mapping of the important research questions to existing reliable systematic reviews

To identify which of the important research questions that we identified in Step 6 (i.e., those for which at least 75% of respondents assigned a rating greater than 6) truly represent research needs, we examined whether each important research question was associated with existing reliable systematic review evidence.

To identify reliable systematic reviews, we first searched for systematic reviews addressing dry eye using our existing up-to-date (as of March 2016) database of eyes and vision systematic reviews. Next, two individuals (I.J.S. and a Cochrane methodologist Ms. Sueko Ng) independently assessed the reliability of each eligible systematic review based on five criteria: (1) explicit eligibility criteria for including studies; (2) comprehensive searches for studies; (3) assessment of risk of bias of included studies; (4) appropriate methods for meta-analysis, when conducted; and (5) conclusions supported by results of the review. We considered a systematic review to be reliable only if *all* five criteria were met.

We analyzed all data using STATA Version 14 (StataCorp, College Station, TX).

RESULTS

Steps 1 and 2: Identification and translation of the 2013 PPP recommendation statements into answerable clinical research questions

From the 2013 AAO PPP on dry eye, we identified 58 recommendations for the management of patients with dry eye. Supplemental Digital Content Appendix 1 lists the 58 answerable clinical research questions we translated from the recommendations and the treatment type and relevant patient subgroup(s) of interest for each. Seventeen of the questions (29%) addressed topical treatments, 16 (28%) addressed surgical treatments, 8 (14%) addressed systemic treatments, 7 (12%) addressed environmental/exogenous/educational treatments, 5 (9%) addressed general treatments (e.g., combinations of treatments), and 5 (9%) addressed other treatments (e.g., spectacles, contact lenses).

Steps 3 to 6: Identification of survey recipients, Rounds 1 and 2 of the Delphi Survey, and Identification of important research questions

Respondent characteristics—In September 2016, there were 5,927 members of TFOS who were invited to participate in the Round 1 Delphi survey. Among these members, the

email invitation was opened by 2,001 members (33.8%), of which 199 members (10.0%) clicked through to the website that contained further information and asked for consent for participation in the study. Among the 199, 108 respondents (54.3%) completed Delphi Round 1. Seventy-five of the 108 respondents to Round 1 (69.4%) completed Delphi Round 2 (i.e., both rounds).

Supplemental Table 1 lists the self-reported characteristics of all survey respondents, by whether they completed Delphi Round 1 or both rounds. Two-thirds of respondents who completed both rounds (67%) were between the ages of 30 and 59 years, inclusive. Round 2 respondents were from at least 21 countries, and involved a higher proportion of respondents from North America than Round 1 (43% vs. 34%). Almost half (44%) and almost one-third (29%) of Round 2 respondents indicated that their primary type of current practice was “Academic center/University” and “Self-employed/Private practice”, respectively.

Respondent familiarity with evidence-based practice—Equal proportions (approximately one-third each) of Round 2 respondents had served as an investigator on 6 trials, 1–5 trials, and no trials. Approximately one-third of Round 2 respondents (37%) had authored a systematic review, while approximately two-third (76%) used systematic reviews to guide their treatment decisions.

Research questions identified as “important” and “moderately important”—Figure 1 displays the interquartile range (boxes) and range (whiskers) of the ratings assigned to each of the 58 clinical research questions during Delphi Round 2, in decreasing order of the 25th percentile. Out of the 58 questions, 48 (83%) were assigned a rating of 5 or higher by at least 75% of respondents. Of these 48 questions, 24 (50%) were classified as “important” (i.e., at least 75% of respondents assigned a rating of 6 or higher) and 24 (50%) were classified as “moderately important” (i.e., at least 75% of respondents assigned a rating of 5 or higher).

Among the 24 research questions classified as “important”, 9 (38%) addressed topical treatments; 7 (29%) addressed systemic treatments; 4 (17%) addressed environmental/exogenous/educational treatments; 2 (8%) addressed general treatments (e.g., omega-3 fatty acids); 1 (4%) addressed surgical treatments; and 1 (4%) addressed other treatments (contact lenses). Of note, each of the four research questions with the highest 25th percentiles (i.e., where at least 75% of respondents rated the importance as 8 or higher) addressed topical treatments (three addressed autologous serum drops and one addressed topical anti-inflammatory agents). For these four questions, 1/4 respondents rated the question as 10 (“highly important”).

All 24 “important” research questions were relevant to patients with mild dry eye, and all but one of the questions were also relevant to patients with moderate or severe dry eye. Half of the questions (12/24) were relevant to patients with evaporative dry eye, and one-sixth of the questions (4/24) were relevant to patients with aqueous deficient dry eye.

Step 7: Mapping of the important research questions to existing reliable systematic reviews

When we searched our eyes and vision systematic reviews database, 7/20 systematic reviews addressing dry eye (40%) were classified as reliable.^{17–23} We found that 3/7 were Cochrane reviews.

We mapped 6/24 important research questions (25%) to reliable systematic review evidence. None of these systematic reviews came to definitive conclusions regarding one treatment being superior to another in terms of effectiveness, however.

Autologous serum tears—We mapped three questions related to autologous serum tears (Question 42 [Rank Order 2], Question 43 [Rank Order 3], and Question 44 [Rank Order 4]) to a reliable 2013 Cochrane systematic review of the effectiveness of autologous serum tears compared with artificial tears or saline.¹⁸ The review authors identified four RCTs examining a total of only 72 patients with dry eye of various etiologies (Sjögren’s-related, non-Sjögren’s related, and dry eye induced by laser-assisted in-situ keratomileusis [LASIK]), and concluded that there was inconsistency in the possible benefits of autologous serum.¹⁸

Topical cyclosporine A—We mapped one question related to topical cyclosporine A (Question 24 [Rank Order 1]) to a reliable 2013 systematic review of the effectiveness of cyclosporine A compared with artificial tears and/or vehicle.²¹ The review authors identified 18 RCTs examining a total of 2,479 patients. The authors concluded that while topical cyclosporine A appeared to be safe, the evidence from the RCTs precluded any definitive conclusions about the drug’s effectiveness for two main reasons. First, meta-analyses could not be conducted because the outcome domains, specific measurements, and time-points for were not consistently reported across the RCTs. Second, the RCTs included patients with dry eye with considerably variable clinical presentations, including Sjögren’s-related, non-Sjögren’s related, and evaporative dry eye of different severities.²¹

Oral omega-3 fatty acids—We mapped one question related to oral omega-3 fatty acids (Question 26 [Rank Order 5]) to a reliable 2014 systematic review of the effectiveness of oral omega-3 fatty acids compared with control interventions such as corn oil and placebo capsules.²³ The review included nine RCTs examining 716 patients with either Sjögren’s Syndrome or xerophthalmia. The review authors concluded that while there was no evidence of benefit from oral omega-3 fatty acids with regard to tear volume, ocular surface stability, and tear film staining, patients receiving this treatment appeared to fare better in terms of ocular symptoms (measured through the ocular surface disease index) when compared with patients receiving control interventions.²³

Artificial tears—We mapped one question related to artificial tears (in the form of emulsions, gels, or ointments) (Question 6 [Rank Order 18]) to a reliable 2014 Cochrane systematic review of the effectiveness of over-the-counter artificial tears compared with another class of over-the-counter artificial tears, no treatment, and/or placebo.¹⁹ The review included 43 RCTs examining 3,497 patients with dry eye of various etiologies. The authors

concluded that while over-the-counter artificial tears were generally safe, there was considerable uncertainty regarding the form of artificial tears that works best for treating dry eye symptoms. The uncertainty mainly arose from the included RCTs being too heterogeneous in terms of study characteristics, patient characteristics, and outcomes reported to allow the conduct of informative meta-analyses.¹⁹

DISCUSSION

Using a two-round Delphi survey of 75 clinicians from at least 21 countries who manage patients with dry eye, we identified 24 important clinical research questions for clinical research. All but one of the 24 questions were relevant for patients with mild, moderate, and severe forms of dry eye. Among the 24 important questions, only six (25%) have been examined by reliable systematic reviews and, importantly, none of the reviews came to a definitive conclusion about the clinical effectiveness of the treatments studied. The four questions that were determined to be most important addressed topical treatments (three addressed autologous serum drops and one addressed topical anti-inflammatory agents).

Our study has important implications because current treatments for dry eye, a very common symptom associated with various etiologies, are not based on strong scientific evidence. Given the scarcity of data regarding the long-term efficacy and safety outcomes of available treatment modalities, these treatments may be failing to ameliorate symptoms of dry eye in the long run.

Dry eye causes a substantial economic burden on society. In the United States, the average annual cost of managing dry eye has been estimated to be \$3.4 billion overall.⁴ In today's resource-constrained environment, such high costs of treatments with unproven effectiveness call for urgent research prioritization efforts. The important clinical research questions identified in our study represent opportunities for the dry eye community to conduct clinical research that could make the greatest impact on clinical practice. Such clinical research includes both systematic reviews and clinical trials. In instances where systematic reviews demonstrate that the clinical trial evidence for a given question is either insufficient or inconsistent, as was often the case during this study, funders of research must seek redress by supporting high quality clinical trials, and by insisting that the methods²⁴ and results²⁵ of the clinical trials are reported in full.

The current study, which identifies clinician priorities for dry eye research, is an important first step towards making sure that the important questions are addressed by clinical research. We believe that the next step is to identify priorities that the entire community of decision-makers, including patients, clinicians, policymakers, funders, and other stakeholders want answered.

Strengths of study

Our study has several strengths. First, we used the Delphi method to formally survey a diverse group of clinicians managing a condition (dry eye) with variable severity. In Round 2 of the survey, clinicians provided their rating for each question in light of the distribution of ratings for that question by their peers. The anonymity of the responses and comments likely

allowed for honest ratings that were unbiased by dominant voices, a challenge commonly encountered during in-person group deliberations. Second, the clinicians surveyed in our study were diverse demographically, geographically, and with regards to their current type of clinical practice and area of vision-related clinical practice expertise. Also, most participants were familiar with evidence-based practice, two-thirds having served as investigators on clinical trials and three-fourths currently using systematic reviews to guide treatment decisions. Third, we mapped the identified important questions to existing reliable systematic reviews in the field of dry eye, thereby providing an up-to-date assessment of whether these questions have, in fact, already been addressed by research or whether evidence gaps exist.

Limitations of study

Our study has some limitations. First, we involved only clinicians in this process and recognize that it is possible that the ratings assigned to the research questions we identified might have been systematically different had we also included patients and other decision-makers. Second, although 2,001/5,927 TFOS members (33.8%) opened the invitation email, only 199/2,001 members (10.0%) clicked through to the website for information about the study. Of the 199, 108 members (54.3%) completed Round 1 of our Delphi Survey, and 75/199 members (37.7%) completed both rounds. Both the fact that we communicated that each of the Rounds would last approximately one hour and that participation would not be compensated could have contributed to the low response rate. In addition, it should be recognized that while we surveyed ophthalmologists and optometrists from around the world, all respondents were identified through one organization (TFOS). Third, we only reviewed the recommendations issued by the AAO, an ophthalmology-based professional society. It is possible that we may have missed some recommendations solely issued by optometry-based professional societies such as the American Optometric Association.

In summary, we identified 24 important research questions for dry eye (listed in Table 1), only six of which have been addressed by reliable systematic review evidence, although none of these reviews came to definitive conclusions. The four most important questions addressed topical treatments (three addressed autologous serum drops and one addressed topical anti-inflammatory agents). The four most important questions addressed topical treatments (three addressed autologous serum drops and one addressed topical anti-inflammatory agents). Those designing future clinical research for the management of patients with dry eye should strongly consider the questions prioritized in this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1**Steps of our study identifying and prioritizing research questions related to dry eye****Step 1: Identification of recommendation statements and relevant patient subgroups**

We reviewed the 2013 American Academy of Ophthalmology Preferred Practice Pattern (PPP) on dry eye and identified all clinical recommendations.

Step 2: Translation of 2013 PPP recommendation statements into answerable clinical research questions

We translated the statements into 58 answerable clinical research questions. A dry eye specialist (E.K.A.) reviewed and updated the questions as appropriate.

Step 3: Identification of survey recipients (clinicians managing patients with dry eye)

We identified members of the Tear Film and Ocular Surface Society (TFOS) as appropriate recipients of the two-round Delphi survey.

Step 4: Round 1 of the Delphi Survey

We asked TFOS members to assign each research question an importance rating of 0 (low) to 10 (high) in Round 1. Round 1 of the survey was completed by 108 respondents.

Step 5: Round 2 of the Delphi Survey

We sent Round 1 respondents the same 58 questions in Round 2, and asked respondents to assign each research question an importance rating of 0 (low) to 10 (high) again, this time after reviewing the distribution of ratings and comments on that question by themselves and their peers. Round 2 of the survey was completed by 75 respondents.

Step 6: Identification of important research questions

We considered a research question to be “important” if at least 75% of respondents to both rounds assigned a rating of 6 or greater in Round 2. We considered a research question to be “moderately important” if at least 75% of respondents to both rounds assigned a rating of 5 or greater in Round 2. We identified 24 “important” research questions.

Step 7: Mapping of the important research questions to existing reliable systematic reviews

We searched an existing updated database of systematic reviews of eyes and vision treatments, and mapped the 24 “important” research questions to six reliable systematic reviews. None of these six reviews came to definitive conclusions, however. We therefore identified 24 “important” clinical research questions unanswered by reliable systematic review evidence.

Figure 1. Box and whiskers plot displaying the ratings assigned to 58 dry eye clinical research questions by 75 Tear Film and Ocular Surface Society (TFOS) member respondents to Round 2 of our Delphi survey, sorted in decreasing order of the 25th percentile

- Y-axis – Ratings of importance assigned in Round 2 of the Delphi survey.
- X-axis – Question numbers, sorted from left to right in decreasing order of the 25th percentile of the rating assigned.
- Boxes – These correspond to the interquartile range (i.e., 25th to 75th percentile) of the rating assigned to each question in Round 2.
- Colors of the boxes –
 - Blue: At least 75% of respondents assigned a rating of 6 or higher (i.e., “important” questions)
 - Yellow: At least 75% of respondents assigned a rating of 5 or higher (i.e., “moderately important” questions)
 - Grey: Fewer than 75% of respondents assigned a rating of 5 or higher
- Whiskers – These correspond to the range (i.e., minimum to maximum) of ratings assigned to each question in Round 2.

Table 1

Important dry eye research questions (i.e., those where at least 75% of respondents assigned a rating of >6)

Rank Order	Type of Intervention	Question Number	Question	Rating	
				Median	(IQR) Range
1	Topical	24	Are topical anti-inflammatory agents such as cyclosporine and corticosteroids effective in treating patients with dry eye?	9	(8–10) (2–10)
2	Topical	42	Are autologous serum tears effective in treating patients with dry eye?	9	(8–10) (2–10)
3	Topical	43	Are autologous serum drops effective in improving ocular irritation in patients with Sjögren's syndrome or graft versus host disease and dry eye?	9	(8–10) (3–10)
4	Topical	44	Are autologous serum drops effective in improving ocular irritation, conjunctival and corneal dye staining in patients with Jorgen syndrome or graft versus host disease and dry eye?	9	(8–10) (2–10)
5	Systemic	26	Are oral omega-3 fatty acids effective in patients with dry eye?	9	(7–10) (0–10)
6	General	1	Is a specific sequence of treatments more effective than another sequence in treating patients with dry eye?	8	(7–9) (4–10)
7	General	2	Is a specific combination of treatments more effective than another combination in treating patients with dry eye?	8	(7–9) (4–10)
8	Systemic	13	Are systemic tetracyclines effective in patients with melibromianitis or rosacea and dry eye?	8	(7–10) (2–10)
9	Systemic	14	Are systemic anti-inflammatory agents effective in patients with dry eye and systemic disease such as rheumatoid arthritis?	8	(7–9) (3–10)
10	Systemic	15	Are systemic immunosuppressive agents effective in patients with dry eye and systemic disease such as rheumatoid arthritis?	8	(7–9) (0–10)
11	E/E/E*	16	Is patient education effective in treating patients with dry eye?	8	(7–10) (0–10)
12	E/E/E*	17	Are environmental modifications effective in treating patients with dry eye?	8	(7–9) (0–10)
13	Topical	25	Are topical anti-inflammatory agents effective alone or in addition to aqueous enhancement therapies in patients with dry eye?	8	(7–9) (3–10)
14	Systemic	27	Is adding systemic omega-3 fatty acids to other treatments more effective than other treatments alone in treating patients with dry eye?	8	(7–9) (5–10)
15	Surgical	56	Is amniotic membrane transplantation effective for treating patients with dry eye?	8	(7–9) (1–10)
16	Other	57	Are contact lenses effective in treating patients with dry eye?	8	(7–9) (1–10)
17	Systemic	45	Are systemic anti-inflammatory agents effective in patients with dry eye?	7	(7–8) (2–10)
18	Topical	6	Are artificial tears in the form of emulsions, gels, or ointments effective in treating patients with dry eye?	8	(6–9) (1–10)
19	Systemic	28	Are systemic anti-inflammatory agents effective in treating patients with dry eye?	8	(6–8) (1–10)
20	Topical	11	Is topical hyaluronic acid effective for patients with dry eye compared with other types of artificial tears?	7	(6–8) (1–10)

Rank Order	Type of Intervention	Question Number	Question	Rating		
				Median	(IQR)	Range
21	E/E/E*	20	Are environmental modifications effective in treating patients with dry eye?	7	(6–10)	(0–10)
22	E/E/E*	21	Does lowering the computer screen to below eye level to decrease lid aperture decrease discomfort associated with computer activities in people with dry eye?	7	(6–8)	(0–10)
23	Topical	40	Are topical mucolytic agents, such as 10% N-acetylcysteine used four times a day, effective in the treatment of filamentary keratopathy?	7	(6–9)	(0–10)
24	Topical	41	Is debridement effective in the treatment of filamentary keratopathy?	7	(6–8)	(2–10)

* E/E/E= Environmental/Exogenous/Educational