

Supplementary Online Content

Saldanha IJ, Lindsley KB, Lum F, Dickersin K, Li T. Reliability of the evidence addressing treatment of corneal diseases: a summary of systematic reviews. *JAMA Ophthalmol*. Published online May 9, 2019.
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eAppendix. Diseases, Interventions, Outcomes, and Number of Studies and Participants, and Conclusions of all 65 Reliable Systematic Reviews Addressing Corneal Diseases

This supplementary material has been provided by the authors to give readers additional information about their work.

Author (Year) ^{Ref}	Condition(s) addressed	Objectives	Type(s) of interventions	Outcomes	Number of included studies	Number of participants in included studies	Conclusion(s) from the abstract
Papaioannou (2016) ¹	Bacterial keratitis	"To assess the efficacy of corneal collagen cross-linking in the management of infectious keratitis"	Surgeries	Symptom resolution; Adverse events; Other outcomes	25	209	"Collagen cross-linking seems promising in the management of infectious keratitis, excluding viral infections."
Herretes (2014) ²	Bacterial keratitis	"To assess the effectiveness and safety of corticosteroids as adjunctive therapy for bacterial keratitis. Secondary objectives included evaluation of health economic outcomes and quality of life outcomes."	Medications	Visual acuity; Treatment success; Anatomic outcomes; Quality of life; Costs; Adverse events	4	611	"There is inadequate evidence as to the effectiveness and safety of adjunctive topical corticosteroids compared with no topical corticosteroids in improving visual acuity, infiltrate/scar size, or adverse events among participants with bacterial keratitis."
McDonald (2014) ³	Bacterial keratitis	"To evaluate the effectiveness of topical antibiotics in the management of bacterial keratitis"	Medications	Treatment success; Symptom resolution; Adverse events; Other outcomes	16	Not reported	"Results of this review suggest no evidence of difference in comparative effectiveness between fluoroquinolones and aminoglycoside–cephalosporin treatment options in the management of bacterial keratitis."
O'Gallagher (2017) ⁴	Blepharitis; conjunctivitis	"To assess and compare data on the efficacy and safety of topical treatments (including antibiotics, steroids, immunosuppressants and lubricants), alone or in combination, for blepharconjunctivitis (BKC) in children from birth to 16 years"	Medications	Visual acuity; Symptom improvement; Quality of life; Costs; Adverse events; Other outcomes	1	137	"There is no high-quality evidence of the safety and efficacy of topical treatments for BKC, which resulted in uncertainty about the indications and effectiveness of topical treatment. Clinical trials are required to test efficacy and safety of current and any future treatments. Outcome measures need to be developed which can capture both objective clinical and patient-reported aspects of the condition and treatments."
O'Gallagher (2016) ⁵	Blepharitis; conjunctivitis	"To assess and compare data on the efficacy and safety of systemic treatments (including antibiotics, nutritional supplements and immunosuppressants), alone or in combination, for blepharconjunctivitis (BKC) in children aged between zero to 16 years"	Medications	Visual acuity; Symptom improvement; Costs; Adverse events; Other outcomes	0	0	"Conjunctival limbal autograft (CLA) has better therapy efficacy against the recurrence of pterygium than mitomycin C."
Lindsley (2012) ⁶	Blepharitis	"To examine the effectiveness of interventions in the treatment of chronic blepharitis"	Medications; Other (Lid hygiene)	Symptom improvement; Quality of life; Costs; Adverse events	34	2169	"Despite identifying 34 trials related to treatments for blepharitis, there is no strong evidence for any of the treatments in terms of curing chronic blepharitis. Commercial products are marketed to consumers and prescribed to patients without substantial evidence of effectiveness. Further research is needed to evaluate the effectiveness of such treatments. Any RCT designed for this purpose should separate participants by type of condition (e.g. staphylococcal blepharitis or MGD) in order to minimize imbalances between groups (type I

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							errors) and to achieve statistical power for analyses (prevent type II errors). Medical interventions and commercial products should be compared with conventional lid hygiene measures, such as warm compresses and eyelid margin washing, to determine effectiveness, as well as head-to-head to show comparative effectiveness between treatments. Outcomes of interest should be patientcentered and measured using validated questionnaires or scales. It is important that participants be followed long-term, at least one year, to assess chronic outcomes properly."
van Zuuren (2015) ⁷	Blepharitis	"To assess the efficacy and safety of treatments for rosacea"	Medications	Quality of life; Adverse events; Other outcomes	106	13631	"There was high quality evidence to support the effectiveness of topical azelaic acid, topical ivermectin, brimonidine, doxycycline and isotretinoin for rosacea. Moderate quality evidence was available for topical metronidazole and oral tetracycline. There was low quality evidence for low dose minocycline, laser and intense pulsed light therapy and ciclosporin ophthalmic emulsion for ocular rosacea. Time needed to response and response duration should be addressed more completely, with more rigorous reporting of adverse events. Further studies on treatment of ocular rosacea are warranted."
Kam (2017) ⁸	Conjunctivitis	"To assess the safety and efficacy of topical olopatadine versus placebo and other topical anti-allergic medications in treating allergic conjunctivitis"	Medications	Symptom improvement; Adverse events	23	3388	"Trials included in this review suggest that treating simple corneal abrasions with a patch may not improve healing or reduce pain."
Castillo (2015) ⁹	Conjunctivitis	"To assess the effects of topical antihistamines and mast cell stabilisers, alone or in combination, for use in treating seasonal and perennial allergic conjunctivitis"	Medications	Symptom improvement; Adverse events; Other outcomes	30	Not reported	"It seems that all reported topical antihistamines and mast cell stabilisers reduce symptoms and signs of seasonal allergic conjunctivitis when compared with placebo in the short term. However, there is no long-term data on their efficacy."
Erekosima (2014) ¹⁰	Conjunctivitis	"To systematically review the effectiveness and safety of subcutaneous immunotherapy (SCIT) for treatment of allergic rhinoconjunctivitis and asthma, using formulations currently approved in the United States"	Medications	Symptom improvement; Quality of life; Costs; Adverse events; Other outcomes	61	3577	"Generally moderate to strong evidence supports the effectiveness of SCIT for treatment of allergic rhinitis and asthma, particularly with single-allergen immunotherapy regimens. Adverse reactions to SCIT are common, but no deaths were reported in the included studies."

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Compalati (2013) ¹¹	Conjunctivitis	"To identify in the most important databases, up to January 2013, the double-blind placebo-controlled randomized trials administering rupatadine in allergic rhinitis"	Medications	Symptom improvement; Adverse events; Other outcomes	10	2573	"Randomized double-blind controlled trials show a favorable risk–benefit ratio in rupatadine for the treatment of allergic rhino-conjunctivitis. This evidence is strengthened when data are pooled in the form of metaanalysis, where accurate and robust effect estimations are derived from a large population."
Gane (2013) ¹²	Conjunctivitis	"To assess the available evidence for an effect of leukotriene receptor antagonists (LTRAs) on the ocular symptoms of allergic eye disease"	Medications	Symptom improvement	18	Not reported	"In seasonal allergic conjunctivitis, LTRAs are more efficacious than placebo but less efficacious than oral antihistamines in adult patients."
Wan (2013) ¹³	Conjunctivitis	"To assess the efficacy and safety of topical cyclosporine versus placebo in the treatment of allergic conjunctivitis"	Medications	Symptom improvement; Adverse events	7	153	"This systematic review and meta-analysis suggests topical cyclosporine could be an effective and safe treatment method for allergic conjunctivitis."
Lin (2013) ¹⁴	Conjunctivitis	"To systematically review the effectiveness and safety of aqueous sublingual immunotherapy for allergic rhinoconjunctivitis and asthma"	Medications	Symptom improvement; Quality of life; Adverse events; Other outcomes	63	1814	"The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review."
Lin (2013) ¹⁵	Conjunctivitis	"To describe the effectiveness and safety of subcutaneous immunotherapy and sublingual immunotherapy (off-label use of subcutaneous-aqueous allergens for sublingual desensitization) compared with other therapies for treatment of allergic rhinoconjunctivitis and asthma"	Medications	Treatment success; Symptom improvement; Adverse events	142	Not reported	"With some variation across outcomes, the overall body of evidence consistently provides moderate to high support for the effectiveness and safety of both subcutaneous and sublingual immunotherapy for the treatment of allergic rhinitis and asthma. The evidence to support the use of immunotherapy in children is somewhat weaker than the evidence supporting its use in adults. The superiority of one route of administration over the other is not known."
Epling (2012) ¹⁶	Conjunctivitis	"To answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with"	Medications	Symptom improvement; Adverse events	44	Not reported	"In this systematic review we present information relating to the effectiveness and safety of the following interventions: ocular decongestants, oral antibiotics, parenteral antibiotics, saline, topical antibiotics, and warm compresses."

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		bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?"					
Sheikh (2012) ¹⁷	Conjunctivitis	"To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis"	Medications	Symptom resolution; Costs; Adverse events; Other outcomes	11	3673	"Although acute bacterial conjunctivitis is frequently self limiting, the findings from this updated systematic review suggest that the use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to the use of placebo. Use of antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection."
CADTH (2016) ¹⁸	Conjunctivitis	"To provide evidence on the efficacy, safety and cost-effectiveness of olopatadine, in comparison with ketotifen, cromolyn, or placebo to assist in the decision making with respect to these agents for the treatment of allergic conjunctivitis"	Medications	Costs; Adverse events; Other outcomes	12	1388	"According to the available data, we suggest that hinge location may have some effect on corneal sensation and dry eye syndrome after LASIK at the early postoperative period. However, there was no significant difference between the groups at 6 months after surgery. Further wellorganized, prospective, randomized studies involving more patients are warranted."
Calderon (2011) ¹⁹	Conjunctivitis	"To evaluate the efficacy of sublingual immunotherapy compared with placebo for reductions in ocular symptoms, topical ocular medication requirements and conjunctival immediate allergen sensitivity"	Medications	Symptom improvement; Other outcomes	42	3399	"Overall, sublingual immunotherapy is moderately effective in reducing total and individual ocular symptom scores in participants with allergic rhinoconjunctivitis and allergic conjunctivitis."
Jefferis (2011) ²⁰	Conjunctivitis	"To determine the benefit of antibiotics for the treatment of acute infective conjunctivitis in primary care and which subgroups benefit most"	Medications	Symptom improvement	3	814	"Acute conjunctivitis seen in primary care can be thought of as a self-limiting condition, with most patients getting better regardless of antibiotic therapy. Patients with purulent discharge or a mild severity of red eye may have a small benefit from antibiotics. Prescribing practices need to be updated, taking into account these results."
Roder (2008) ²¹	Conjunctivitis	"To systematically review randomized controlled trials (RCTs) to evaluate the effect of immunotherapy with inhalant allergens on symptoms and medication use in children and adolescents with allergic	Medications	Symptom improvement; Other outcomes	28	Not reported	"In conclusion, there is at present insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis."

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		rhinoconjunctivitis"					
Swamy (2007) ²²	Conjunctivitis	"To assess the effect of topical Non-Steroidal Anti Inflammatory drugs in the treatment of allergic conjunctivitis"	Medications	Symptom improvement; Symptom resolution	8	712	"This meta-analysis confirms that topical NSAID are significantly more effective at relieving the cardinal symptom: conjunctival itching and improving the cardinal sign: conjunctival injection than placebo treatment."
Sopo (2004) ²³	Conjunctivitis	"To evaluate the clinical efficacy of sublingual immunotherapy (SLIT) in respiratory allergy in children"	Medications	Symptom improvement; Other outcomes	8	372	"SLIT can be currently considered to have low to moderate clinical efficacy in children of at least 4 years of age, monosensitised to house dust mites (HDM), and suffering from mild to moderate persistent asthma. This benefit seems to be adjunctive with respect to the environmental preventive measures against HDM."
Owen (2004) ²⁴	Conjunctivitis	"To assess the effectiveness and relative efficacy of topical treatments for the management of seasonal allergic conjunctivitis"	Medications	Treatment success; Symptom improvement	40	Not reported	"Overall, these findings confirm the benefit of topical mast cell stabilisers and antihistamines over placebo for the treatment of allergic conjunctivitis."
Gonzalez-Lopez (2012) ²⁵	Conjunctivitis	"To determine the efficacy and gather evidence on safety from randomised controlled trials (RCTs) of topical CsA in patients with allergic keratonjunctivitis (AKC)"	Medications; Supplements	Symptom improvement; Quality of life; Adverse events	3	58	"This systematic review highlights the relative scarcity of controlled clinical trials assessing the efficacy of topical CsA therapy in AKC and suggests that evidence on the efficacy and safety of topical CsA treatment in patients with CsA remains limited. However, the data suggest that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. No serious adverse events were reported. Reported adverse events in patients treated with topical CsA include intense stinging and eyelid skin maceration. One patient in the placebo group developed a severe allergic response to maize antigens. However, the total number of patients in the trials was too small to assess the safety of this treatment. Additional well-designed and powered RCTs of topical CsA in AKC are needed. Ideal study designs should include adequate randomisation and concealment of allocation; masking of participants, personnel and outcome assessors; adequate follow-up periods and minimisation of attrition bias; and comparison groups with similar clinical and epidemiologic characteristics. Samples should be large enough to provide sufficient statistical power to assess the safety of CsA and to detect clinically relevant treatment effect sizes of the primary outcomes. Analyses should be

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							appropriate to the study's design and outcome measures. Moreover, standardisation of outcome measures and follow-up periods across studies would be beneficial to maximise study comparability."
Mantelli (2007) ²⁶	Conjunctivitis; Corneal edema/opacification	"To assess the efficacy of currently available topical drugs for vernal keratoconjunctivitis (VKC) through a meta-analysis of randomised clinical trials (RCTs)"	Medications	Symptom improvement	10	245	"The currently available topical drugs are effective in treating acute phases of VKC. However, there is a lack of evidence to support the recommendation of one specific type of medication for treating this disorder. There is a need for standard criteria to assess diagnosis and therapy based on severity. There is also a need for RCTs assessing long-term effects of single drugs to control the disease and to prevent complications."
Chen (2016) ²⁷	Corneal ectasia; Corneal edema/opacification	"To evaluate the efficacy and safety of deep anterior lamellar keratoplasty (DALK) compared with penetrating keratoplasty (PK) for patients who had corneal stromal pathologies without endothelial abnormalities"	Surgeries	Visual acuity; Adverse events	5	Not reported	"DALK is an alternative surgical procedure for corneal stromal pathologies without endothelial abnormalities, with lower efficacy but better safety."
Sykakis (2015) ²⁸	Corneal ectasia; keratoconus	"To assess whether there is evidence that collagen cross-linking (CXL) is an effective and safe treatment for halting the progression of keratoconus compared to no treatment"	Surgeries	Visual acuity; Anatomic outcomes; Quality of life; Costs; Adverse events; Other outcomes	3	444	"The evidence for the use of collagen cross-linking (CXL) in the management of keratoconus is limited due to the lack of properly conducted RCTs."
Fischer (2015) ²⁹	Corneal ectasia; keratoconus	"To analyse whether corneal implants are more or equally effective and safer than corneal transplantation or no intervention"	Devices; Surgeries	Visual acuity; Quality of life; Adverse events; Other outcomes	5	627	"The current evidence is not sufficient to prove that intrastromal corneal implants are equally or more effective and safe than corneal transplantation or no intervention for treating keratoconus or post-LASIK corneal ectasia. However, the comparison before and after the ring implantations of the single-arm studies have shown that the visual acuity has improved and that improvement has been clinically relevant in a large proportion of patients. Furthermore, the implantation of intrastromal corneal rings seems to be relatively safe and adverse events were minor."
Keane (2014) ³⁰	Corneal ectasia; keratoconus	"To compare visual outcomes after deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty for keratoconus, and to compare additional outcomes relating	Surgeries	Visual acuity; Visual function; Adverse events	2	111	"We found no evidence to support a difference in outcomes with regards to best-corrected visual acuity (BCVA) at three months post-graft or at any of the other time points analysed."

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		to factors which may contribute to poor visual outcomes (e.g. astigmatism, graft rejection and failure)"					
Health Quality Ontario (2009) ³¹	Corneal ectasia; keratoconus	"To determine the role of corneal implants in the management of corneal thinning disease conditions"	Devices	Treatment success; Quality of life; Adverse events	10	609	"Information on the durability of the implants' treatment effects and their affects on underlying disease processes is limited. This information is becoming more important as alternative treatment strategies, such as collagen cross-linking aimed at strengthening the underlying corneal tissue, are emerging and which might prove to be more effective or increase the effectiveness of the implants, particularly in advances stages of corneal thinning."
Nanavaty (2014) ³²	Corneal edema/opacification	"To compare the benefits and complications related to two surgical methods (endothelial keratoplasty (EK) and penetrating keratoplasty (PKP)) of replacing the diseased endothelial layer of the cornea with a healthy layer in people with Fuchs endothelial dystrophy (FED)"	Surgeries	Visual acuity; Anatomic outcomes; Quality of life; Costs; Adverse events; Other outcomes	3	136	"The rapid growth of endothelial keratoplasty as the treatment of choice for FED is based upon the belief that visual recovery is more rapid, surgically induced astigmatism (regular and irregular) is less and rates of transplant rejection are lower with EK. This change in practice also assumes that the rates of long term transplant survival are equal for the two procedures. The practical differences between the surgical procedures mean that visual recovery is inherently more rapid following EK, but this review found no strong evidence from RCTs of any difference in the final visual outcome between EK and PKP for people with FED. This review also found that higher order aberrations are fewer following EK but endothelial cell loss is greater following EK. The RCTs that we included employed different EK techniques, which may have a bearing on these findings. EK procedures have evolved over the years and can be performed using different techniques, for example deep lamellar endothelial keratoplasty, Descemets stripping endothelial keratoplasty (DSEK), Descemets stripping automated endothelial keratoplasty (DSAEK), femtosecond laser-assisted endothelial keratoplasty and Descemet membrane endothelial keratoplasty (DMEK). More RCTs are needed to compare PKP with commonly performed EK procedures such as DSEK, DSAEK and DMEK in order to determine the answers to two key questions, whether there is any difference in the final visual outcome between these techniques and whether there are differences in the rates of graft survival in the long term?"

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Calder (2005) ³³	Corneal abrasion; corneal injury	"To determine the effectiveness of topical non-steroidal anti-inflammatory drugs (NSAIDs) in traumatic corneal abrasions"	Medications	Treatment success	11	Not reported	"Topical NSAIDs are effective analgesics for traumatic corneal abrasions."
Flynn (1998) ³⁴	Corneal abrasion	"To determine if eye patching is a useful treatment for corneal abrasions"	Devices	Symptom resolution; Other outcomes	7	550	"Eyepatching was not found to improve healing rates or reduce pain in patients with corneal abrasions."
Song (2017) ³⁵	Dry eye	"To compare the efficacy of two artificial tears, carboxymethylcellulose (CMC) and hyaluronate (HA), in the treatment of patients with dry eye disease"	Medications	Other outcomes	5	251	"The efficacy of CMC appeared to be better than that of HA in treating dry eye disease, although metaanalysis results were not statistically significant."
Pan (2017) ³⁶	Dry eye	"To evaluate the efficacy and safety of autologous serum (AS) compared to artificial tears for treating dry eye"	Supplements	Tear production; Tear film stability; Tear osmolarity; Tear fluorescein clearance; Impression cytology; Ocular surface staining; Symptom improvement; Corneal topography	4	72	"Overall there was inconsistency in the possible benefits of AS in improving participant-reported symptoms and TBUT and lack of effect based on other objective clinical measures. Well-planned, large, high-quality RCTs are warranted, in different severities of dry eye and using standardized questionnaires to measure participant-reported outcomes and objective clinical tests as well as objective biomarkers to assess the benefit of AS therapy for dry eye."
Pucker (2016) ³⁷	Dry eye	"To evaluate the effectiveness and toxicity of over-the-counter (OTC) artificial tear applications in the treatment of dry eye syndrome compared with another class of OTC artificial tears, no treatment, or placebo"	Supplements	Tear production; Tear film stability; Tear osmolarity; Ocular surface staining; Symptom improvement; Visual acuity; Contrast sensitivity; Adverse events	43	3497	"OTC artificial tears may be safe and effective means for treating dry eye syndrome; the literature indicates that the majority of OTC artificial tears may have similar efficacies. This conclusion could be greatly skewed by the inconsistencies in study designs and inconsistencies in reporting trial results. Additional research is therefore needed before we can draw robust conclusions about the effectiveness of individual OTC artificial tear formulations."
Wu (2015) ³⁸	Dry eye	"To evaluate the efficacy and safety of topical diquafosol ophthalmic solution for treatment of dry eye"	Medications; Supplements	Tear production; Tear film stability; Symptom improvement; Adverse events	8	1516	"Topical diquafosol seems to be a safe therapeutic option for the treatment of dry eye. The high variability of the selected RCTs compromised the strength of evidence and limits the determination of efficacy. However, the topical administration of diquafosol seems to be beneficial in improving the integrity of the epithelial cell layer of the ocular surface and mucin secretion in patients with dry eyes. This review indicates a need for standardized criteria and methods for evaluation to assess the efficacy of diquafosol in the future clinical trials."
Zhu (2014) ³⁹	Dry eye	"To clarify the effects of	Supplements	Tear production; Tear	9	716	"This comprehensive meta-analysis supports the

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		polyunsaturated fatty acids (PUFAs) on dry eye syndrome (DES) through meta-analysis of all relevant randomized controlled trials (RCTs)"		film stability; Ocular surface staining; Symptom improvement			use of PUFA supplementation as a potential effective therapy for DES."
Sacchetti (2014) ⁴⁰	Dry eye	"To systematically review data from randomised clinical trials (RCTs) evaluating efficacy and safety of topical cyclosporine A (CsA) treatment for dry eye disease (DED)"	Medications; Supplements	Tear production; Tear film stability; Tear osmolarity; Ocular surface staining; Artificial tear use; Symptom improvement; Adverse events	18	2479	"Although topical CsA appears to be a safe treatment for DED, evidence emerging from RCTs is limited, and this affects the strength of recommendations to healthcare providers and policymakers for optimal management. Standardised diagnostic criteria to assess the efficacy of topical CsA are recommended to improve the design of future RCTs in DED."
Akpek (2011) ⁴¹	Dry eye	"Outcomes-based review of reported treatment options for patients with dry eye secondary to Sjögren's syndrome (SS)"	Medications; Devices; Supplements	Tear production; Tear film stability; Artificial tear use; Impression cytology; Ocular surface staining; Corneal sensitivity; Symptom improvement; Adverse events; Other outcomes	62	Not reported	"In the current literature on SS-associated dry eye, there is a paucity of rigorous clinical trials to support therapy recommendations. Nonetheless, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies. The efficacy of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgias, the literature lacks strong evidence for the efficacy of this treatment for dry eye."
Lee (2011) ⁴²	Dry eye	"To assess the effectiveness of acupuncture as a treatment option for treating the condition of dry eye"	Other procedures	Tear production; Tear film stability	6	248	"These results provide limited evidence for the effectiveness of acupuncture for treating dry eye. However, the total number of RCTs, the total sample size and the methodological quality were too low to draw firm conclusions."
Ervin (2010) ⁴³	Dry eye	"To assess the safety and efficacy of punctal plugs for the management of dry eye"	Devices	Tear production; Tear osmolarity; Artificial tear use; Ocular surface staining; Symptom improvement; Adverse events	7	305	"This systematic review shows a relative scarcity of controlled clinical trials assessing the efficacy of punctal occlusion therapy in dry eye. Although the evidence is very limited, the data suggest that silicone plugs can provide symptomatic relief in severe dry eye. Moreover, temporary collagen plugs appear similarly effective to silicone plugs on a short-term basis."
Ramos-Casals (2010) ⁴⁴	Dry eye	"To summarize evidence on primary Sjögren syndrome drug therapy from randomized controlled trials"	Medications; Supplements	Adverse events	56	Not reported	"In primary Sjögren syndrome, evidence from controlled trials suggests benefits for pilocarpine and cevimeline for sicca features and topical cyclosporine for moderate or severe dry eye. Anti-tumor necrosis factor agents have not shown clinical efficacy, and larger controlled trials are needed to establish the efficacy of rituximab."
FlorCruz	Other (non-	"To assess the effects of	Medications	Visual acuity; Quality of	12	981	"The trials included in this review were of variable

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(2015) ⁴⁵	bacterial keratitis	different antifungal drugs in the management of fungal keratitis"		life; Adverse events; Other outcomes			quality and were generally underpowered. There is evidence that natamycin is more effective than voriconazole in the treatment of fungal ulcers. Future research should evaluate treatment effects according to fungus species."
Wilhelmus (2015) ⁴⁶	Other (non-bacterial) keratitis	"To compare the relative effectiveness of antiviral agents, interferon, and corneal debridement in the treatment of HSV epithelial keratitis"	Medications; Surgeries	Symptom resolution; Adverse events; Other outcomes	137	8333	"Placebo-controlled studies of HSV epithelial keratitis are limited to superseded interventions. Trifluridine and acyclovir are more effective than idoxuridine or vidarabine and similar in therapeutic effectiveness. Brivudine and foscarnet do not substantially differ in effectiveness from trifluridine or acyclovir. Ganciclovir is at least as effective as acyclovir. The addition of interferon to a nucleoside antiviral agent and the combination of debridement with antiviral treatment need to be further assessed to substantiate any possible advantage in healing."
Alkharashi (2015) ⁴⁷	Other (non-bacterial) keratitis	"To evaluate the relative effectiveness and safety of medical therapy for the treatment of acanthamoeba keratitis"	Medications	Visual acuity; Symptom resolution; Adverse events; Other outcomes	1	55	"There is insufficient evidence to evaluate the relative effectiveness and safety of medical therapy for the treatment of acanthamoeba keratitis."
Barker (2008) ⁴⁸	Other (non-bacterial) keratitis	"To answer the following clinical questions: What are the effects of treatments in people with epithelial keratitis? What are the effects of treatments in people with stromal keratitis? What are the effects of interventions to prevent recurrence of ocular herpes simplex? What are the effects of interventions to prevent recurrence of ocular herpes simplex in people with corneal grafts?"	Surgeries	Adverse events; Other outcomes	7	Not reported	"In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding oral aciclovir to topical corticosteroids plus topical antiviral treatment; adding topical corticosteroids to topical antiviral treatment; antiviral agents (topical); debridement; interferons (topical); and oral aciclovir."
Lindsley (2017) ⁴⁹	Hordeolum	"To investigate the effectiveness, and when possible, the safety, of non-surgical treatments for acute internal hordeola compared with observation or placebo"	Medications; Other (Lid hygiene)	Symptom improvement; Symptom resolution; Quality of life; Costs; Adverse events	0	0	"We did not find any evidence for or against the effectiveness of non-surgical interventions for the treatment of an internal hordeolum. Controlled clinical trials would be useful to determine which interventions are effective for the treatment of acute internal hordeola."
Cheng (2017) ⁵⁰	Hordeolum	"To investigate the effectiveness and safety of acupuncture to treat acute hordeolum compared with no treatment, sham acupuncture,	Medications; Surgeries	Symptom resolution; Adverse events; Other outcomes	6	531	"Low-certainty evidence suggests that acupuncture with or without conventional treatments may provide short-term benefits for treating acute hordeolum when compared with conventional treatments alone. The certainty of the evidence

Author (Year) ^{Ref}	Condition(s) addressed	Objectives	Type(s) of interventions	Outcomes	Number of included studies	Number of participants in included studies	Conclusion(s) from the abstract
		or other active treatment. We also compared the effectiveness and safety of acupuncture plus another treatment with that treatment alone."					was low to very low mainly due to small sample sizes, inadequate allocation concealment, lack of masking of the outcome assessors, inadequate or unclear randomization method, and a high or unreported number of dropouts. All RCTs were conducted in China, which may limit their generalizability to non-Chinese populations. Because no RCTs included a valid sham acupuncture control, we cannot rule out a potential expectation/placebo effect associated with acupuncture. As resolution is based on clinical observation, the outcome could be influenced by the observer's knowledge of the assigned treatment. Adverse effects of acupuncture were reported sparsely in the included RCTs, and, when reported, were rare. RCTs with better methodology, longer follow-up, and which are conducted among other populations are warranted to provide more general evidence regarding the benefit of acupuncture to treat acute hordeolum."
Clearfield (2016) ⁵¹	Pterygium	"To assess the safety and effectiveness of conjunctival autograft (with or without adjunctive therapy) compared with amniotic membrane graft (with or without adjunctive therapy) for pterygium. We also planned to determine whether use of MMC yielded better surgical results and to assess the direct and indirect comparative costs of these procedures."	Surgeries	Visual acuity; Symptom improvement; Quality of life; Costs; Other outcomes	20	1866	"In association with pterygium excision, conjunctival autograft is associated with a lower risk of recurrence at six months' after surgery than amniotic membrane transplant. Participants with recurrent pterygia in particular have a lower risk of recurrence when they receive conjunctival autograft surgery compared with amniotic membrane transplant. There are few studies comparing the two techniques with respect to visual acuity outcomes, and we identified no studies that reported on vision-related quality of life or direct or indirect costs. Comparison of these two procedures in such outcome measures bears further investigation. There were an insufficient number of studies that used adjunctive mitomycin C to estimate the effects on pterygium recurrence following conjunctival autograft or amniotic membrane transplant."
Hu (2014) ⁵²	Pterygium	"To assess the efficacy and safety of bevacizumab in the treatment of pterygium and to mainly explore its effects on recurrence rate and complications"	Medications	Adverse events; Other outcomes	9	474	"Topical or subconjunctival bevacizumab was relatively safe and well tolerated, but it had no statistically significant effect on preventing pterygium recurrence. A large-scale trial with a suitable dosage and a longer follow-up would be required to rule out the possibility of any treatment benefit."
Zheng (2012) ⁵³	Pterygium	"To compare pterygium surgery outcomes using limbal	Surgeries	Other outcomes	13	1776	"According to the current evidence from literature, recurrence rates after pterygium excision with

Author (Year) ^{Ref}	Condition(s) addressed	Objectives	Type(s) of interventions	Outcomes	Number of included studies	Number of participants in included studies	Conclusion(s) from the abstract
		conjunctival autograft (LCAG) and other techniques"					LCAG are lower when compared with the use of bare sclera, bulbar conjunctival autograft, or intraoperative mitomycin C. Although recurrence rates of LCAG were similar to the amniotic membrane graft, further large-scale randomized controlled trials would be required to confirm these results."
Xu (2012) ⁵⁴	Pterygium	"To determine the risk for postoperative pterygium recurrence comparing autologous conjunctival transplantation (ACT) versus mitomycin C (MMC)"	Medications; Surgeries	Treatment success; Symptom improvement	8	663	"Conjunctival limbal autograft has better therapy efficacy against the recurrence of pterygium than mitomycin C."
Henein (2017) ⁵⁵	Keratoconus	"To compare the visual, refractive and graft outcomes after penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) for keratoconus"	Surgeries	Visual acuity; Anatomic outcomes; Other outcomes	18	3367	"We found no evidence to support a difference in outcomes with regards to best-corrected visual acuity (BCVA) at three months post-graft or at any of the other time points analysed."
McAnena (2017) ⁵⁶	Keratoconus	"To systematically review the literature to determine the effectiveness of corneal collagen cross-linking (CXL) in children"	Surgeries	Visual acuity; Treatment success; Anatomic outcomes	13	401	"In conclusion it was found that standard CXL may be effective in halting progression of keratoconus in pediatric patients at 1 year. However, larger, more long-term studies are required to ascertain its effectiveness."
Kobashi (2017) ⁵⁷	Keratoconus	"To evaluate the efficacy of collagen cross-linking one year after treatment for keratoconus compared to no treatment by summarizing randomized controlled trials using a systematic review"	Surgeries	Visual acuity; Anatomic outcomes; Other outcomes	5	289	"The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review."
Alhassan (2014) ⁵⁸	Corneal abrasion	"To assess the effectiveness of the various interventions (medical and surgical) for Mooren's ulcer"	Medications; Surgeries	Visual acuity; Quality of life; Costs; Adverse events; Other outcomes	0	0	"We found no evidence in the form of RCTs to assess the treatment effect for the various interventions for Mooren's ulcer. High quality RCTs that compare medical or surgical interventions across different demographics are needed. Such studies should make use of various outcome measures, (i.e. healed versus not healed, percentage of area healed, speed of healing etc.) as well as ensuring high quality. randomisation and data analysis, as highlighted in this review."
Lim (2016) ⁵⁹	Corneal abrasion	"To assess the effects of patching for corneal abrasion on healing and pain relief"	Medications; Surgeries	Visual acuity; Symptom resolution; Quality of life; Adverse events;	12	54	"Trials included in this review suggest that treating simple corneal abrasions with a patch may not improve healing or reduce pain."

Author (Year) ^{Ref}	Condition(s) addressed	Objectives	Type(s) of interventions	Outcomes	Number of included studies	Number of participants in included studies	Conclusion(s) from the abstract
				Other outcomes			
Watson (2012) ⁶⁰	Corneal abrasion	"To assess the effectiveness and safety of prophylactic and treatment regimens for recurrent corneal erosion"	Medications; Devices; Surgeries	Adverse events; Other outcomes	8	441	"Well-designed, masked, randomised controlled trials using standardised methods are needed to establish the benefits of new and existing prophylactic and treatment regimes for recurrent corneal erosion. International consensus is also needed to progress research efforts towards evaluation of the major effective treatments for recurrent corneal erosions."
Wakai (2017) ⁶¹	Corneal injury	"To identify and evaluate all randomised controlled trials (RCTs) comparing the use of topical NSAIDs with placebo or any alternative analgesic interventions in adults with traumatic corneal abrasions (including corneal abrasions arising from foreign body removal), to reduce pain, and its effects on healing time"	Medications; Devices	Other outcomes	9	637	"The findings of the included studies do not provide strong evidence to support the use of topical NSAIDs in traumatic corneal abrasions. This is important, since NSAIDs are associated with a higher cost compared to oral analgesics. None of the trials addressed our primary outcome measure of participant-reported pain intensity reduction of 30% or more or 50% or more at 24 hours."
Abudou (2015) ⁶²	Patients undergoing corneal transplant	"To assess the effectiveness of immunosuppressants in the prophylaxis of corneal allograft rejection after high- and normal-risk kerato-plasty"	Medications	Visual acuity; Treatment success; Quality of life; Costs; Adverse events	6	561	"Current evidence on the effect of immunosuppressants in the prevention of graft failure and rejection after high- and normal-risk keratoplasty is largely low quality because the number of trials was limited, and, in general, the trials were small and at risk of bias."
Akpek (2014) ⁶³	Patients undergoing corneal transplant	"To assess the effectiveness of artificial versus donor corneas in individuals who have had one or more failed donor corneal transplantations"	Devices	Visual acuity; Treatment success; Quality of life; Costs; Adverse events	0	0	"The optimal management for those individuals who have failed a conventional corneal transplantation is not known."
Bali (2016) ⁶⁴	Patients undergoing keratoplasty	"To conduct a systematic review on the efficacy and side effects of systemic immunosuppression for high-risk cornea transplantation"	Medications	Other outcomes	29	Not reported	"Topical or subconjunctival bevacizumab was relatively safe and well tolerated, but it had no statistically significant effect on preventing pterygium recurrence. A large-scale trial with a suitable dosage and a longer follow-up would be required to rule out the possibility of any treatment benefit."
Feng (2013) ⁶⁵	Patients undergoing LASIK	"To investigate the possible effect of hinge location on corneal sensation and dry eye syndrome after laser-assisted in situ keratomileusis (LASIK)"	Surgeries	Other outcomes	8	366	"Acute conjunctivitis seen in primary care can be thought of as a self-limiting condition, with most patients getting better regardless of antibiotic therapy. Patients with purulent discharge or a mild severity of red eye may have a small benefit from antibiotics. Prescribing practices need to be updated, taking into account these results."

eAppendix. Diseases, Interventions, Outcomes, and Number of Studies and Participants, and Conclusions of all 65 Reliable Systematic Reviews Addressing Corneal Diseases

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