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Interventions for central serous chorioretinopathy: a network meta-analysis (Review)

Salehi M, Wenick AS, Law HA, Evans JR, Gehlbach P

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[Intervention Review]

Interventions for central serous chorioretinopathy: a network meta-analysis

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ABSTRACT

Background

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neural retina with dysfunction of the choroid and retinal pigment epithelium (RPE). The effects on the retina are usually self limited, although some people are left with irreversible vision loss due to progressive and permanent photoreceptor damage or RPE atrophy. There have been a variety of interventions used in CSC, including, but not limited to, laser treatment, photodynamic therapy (PDT), and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents. However, it is not known whether these or other treatments offer significant advantages over observation or other interventions. At present there is no evidence-based consensus on the management of CSC. Due in large part to the propensity for CSC to resolve spontaneously or to follow a waxing and waning course, the most common initial approach to treatment is observation. It remains unclear whether this is the best approach with regard to safety and efficacy.

Objectives

To compare the relative effectiveness of interventions for central serous chorioretinopathy.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to February 2014), EMBASE (January 1980 to October 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 October 2015.

Selection criteria

Randomized controlled trials (RCTs) that compared any intervention for CSC with any other intervention for CSC or control.

Data collection and analysis

Two review authors independently selected studies and extracted data. We pooled data from all studies using a fixed-effect model. For interventions applied to the eye (i.e. not systemic interventions), we synthesized direct and indirect evidence in a network meta-analysis model.

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Main results

We included 25 studies with 1098 participants (1098 eyes) and follow-up from 16 weeks to 12 years. Studies were conducted in Europe, North and South America, Middle East, and Asia. The trials were small (most trials enrolled fewer than 50 participants) and poorly reported; often it was unclear whether key aspects of the trial, such as allocation concealment, had been done. A substantial proportion of the trials were not masked.

The studies considered a variety of treatments: anti-VEGF (ranibizumab, bevacizumab), PDT (full-dose, half-dose, 30%, low-fluence), laser treatment (argon, krypton and micropulse laser), beta-blockers, carbonic anhydrase inhibitors, *Helicobactor pylori* treatment, and nutritional supplements (Icaps, lutein); there were only one or two trials contributing data for each comparison. We downgraded for risk of bias and imprecision for most analyses, reflecting study limitations and imprecise estimates. Network meta-analysis (as planned in our protocol) did not help to resolve this uncertainty due to a lack of trials, and problems with intransitivity, particularly with respect to acute or chronic CSC.

Low quality evidence from two trials suggested little difference in the effect of anti-VEGF (ranibizumab or bevacizumab) or observation on change in visual acuity at six months in acute CSC (mean difference (MD) 0.01 LogMAR (logarithm of the minimal angle of resolution), 95% confidence interval (CI) -0.02 to 0.03; 64 participants). CSC had resolved in all participants by six months. There were no significant adverse effects noted.

Low quality evidence from one study (58 participants) suggested that half-dose PDT treatment of acute CSC probably results in a small improvement in vision (MD -0.10 logMAR, 95% CI -0.18 to -0.02), less recurrence (risk ratio (RR) 0.10, 95% CI 0.01 to 0.81) and less persistent CSC (RR 0.12, 95% CI 0.01 to 1.02) at 12 months compared to sham treatment. There were no significant adverse events noted.

Low quality evidence from two trials (56 participants) comparing anti-VEGF to low-fluence PDT in chronic CSC found little evidence for any difference in visual acuity at 12 months (MD 0.03 logMAR, 95% CI -0.08 to 0.15). There was some evidence that more people in the anti-VEGF group had recurrent CSC compared to people treated with PDT but, due to inconsistency between trials, it was difficult to estimate an effect. More people in the anti-VEGF group had persistent CSC at 12 months (RR 6.19, 95% CI 1.61 to 23.81; 34 participants).

Two small trials of micropulse laser, one in people with acute CSC and one in people with chronic CSC, provided low quality evidence that laser treatment may lead to better visual acuity (MD -0.20 logMAR, 95% CI -0.30 to -0.11; 45 participants). There were no significant adverse effects noted.

Other comparisons were largely inconclusive.

We identified 12 ongoing trials covering the following interventions: aflibercept and eplerenone in acute CSC; spironolactone, eplerenone, lutein, PDT, and micropulse laser in chronic CSC; and micropulse laser and oral mifepristone in two trials where type of CSC not clearly specified.

Authors' conclusions

CSC remains an enigmatic condition in large part due to a natural history of spontaneous improvement in a high proportion of people and also because no single treatment has provided overwhelming evidence of efficacy in published RCTs. While a number of interventions have been proposed as potentially efficacious, the quality of study design, execution of the study and the relatively small number of participants enrolled and followed to revealing endpoints limits the utility of existing data. It is not clear whether there is a clinically important benefit to treating acute CSC which often resolves spontaneously as part of its natural history. RCTs comparing individual treatments to the natural history would be valuable in identifying potential treatment groups for head-to-head comparison. Of the interventions studied to date, PDT or micropulse laser treatment appear the most promising for study in future trials.

PLAIN LANGUAGE SUMMARY

Interventions for central serous chorioretinopathy

Review question
What is the effect of treatments for central serous chorioretinopathy (CSC)? Is any treatment better than any other treatment?

Background
CSC is a disorder of the back of the eye. The 'retina' (which captures light and turns it into electric impulses to be sent to the brain) becomes detached. CSC typically affects young and middle-aged adults, particularly men. It can lead to problems with vision. Most people who develop CSC recover on their own but some people continue to have problems and can lose vision permanently. A variety of treatments have been proposed for CSC including laser treatment and injections of biological agents to reduce the amount of fluid in the back of the eye.

Study characteristics
The evidence is current to 5 October 2015. A total of 1098 participants were enrolled from Brazil, China, Germany, India, Iran, Italy, Japan, Mexico, South Korea, Thailand, Turkey, the UK and the US. All enrolled participants were similar with respect to age and most were men.

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The participants had varying severity of the disease; some displayed symptoms for less than 20 days up to six months. Most studies did not report their source of funding, four studies were industry funded, and six studies were non-industry funded.

Key results
The studies considered a wide range of treatments. As a result, there were not enough studies of any one treatment to provide good evidence of treatment effects. In general, no significant side effects were noted.

Quality of the evidence
The overall quality of the presently available published evidence was either low or very low. This finding indicates that future published research is very likely to have an important impact on the conclusions currently provided in this review.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interventions for central serous chorioretinopathy: direct comparisons

Interventions for central serous chorioretinopathy: direct comparisons

Patient or population: people with central serous chorioretinopathy

Settings: eye hospital

Comparison (intervention vs. comparator)	Anticipated absolute effects (95% CI)		Effect estimate from direct comparison			Comments
	Risk with comparator	Mean difference (95% CI) Negative values are in favor of intervention; positive values in favor of comparator	Relative effect (95% CI)	No of participants (studies)	Quality	
Change in visual acuity at 12 months (logMAR)						
Anti-VEGF vs. observation	-	0.01 LogMAR (-0.02 to 0.03)	-	64 (2)	Low[1,2]	Both studies enrolled participants with acute CSC and reported mean change in visual acuity at 6 months
Anti-VEGF vs. low-fluence PDT	-	0.03 logMAR (-0.08 to 0.15)	-	56 (2)	Low[1,2]	Both studies enrolled participants with chronic CSC
Anti-VEGF and 50% PDT vs. 50% PDT	-	0.30 logMAR (0.09 to 0.51)	-	15 (1)	Low[1,2]	Participants had chronic CSC
6-dose anti-VEGF vs. 4-dose anti-VEGF	-	-0.02 logMAR (-0.31 to 0.27)	-	12 (1)	Low[1,2]	Participants had chronic CSC and were followed to 6 months
50% PDT vs. observation or sham treatment	-	-0.10 logMAR (-0.18 to -0.02)	-	58 (1)	Low[1,2]	Participants had acute CSC
30% PDT vs. PDT	-	-0.16 logMAR (-0.22 to -0.10)	-	60 (1)	Low[1,2]	Type of CSC not specified
30% PDT vs. 50% PDT	-	-0.12 logMAR (-0.15 to -0.08)	-	60 (1)	Low[1,2]	Type of CSC not specified

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50% PDT vs. PDT	-	0.04 logMAR (-0.04 to 0.12	-	60 (1)	Low[1,2]	Type of CSC not specified
Selective retina therapy vs. observation	-	-0.13 logMAR (-0.24 to -0.01)	-	30 (1)	Low[1,2]	Participants had acute CSC, followed up to 3 months
Micropulse diode laser vs. sham laser	-	-0.38 logMAR (-0.56 to -0.20)	-	15 (1)	Low[1,2]	Participants had chronic CSC
Antioxidant vs. placebo	-	0.01 logMAR (-0.04 to 0.06)	-	14 (1)	Low[1,2]	Lutein and acute CSC
Propranolol vs. placebo	-	0.01 logMAR (-0.07 to 0.09)	-	60 (1)	Low[1,2]	Type of CSC not specified
Carbonic anhydrase inhibitors vs. placebo	See comment	-	-	13 (1)	-	Outcome not reported
Helicobacter pylori treatment vs. placebo	-	-0.04 logMAR (-0.07 to -0.02)	-	103 (2)	Low[1,2]	Participants had acute CSC, follow-up 12-16 weeks
Comparison (intervention vs. comparator)	**Anticipated absolute effects (95% CI)**		**Effect estimate from direct comparison**			**Comments**
	Risk with comparator*	**Risk with intervention**	**Relative effect (95% CI)**	**No of participants (studies)**	**Quality**	
Persistent CSC at 12 months						
Anti-VEGF vs. observation	See comment	-	-	64 (2)	-	Participants had acute CSC. Both trials reported that all participants in treatment and control groups were resolved by 6 months
Anti-VEGF vs. low-fluence PDT	111 per 1000	688 per 1000 (179 to 1000)	RR 6.19 (1.61 to 23.81)	34 (1)	Low[1,2]	Participants had chronic CSC
Anti-VEGF and 50% PDT vs. 50% PDT	143 per 1000	126 (10 to 1000)	RR 0.88 (0.07 to 11.54)	15 (1)	Very low[1,2,3]	Participants had chronic CSC
6-dose anti-VEGF vs. 4-dose anti-VEGF	See comment	-	-	12 (1)	-	Outcome not reported

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50% PDT vs. sham treatment	211 per 1000	25 per 1000 (2 to 215)	RR 0.12 (0.01 to 1.02)	58 (1)	Low[1,2]	Participants had acute CSC
30% PDT vs. PDT	See comment	-	-	60 (1)	-	Outcome not reported
30% PDT vs. 50% PDT	See comment	-	-	60 (1)	-	Outcome not reported
50% PDT vs. PDT	See comment	-	-	60 (1)	-	Outcome not reported
Selective retina therapy vs. observation	See comment	-	-	30 (1)	-	Outcome not reported
Micropulse diode laser	See comment	-	-	15 (1)	-	Outcome not reported
Antioxidant vs. placebo	See comment	-	-	51 (1)	-	People in the antioxidant group were less likely to have "complete resolution" at 3 months (RR 0.35, 95% CI 0.13 to 0.95; 51 participants)
Propranolol vs. placebo	See comment	-	-	60 (1)	-	Outcome not reported
Brinzolamide vs. placebo	167 per 1000	48 (2 to 1000)	RR 0.29 (0.01 to 6.07)	13 (1)	Very low[2,3]	Participants had acute CSC
Helicobacter pylori treatment vs. placebo	314 per 1000	210 (113 to 383)	RR 0.67 (0.36 to 1.22)	103 (2)	Low[1,2]	Participants had acute CSC
Comparison (intervention vs. comparator)	**Anticipated absolute effects (95% CI)**		**Effect estimate from direct comparison**			
	Risk with comparator*	**Risk with intervention**	**Relative effect (95% CI)**	**No of participants (studies)**	**Quality**	**Comment**
Recurrent CSC at 12 months						
Anti-VEGF vs. observation	See comment	-	-	64 (2)	-	Outcome not reported
Anti-VEGF vs. low-fluence PDT	See comment	-	-	56 (2)	Very low[1,2,4]	Participants had chronic CSC. The 2 studies had different results for this outcome (I^2 = 71%). In Bae 2011, there was a much higher risk of recurrence in the anti-VEGF group (ranibizumab) compared with the PDT group (RR 19.83, 95% CI 1.19 to

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						330.50; 21 eyes); in Semeraro 2012, there was also an increased risk of recurrence in the anti-VEGF (bevacizumab) group but the size of the effect was much smaller and the CIs include 1 (no effect) (RR 1.46, 95% CI 0.59 to 3.58; 22 eyes)
Anti-VEGF and 50% PDT vs. 50% PDT	See comment	-	-	15 (1)	-	Outcome not reported
6-dose anti-VEGF vs. 4-dose anti-VEGF	See comment	-	-	12 (1)	-	Outcome not reported
50% PDT vs. sham treatment	267 per 1000	27 per 1000 (3 to 216)	RR 0.10 (0.01 to 0.81)	53 (1)	Low[1,2]	Participants had acute CSC
30% PDT vs. PDT	See comment	-	-	60 (1)	-	Outcome not reported
30% PDT vs. 50% PDT	See comment	-	-	60 (1)	-	Outcome not reported
50% PDT vs. PDT	270 per 1000	338 per 1000 (154 to 737)	RR 1.25 (0.57 to 2.73)	60 (1)	-	Type of CSC not specified
Selective retina therapy vs. observation	See comment	-	-	30 (1)	-	Outcome not reported
Micropulse diode laser	See comment	-	-	15 (1)	-	Outcome not reported
Antioxidant vs. placebo	143 per 1000	46 (4 to 456)	RR 0.32 (0.03 to 3.19)	36 (1)	Very low[2,3]	Participants had acute CSC
Propranolol vs. placebo	167 per 1000	100 (27 to 382)	RR 0.60 (0.16 to 2.29)	60 (1)	Low[1,2]	Type of CSC not reported
Brinzolamide vs. placebo	314 per 1000	140 (20 to 953)	RR 0.21 (0.03 to 1.43	13 (1)	Low[1,2]	Participants had acute CSC
Helicobacter pylori treatment vs. placebo	See comment	-	-	103 (2)	-	Outcome not reported
Adverse effects						
All studies reported no ocular or systematic adverse effects, or did not comment on adverse effects						

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anti-VEGF: anti-vascular endothelial growth factor; CI: confidence interval; CSC: central serous chorioretinopathy; logMAR: logarithm of the minimal angle of resolution; PDT: photodynamic therapy; RR: risk ratio.

* Risk was estimated from the comparator group in the included studies

1 Downgraded for imprecision (-1)

2 Downgraded for risk of bias (-1)

3 Downgraded for imprecision (-2)

4 Downgraded for inconsistency (-1)

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BACKGROUND

Description of the condition

Central serous chorioretinopathy (CSC) has been known by many names including capillarospastic central retinitis, central angiospastic retinopathy and central serous retinopathy (CSR). The hallmark of CSC is the accumulation of subretinal fluid between the neurosensory retina and the retinal pigment epithelium (RPE). The incidence of CSC is greater in men than women; a survey conducted in Minnesota (US) reported that the annual incidence of CSC was higher among men (9.9 per 100,000; 95% confidence interval (CI) 7.4 to 12.4) compared with women (1.7 per 100,000; 95% CI 0.7 to 2.7) (Kitzmann 2008). The odds of CSC is higher among people taking corticosteroids than people not taking corticosteroids (odds ratio (OR) 37.1, 95% CI 6.2 to 221.8) (Haimovici 2004). Type A personality, body type and age are also potential factors correlated with CSC (Nicholson 2013; Yannuzzi 1987). The precise etiology of CSC remains unknown, but the pathogenesis appears to involve dysfunction of the choroid (the major blood vessel network serving the outer portion of the retina) and RPE (Prunte 1996).

The location and amount of subretinal fluid determines what symptoms are experienced. CSC is commonly associated with fluid accumulation under the macula and detachment of the retina. When the detachment occurs in the central macula, symptoms may include reduction of best-corrected visual acuity (BCVA), distortion of vision, changes in image size, altered color vision, a decrease in contrast sensitivity, the perception of blind spots, or a combination of these symptoms (Cassin 2006; Gass 1967; Wang 2008). Symptoms typically present acutely in one eye without pain. There may be no symptoms when the fluid is located outside the macula. Cases of bilateral involvement are not uncommon, though symptoms may be present in one eye only. People seeking treatment generally have reduced vision, distorted vision, or both. The physician's goal is to improve the visual acuity and other visual symptoms and prevent permanent vision loss related to RPE and outer retinal atrophy by eliminating the fluid between the neurosensory retina and RPE.

CSC is classified as acute or chronic depending on multiple considerations. Various clinical investigators have used different cut-off time points (e.g. persistent fluid for less than six months or longer than six months) to define acute versus chronic CSC (Nicholson 2013). Others have approached the classification differently: for example acute CSC is defined as the first attempted treatment to improve visual acuity and chronic CSC is defined as being refractory to treatment (Chan 2008; Quin 2013).

The diagnosis of CSC is made by dilated fundus exam combined with imaging of the retina and choroid with optical coherence tomography (OCT), fluorescein angiography (FA), indocyanine green angiography (ICGA), or combinations of these imaging techniques (Nicholson 2013; Quin 2013; Wang 2008). OCT is an imaging technique that allows for the identification of and quantification of subretinal fluid as well as estimation of the thickness of the choroid, which may be abnormally thickened in the setting of CSC. In some cases, OCT may reveal pathologic changes of CSC that are subtle on fundoscopy, such as shallow subretinal fluid, small pigment epithelial detachments, and retinal atrophy that can occur with chronic disease (Montero 2005). FA and ICGA are imaging techniques that allow for the identification of abnormal leakage of fluid from the choroidal and retinal vessels as well as through the RPE layer. Serial exams and strategic choices among these imaging techniques are used to follow the progress of disease and response to treatment.

Many diseases of the choroid, RPE, and retina can produce serous detachment of the neurosensory retina. Considerations for differential diagnosis in CSC include disorders that involve central vision loss associated with central neurosensory retinal detachment. These include choroidal neovascularization (CNV), pattern dystrophy, optic disc pits, polypoidal choroidal vasculopathy, choroidal melanoma, and choroidal metastasis (Yanoff 2013). Choroidal hemangioma, uveitis, Harada disease, optic neuritis, papilledema, vitreous traction, macular holes, and systemic hypertension can also produce neural retinal detachments (Gass 1967). While in its earliest stages retinal detachment due to small tears or holes may present as subretinal fluid, the peripheral location, subsequent course, and discovery of retinal defect usually removes it from the differential diagnosis. Pigment epithelial detachments most often in the setting of macular degeneration are sometimes confused with CSC.

Generally, acute CSC has an excellent prognosis including full visual recovery to premorbid levels (Klein 1974; Loo 2002; Maruko 2010). However, people with chronic CSC with long-standing subretinal fluid accumulation may develop RPE atrophy and changes in the neurosensory retina that result in a permanent loss of visual function (Baran 2005). While recovery of visual acuity usually occurs within one to four months (Klein 1974; Mudvari 2007; Nicholson 2013), some visual abnormalities, such as alterations in night vision, contrast sensitivity, and color vision, may persist. It has also been observed that the severity of the disease is directly proportional to its duration (Castro-Correia 1992). One-third to one-half of CSC cases will recur in one year (Loo 2002). A waxing and waning course is not unusual and contributes to the difficulty in attributing visual improvement to treatment benefit. A minority of cases become chronic in nature and these may progress to diffuse abnormalities in the RPE and permanently poor vision (Baran 2005). Certain features and coexistent conditions are associated with lower final visual acuity, such as recurrent foveal detachments, chronic foveal detachment, CNV, subretinal fibrosis, subfoveal RPE atrophy, and diffuse involvement.

Management of CSC usually involves careful observation with risk factor modification. Corticosteroid use is the most frequent modifiable risk factor for CSC and physicians first may reduce corticosteroid use to treat CSC (Bouzas 2002). While discontinuation of corticosteroids can benefit some people, some people do not respond and many are not taking corticosteroids at all. Persistent submacular fluid or reduced visual acuity are potential indications for next treatment, as are cases where untreated CSC has previously resulted in a poor visual outcome in the fellow eye (Nicholson 2013). Rare indication may include vocational needs in, for example, airline pilots, professional athletes, or police/military officers.

Description of the intervention

Treatments for CSC generally target the RPE, choroid, or both. The RPE is responsible for maintaining the blood-retinal barrier between the retina and choroid as well as for removing any subretinal fluid that accumulates. In CSC, the source of the subretinal fluid is the choroidal vasculature. Treatments for CSC aim to improve the ability of the RPE to remove the subretinal

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fluid, to diminish leakage from the choroidal vessels, or to decrease fluid flux across the RPE barrier. Determining the effectiveness of treatments for CSC is difficult as a waxing and waning of disease activity is typical of the natural history. This natural variation and the tendency for people to present when their symptoms are worse creates uncertainty of whether disease improvement is the result of an intervention or the natural course of the disease. Further confounding the assessment of treatment response is a lack of direct correlation between the person's visual symptoms and the amount of subretinal fluid present (Maalej 2014; Nicholson 2013; Quin 2013; Shuler 2006; Wang 2008).

There have been a variety of interventions used, or proposed for use, in CSC. These interventions include laser treatments, most commonly photodynamic therapy (PDT); intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents; medications that alter steroid hormones; and others.

How the intervention might work

The interventions have various potential modes of action directed at either accelerating absorption of subretinal fluid or decreasing the production of fluid that accumulates in the subretinal space. Presently the target cells are in the choroidal vascular network and the RPE.

Laser treatments

Argon laser photocoagulation

Argon laser photocoagulation uses a low-intensity green or yellow argon laser to coagulate tissue by heat generated from an intense beam of light focused on the RPE (Hofstetter 2000). Lower intensity laser with longer duration and moderate spot size (100 to 200 microns) is preferred to minimize the likelihood of rupture of Bruch's membrane, subsequent development of CNV, and development of progressive atrophy over time in the area of the laser treatment (Robertson 1983). This procedure is commonly used to accelerate the absorption of subretinal fluid in acute and chronic CSC. Typically, laser burns are applied to areas of focal leakage that have been identified on FA as the principal sources of subretinal fluid. The mechanism of subretinal fluid resolution after laser photocoagulation treatment is not well understood. Benefit has been hypothesized to result from the sealing of focal defects in the RPE monolayer, the recruitment of healthy RPE cells after laser injury as a healing response, or the direct stimulation of improved pumping function of RPE cells near the treated areas (Mitsui 1969).

Micropulse diode laser photocoagulation

Micropulse diode laser treatment involves a series of repetitive ultrashort laser pulses that more broadly treat the RPE (Sivaprasad 2010). Improved RPE function is proposed to result from the targeted cells' response to therapy. Direct effects on points of leakage at the level of the RPE also have been postulated. Because of the relatively small amounts of energy delivered, little adverse thermal effect on the underlying neural retina and choroid is anticipated (Chen 2008; Ricci 2004; Roisman 2013). Historically, targeting of focal leaks outside of the macula with thermal laser has been more common than with micropulse laser; however, treatment of diffuse disease with micropulse treatment is increasing in use.

Verteporfin photodynamic therapy

Verteporfin photodynamic therapy (VPDT) has been used to treat acute CSC and to prevent recurrences (Nicholson 2013). The exact mechanism of PDT in treating chronic CSC is not known, but the treatment effects are postulated to result from short-term choriocapillaris hypoperfusion (decreased blood flow through choroid vessels) and long-term choroidal vascular remodeling, leading to reduction in choroidal congestion, vascular hyperpermeability, and extravascular leakage (Chan 2003). At present, PDT typically is used in cases of CSC involving the macula that have not responded to other treatments or observation. Despite potential benefits of PDT, there may be dose-dependent complications such as the development of RPE atrophy, choriocapillaris ischemia, CNV, and RPE tear (Cardillo Piccolino 2003; Kim 2009; Schlötzer-Schrehardt 2002; Schmidt-Erfurth 2002). Some studies have reported the treatment of CSC with modified PDT parameters, including reduced dose of verteporfin, reduced time of treatment, or reduced fluence (energy/area/second) of laser. These modifications to treatment parameters have been hypothesized to reduce the risk of complications while maintaining the potential treatment benefit (Chan 2008; Lai 2006; Reibaldi 2010).

Anti-vascular endothelial growth factor agents

The aim of anti-VEGF therapy is to stop neovascular vessel growth and leakage. Anti-VEGF agents bind to, and block the effects of, vascular endothelial growth factor (VEGF) thereby slowing down the growth of new blood vessels in the eye and reducing vascular permeability. Therefore, anti-VEGFs may have a role in eyes with CSC that are complicated by secondary CNV. Anti-VEGF therapy is typically not expected to provide benefit in cases of CSC that are not complicated by active CNV. Increased levels of VEGF have not been found in aqueous humor of people with CSC (Lim 2010).

There are several anti-VEGF agents used by ophthalmologists: aflibercept (Eylea®), bevacizumab (Avastin®), ranibizumab (Lucentis®), and pegaptanib (Macugen®). Currently each of these, with the exception of bevacizumab, has been approved by the US Food and Drug Administration (FDA) for use in the eye (FDA 2015). Anti-VEGF agents often are used for, and have been shown to be effective for, a number of ocular diseases; however, none of these medications has been approved specifically for use in the treatment of CSC or for the treatment of CNV in the setting of CSC.

Medications that alter steroid hormones

The exact role of steroids in CSC pathogenesis is not well understood. Proposed mechanisms in the choroid include effects on vascular autoregulation, potentiation of vascular reactivity, or prothrombotic steroid effect (Nicholson 2013). The following medications that target steroid hormone pathways have been proposed for treatment of CSC but are not currently licensed for that indication.

Ketoconazole

Ketoconazole is an anti-fungal agent used to treat candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, or paracoccidioidomycosis (FDA 2015).

Ketoconazole is an anti-fungal agent that is thought to halt endogenous glucocorticoid production in part by inhibiting

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the conversion of 11-deoxycortisol to cortisol. Because of this inhibition, ketoconazole was established as effective in the treatment of Cushing disease (Chou 2000; Winquist 1995). Thus, it is believed that, given the association of corticosteroids in the pathogenesis of CSC, lowering endogenous cortisol production by pharmacologic intervention would be a rational approach to the treatment of CSC (Jampol 2002; Meyerle 2007).

Mifepristone

Mifepristone (RU-486) is classified as a high-affinity, glucocorticoid receptor antagonist (Clark 2008). It is used to end an early pregnancy for women who have been pregnant for 49 days (seven weeks) or less since their last menstrual period began. The rationale for its use in CSC is similar to that for ketoconazole.

Rifampin

Rifampin, also known as rifampicin, is an antibacterial drug that is typically used to treat tuberculosis and meningococcal carriers. It is believed to suppress endogenous glucocorticoid production by inducing cytochrome P450 3A4 (Guengerich 1999); and altering reactions in steroid synthesis.

Finasteride

In addition to glucocorticoids, androgens, such as testosterone, have been implicated in the pathophysiology of CSC (Ahad 2006; Grieshaber 2007). Finasteride is a 5-alfa-reductase inhibitor that prevents conversion of testosterone to dihydrotestosterone, the latter of which has a higher binding affinity to androgen receptors (Forooghian 2011). Finasteride (5 mg) is used to treat benign prostatic hyperplasia (enlarged prostate gland), while finasteride (1 mg) is used to treat male pattern hair loss (androgenetic alopecia).

Eplerenone and spironolactone

It has been proposed that CSC results from over-activation of the mineralocorticoid receptor pathway in the choroid. These receptors are bound and activated by mineralocorticoids, such as aldosterone, and by glucocorticoids. Eplerenone and spironolactone are aldosterone receptor antagonists; therefore, they inhibit binding of both aldosterone and glucocorticoids to mineralocorticoid receptors. Eplerenone is used to treat hypertension among people with stable left ventricle systolic dysfunction and congestive heart failure after an acute myocardial infarction (FDA 2015). Spironolactone is used to establish the diagnosis of primary hyperaldosteronism by therapeutic trial. The retinal and choroidal vasculature of the rat expresses glucocorticoid and mineralocorticoid receptors, and aldosterone injection causes choroidal enlargement in this animal model (Zhao 2012). Because of these findings, Bousquet 2013 treated 13 participants with chronic CSC with eplerenone and noted a decrease in mean macular thickness and subretinal fluid.

Carbonic anhydrase inhibitors

Acetazolamide is a carbonic anhydrase inhibitor used to treat chronic simple (open-angle) glaucoma, secondary glaucoma, preoperatively in acute angle-closure glaucoma to lower intraocular pressure, and prevention of amelioration. It is being used off-label to treat CSC. It has been investigated on the basis that inhibition of carbonic anhydrase IV in the RPE seems to promote resorption of subretinal fluid and retinal adhesion (Cox 1988).

Helicobacter pylori treatment

Several studies indicated that people with CSC may have a higher incidence of serum anti-*Helicobacter pylori* antibodies and that the treatment for *H. pylori* could have a positive impact on the outcome of the disease (Cotticelli 2006). It has been posited that an immune response to host proteins of the choroidal vasculature and RPE may be caused by molecular mimicry with antigens of *H. pylori* (Giusti 2004).

Aspirin

In some cases of CSC, increased levels of plasminogen activator inhibitor have been demonstrated compared with controls (Iijima 1999). Consequently, it has been suggested that hypercoagulability (abnormal blood coagulation that may lead to blood clots) may play a role in CSC pathogenesis (Cotticelli 2006).

Hypothalamic–pituitary–adrenal axis regulation

The hypothalamic-pituitary-adrenal (HPA) axis is a complex feedback system among the hypothalamus, pituitary gland, and adrenal glands. The HPA axis responds to stress by modifying hormone levels released by the glands. Increased stress levels can increase the amount of glucocorticoid in the body. Hormone level information feeds back to the HPA axis; high levels of glucocorticoids are believed to suppress HPA axis activity. Medications that may alter the HPA axis regulation include anti-glucocorticoids and antidepressants.

Why it is important to do this review

Currently there is no consensus on the management of CSC. Due to the recurrent and chronic nature of some cases of CSC and uncertainty relating to best therapy, CSC remains a significant threat to vision and vocational stability. An evidence synthesis is needed to assess the relative effectiveness of interventions in order to determine which are the most promising and to identify any necessary future primary research.

As there are several different possible interventions, not all of which will have been compared in head-to-head studies, a network meta-analysis, if possible, will provide quantitative comparisons of interventions and a treatment hierarchy useful for decision makers.

OBJECTIVES

To compare the relative effectiveness of interventions for central serous chorioretinopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs) in this review.

Types of participants

We included studies of adults (aged 18 years or over) with CSC diagnosed using either OCT or FA, or as defined by study investigators.

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Types of interventions

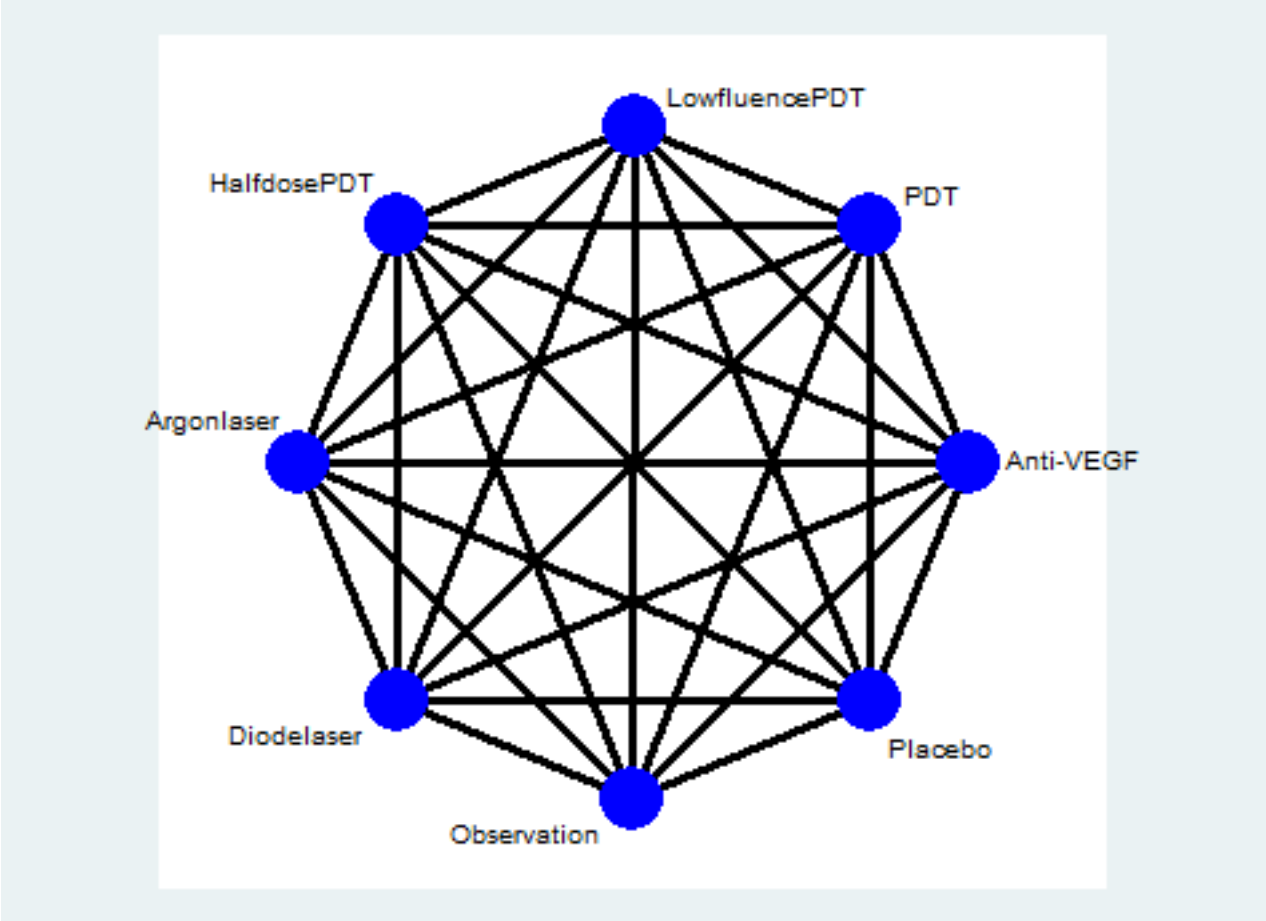
We included trials that compared any intervention for CSC with any other intervention for CSC or control. The control could be placebo, sham treatment, no treatment, or observation. We excluded trials of traditional Chinese medicine. This was a protocol amendment - see Differences between protocol and review.

We specified the following interventions in our protocol:

- argon laser photocoagulation;
- micropulse diode laser photocoagulation;
- VPDT (full-dose, half-dose or half-fluence);
- anti-VEGF agents;
- any other intervention (including the use of the specific medical treatments detailed above).

Figure 1 presents a theoretical treatment network based on interventions in current use and the classes of treatment as listed above. In our protocol, we planned to construct an alternative formulation of the network using specific anti-VEGF agents (i.e. ranibizumab, bevacizumab, and aflibercept) and possibly different treatment regimens for laser and PDT); however, due to the sparse number of trials identified, this alternative formulation resulted in two disconnected networks and we felt it was unwise to proceed.

Figure 1. Theoretical treatment network.



A key assumption of the network is that any participant that met the inclusion criteria is, in principle, equally likely to be randomized to any of the interventions included in the network. In our protocol, we planned to exclude trials of treatment for *H. pylori* from the network as it is likely that these trials have only recruited participants with evidence of *H. pylori* infection and, therefore, the participants are unlikely to be comparable to participants enrolled in other trials. We identified a few trials of systemic treatments (e.g. antioxidant supplements, beta-blockers). We felt that it was unlikely that participants would be randomized to a comparison of these interventions and ocular interventions (i.e. interventions applied directly to the eye), so we excluded these systemic interventions from the network. This was a protocol amendment - see Differences between protocol and review.

Types of outcome measures

Primary outcomes

- Mean change in BCVA of CSC eyes from baseline (before treatment) to 12 months, measured by a LogMAR (logarithm of the minimal angle of resolution) chart or equivalent.

Secondary outcomes

- Proportion of CSC eyes with a recurrence of CSC between baseline and 12 months, as defined by study investigators.

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- Proportion of CSC eyes with persistent CSC, as defined by study investigators.
- Mean change in contrast sensitivity from baseline to 12 months, measured using the Pelli-Robson chart or equivalent.
- Mean change in central retinal subfield thickness (CRST) from baseline and 12 months, measured using OCT.
- Proportion of CSC eyes with BCVA 20/40 or better at 12 months.
- Proportion of CSC eyes with BCVA 20/200 or worse at 12 months.
- Quality of life at 12 months, measured using a validated questionnaire.
- Adverse events (e.g. loss of vision due to treatment, retinal atrophy, CNV).

Follow-up: we analyzed any measurement within the period of six to 18 months' follow-up as the 12-month measurement when a measurement at 12 months was not available.

BCVA; when logMAR score was not reported, we used the following formula to convert the number of letters read on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart to logMAR score: logMAR = (total number of letters on the chart-number of letters read correctly) x 0.02.

The total number of participant at risk of recurrence of CSC between baseline and 12 months was calculated using:

- total number of participants at risk for each group = number randomized - number lost to follow-up - number of participants with persistent CSC.

We planned to estimate the relative ranking of the competing interventions according to the following outcomes:

- mean change in BCVA of CSC eyes from baseline and 12 months;
- proportion with a recurrence of CSC between baseline and 12 months;
- proportion of participants with one or more adverse events.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to February 2014), EMBASE (January 1980 to October 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 October 2015.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), ISRCTN (Appendix 4), ClinicalTrials.gov (Appendix 5), and the ICTRP (Appendix 6).

Searching other resources

We searched the reference lists of all included studies and the Science Citation Index for papers that have cited included studies. We did not handsearch conference proceedings or journals specifically for the purposes of this review.

Data collection and analysis

Selection of studies

Two review authors independently screened titles and abstracts identified from searches using web-based software (Covidence); and classified each reference as 'relevant', 'possibly relevant', or 'definitely not relevant'. We resolved any discrepancy by discussion. We retrieved full-text reports of all records classified as 'relevant' or 'possibly relevant', and grouped citations by study. Two review authors independently assessed the eligibility for each study based on the full-text reports. We resolved any discrepancy during full-text assessment by discussion. We documented reasons for excluding studies after review of the full-text reports. We contacted trial investigators for clarification of study eligibility as needed.

For potentially eligible studies identified from trial registers we did the following:

- if the study had a completion date more than two years previously, we looked for publications of this trial and contacted the investigators as necessary to obtain published or unpublished data from the trial;
- if an eligible study had a completion date less than two years previously, or in the future, we documented the study in the ongoing studies section of the review.

Data extraction and management

We adapted data collection forms developed and piloted by Cochrane Eyes and Vision using web-based software (Systematic Review Data Repository). Two review authors independently extracted data from each study using all available study reports (protocols, journal publications, conference abstracts, etc.). We resolved any discrepancy by discussion. We abstracted data relevant to study design, methods, participants' characteristics, intervention, table of included studies, and outcomes (Appendix 7). We contacted trial investigators at the email address listed in their publications where we needed clarification. If we received no response after two weeks or we were unable to find current contact information, we used the data as available.

Assessment of risk of bias in included studies

We used the 'Risk of bias' tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors independently assessed each trial for each of the risk of bias domains listed below. We classified each domain as 'low risk', 'high risk', or 'unclear risk' for each trial. We resolved any disagreement by discussion. We discussed the potential impact of trials with high or unclear risks of bias on the treatment effect.

Sequence generation (selection bias)

- **Low risk of bias:** computer-generated, random number table.
- **Unclear risk of bias:** not clearly described or not reported.
- **High risk of bias:** non-random process (e.g. alternation) (we excluded these trials).

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Allocation concealment (selection bias)

- **Low risk of bias**: data co-ordination center, opaque sealed envelope.
- **Unclear risk of bias:** low risk (random) sequence generation but not described clearly how this was assigned/stored.
- **High risk of bias:** investigator was involved in sequence generation or assignment, or both.

Masking (blinding) of participants and study personnel (performance bias)

- **Low risk of bias:** masking reported.
- **Unclear risk of bias:** masking not reported or not reported clearly (e.g. 'double blinded' without explicit description of masking) but treatments similar.
- **High risk of bias:** no masking or masking not reported clearly (e.g. 'double blinded' without explicit description of masking) and treatments different (e.g. intervention versus observation).

Masking of outcome assessors (detection bias)

- **Low risk of bias:** masking of outcome assessors reported.
- **Unclear risk of bias:** masking of outcome assessors not reported or not reported clearly (e.g. 'double blinded' without explicit description of masking) but treatments similar.
- **High risk of bias:** no masking of outcome assessors or masking not reported clearly (e.g. 'double blinded' without explicit description of masking) and treatments different (e.g. intervention versus observation).

Incomplete outcome data (attrition bias)

- **Low risk of bias:** missing data less than 20% and no obvious reason why loss to follow-up should be related to outcome.
- **Unclear risk of bias:** not reported or 20% or greater loss to follow-up but follow-up similar in both groups.
- **High risk of bias:** loss to follow-up different in different groups or follow-up clearly related to outcome.

Selective outcome reporting (reporting bias)

- **Low risk of bias:** all outcomes reported as per protocol or trial registry entry.
- **Unclear risk of bias:** protocol and trial registry not available for comparison.
- **High risk of bias:** reported primary/secondary outcomes different from protocol/trial registry or outcomes mentioned in methods section not reported in results.

Other biases (e.g. funding source)

- **Low risk of bias:** reported either non-industry funding or reported no conflict of interest, or both, but did not report either industry funded or conflict of interest.
- **Unclear risk of bias:** source of funding and conflict of interest not reported.
- **High risk of bias:** industry funding or declared conflict of interest, or both.

Measures of treatment effect

Dichotomous data

For dichotomous outcome variables, we used risk ratios (RRs) with corresponding 95% confidence intervals (CIs) to measure the treatment effect. Dichotomous variables were BCVA 20/40 or better, BCVA 20/200 or worse, recurrence/persistence, and adverse events at one year.

Continuous data

For continuous variables, we used mean differences (MDs) and 95% CIs to measure the treatment effect. The continuous variables were change in BCVA, CRST, contrast sensitivity, and quality-of-life scores.

None of the included studies reported continuous outcomes using different scales. However, when future studies are included in the review, we will use the standardized mean difference (SMD) whenever a continuous outcome*has been* measured on different scales, as may be the case for quality-of-life outcomes. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. If one scale increases with severity while another decreases, we will ensure that all the scales point in the same direction either by multiplying the mean values of studies using one type of scale by -1 or by subtracting the mean from the maximum possible value for the scale.

We presented results from the network meta-analysis as summary effect sizes (RRs or MDs) for each possible pair of treatments.

Unit of analysis issues

Eyes and people

The unit of analysis was the person as CSC generally involves one symptomatic eye at the time of presentation. As far as we could determine, all included studies only included one eye per participant and none of the included studies enrolled bilateral CSC cases.

Studies with multiple treatment groups

We treated multi-arm studies as multiple independent two-arm studies in the network meta-analysis.

Dealing with missing data

We contacted all study authors, but they were unable to provide more data. Authors were given two weeks to respond to our request. When we received no response, we proceeded using the available data. We did not attempt imputation for missing data. We conducted meta-analysis only when there was sufficient quantitative information (e.g. measures of variability, number of participants at risk). Otherwise, we described the results narratively.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we generated descriptive statistics for trial and study population characteristics across all eligible trials that compared each pair of interventions.

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We assessed the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

We planned to assess the assumption of transitivity epidemiologically by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons. We expected the transitivity assumption will hold as long as treatment comparisons were not related to:

- study design (parallel group or within-person);
- acute or chronic CSC;
- date the study was conducted;
- whether the trial was industry sponsored.

In the event, all trials were parallel group, so we did not consider this factor.

Assessment of reporting biases

None of the meta-analyses included 10 or more studies, so we did not prepare a funnel plot as planned in our protocol. We assessed selective outcome reporting bias using the 'Risk of bias' tool.

Data synthesis

Methods for direct treatment comparisons

We performed standard pairwise meta-analyses using a random-effects model in Review Manager 5 (RevMan 2014). We used a fixed-effect model when there were fewer than three studies.

Methods for indirect and mixed comparisons

We performed network meta-analysis using the methodology of multivariate meta-analysis model where different treatment comparisons are treated as different outcomes (White 2012). For this analysis, we used the 'mvmeta' command in STATA (StataCorp, 2011; Stata Statistical Software: Release 13. College Station, TX) (White 2009; White 2011).

We planned to estimate the ranking probabilities for all treatments of being at each possible rank of intervention effectiveness (e.g. best to worst) and then to calculate the surface under the cumulative ranking curve (SUCRA) and mean ranks, but did not do so due to a lack of data in the network.

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In standard pairwise meta-analyses, we estimated heterogeneity variances for each pairwise comparison. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We assessed statistically the presence of heterogeneity within each pairwise comparison using the I^2 statistic (Higgins 2003). The I^2 statistic measures the percentage of variability that cannot be attributed to random error.

The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter ($\tau 2$) estimated from the network meta-analysis models.

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we used the loop-specific approach (Bucher 1997). This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer the presence of inconsistency in each loop. We assumed a common heterogeneity estimate within each loop. We planned to present the results of this approach graphically in a forest plot using the 'ifplot' command in STATA (Chaimani 2013), but in the event, there were not enough loops to make this necessary.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network, we used the 'design-by-treatment' model using the 'mvmeta' command in STATA (Higgins 2012). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we judged the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Subgroup analysis and investigation of heterogeneity

There were insufficient data available to perform subgroup analyses by type of CSC (acute versus chronic).

Sensitivity analysis

We planned the following sensitivity analyses but there were not enough studies contributing to each analysis to enable this.

In standard pairwise comparisons or meta-analyses, we planned to exclude the following studies to determine their impact on effect size for the primary outcome:

- studies with high risk of bias on any domain;
- studies with unpublished data only; and
- industry-funded studies.

'Summary of findings' table

We prepared a 'Summary of findings' table for all comparisons including relative and absolute effects for the following outcomes: mean change in BCVA, persistent CSC, recurrence of CSC and adverse effects. We used GRADE (Guyatt 2011) to assess the overall quality of the evidence for each outcome in pairwise and network meta-analyses (Puhan 2014).

RESULTS

Description of studies

Results of the search

The electronic searches yielded 1168 references (Figure 2). The Trials Search Co-ordinator scanned the search results, removed 299 duplicates and then removed 229 references that were not relevant to the scope of the review. We screened the remaining 640 reports and discarded 554 records as not relevant. We obtained

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86 full-text reports for potential inclusion in the review and we included 25 studies (see Characteristics of included studies table) and excluded 49 studies (see Characteristics of excluded studies table). We also included 12 reports of ongoing studies and will assess the data for these studies when the results become available (see Characteristics of ongoing studies table).

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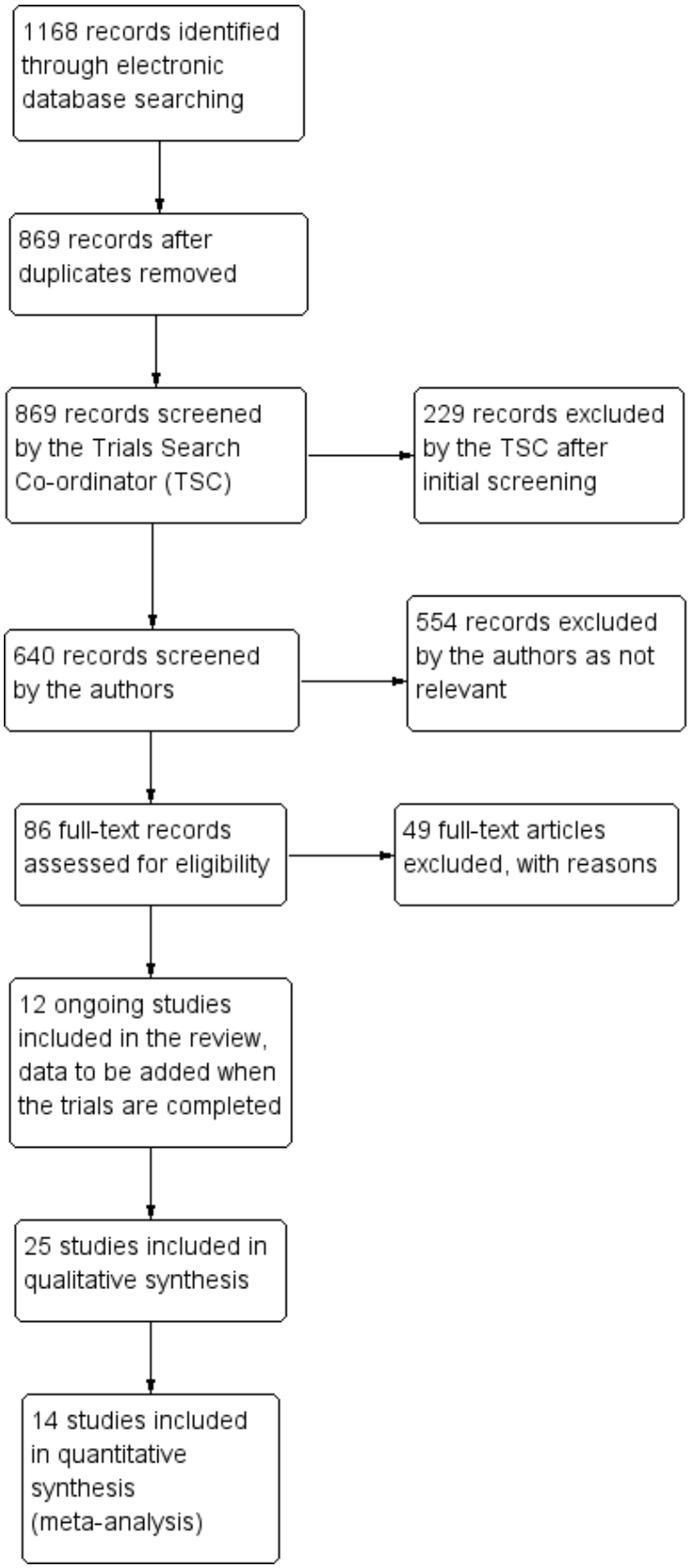
Figure 2. Study flow diagram.



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Included studies

We included 25 studies of 30 full-text articles, of which four studies only had abstracts available (Boscia 2008; Brancato 1994; Chan 2006; Coskun 2014). We contacted the authors of studies with abstracts only; authors of Boscia 2008 and Brancato 1994 did not respond, authors of Coskun 2014 reported not publishing the abstract as a full-text article, and authors of Chan 2006 were not able to provide the corresponding full-text. We provided a summary describing each of the included studies in the Characteristics of included studies table. Thirteen of 25 included studies did not report either the number of eyes or number of participants enrolled; we assumed that all included studies were parallel RCTs, where only one eye per participant was enrolled (Bae 2011; Boscia 2008; Brancato 1994; Browning 1993; Chan 2006; Klatt 2011; Leaver 1979; Ontiveros-Orozco 2004; Rahbani-Nobar 2011; Sawa 2014; Shang 1999; Verma 2004; Zhang 2012).

Types of participants

A total of 1098 participants from 25 included studies were enrolled from Brazil, China, Germany, India, Iran, Italy, Japan, Mexico, South Korea, Thailand, Turkey, the UK, and the US. The baseline characteristics of participants in all trials were similar with respect to age (mean age ranged from 35.0 to 50.8 years). However, 79% (685 of 872 participants) of participants were men; three studies did not report the number of men and women enrolled (Boscia 2008; Coskun 2014; Shang 1999). One study enrolled men only (Pitcher 2015).

Nine studies enrolled participants with acute CSC alone, six studies enrolled participants with chronic CSC alone, and two studies enrolled participants with both acute and chronic CSC. Seven studies did not specify type of CSC. The definition of acute CSC varied between studies; the duration of onset ranged from less than 20 days to six months. Likewise, the definition of chronic CSC varied; the duration of onset ranged from greater than 12 weeks to six months.

Types of interventions

Five classes of interventions were investigated: laser treatments (argon laser photocoagulation, micropulse diode laser photocoagulation, PDT), anti-VEGF, medications that alter steroid hormones (carbonic anhydrase inhibitors), *H. pylori* treatment, and other treatments (antioxidant, calcium antagonist, beta-blocker). In the studies of PDT, where it was specified, treatment was applied to areas of choroidal hyperpermeability, usually identified using ICGA.

The 25 included studies alluded to 19 pair-wise comparisons:

- anti-VEGF versus observation;
- anti-VEGF versus PDT;
- 50% PDT plus anti-VEGF versus 50% PDT;
- different dose regimens of anti-VEGF (six-dose versus four-dose aflibercept);
- 50% PDT versus observation or sham treatment;
- 50% PDT versus PDT;
- 30% PDT versus PDT;
- 30% PDT versus 50% PDT;
- laser versus observation or sham treatment;
- micropulse diode laser versus argon laser;
- indirect argon laser versus direct argon laser;
- antioxidant supplements versus placebo;
- beta-blocker versus placebo;
- beta-blocker versus calcium antagonist;
- *H. pylori* treatment versus placebo or observation;
- carbonic anhydrase inhibitors versus placebo;
- yellow versus red wavelength laser;
- yellow versus green wavelength laser;
- red versus green wavelength laser.

Types of outcomes

Fourteen studies were include in the quantitative analysis. Studies reported BCVA was measured using Snellen chart and LogMAR. When authors reported the number of letters read on a logMAR chart, we converted it to a LogMAR score (Types of outcome measures). Many included studies did not clearly describe the adverse events reported, often not reporting which adverse events were collected.

Follow-up duration ranged from 16 weeks to 12 years. None of the studies reported the proportion of CSC with BCVA 20/40 or better at 12 months, proportion of CSC with BCVA 20/200 or better at 12 months, or quality of life at 12 months.

Excluded studies

We excluded 49 studies of 47 full-text articles and two trial registries. We documented our reasons for exclusion in the Characteristics of excluded studies table. The reasons for exclusion were: 37 studies were not RCTs, 10 studies were of traditional Chinese medication, one study (a trial registry) was terminated early due to lack of enrollment, and one study (a trial registry) enrolled participants with age-related macular degeneration.

Ongoing studies

We identified 12 ongoing studies from the trials registers. These studies are evaluating the following interventions and comparators.

In acute CSC:

- PDT versus observation (EUCTR2009-017959-98-NL);
- aflibercept versus sham injection (NCT01971190);
- eplerenone versus placebo (NCT01990677; NCT02215330).

In chronic CSC;

- lutein versus placebo (JPRN-UMIN000005372);
- spironolactone versus placebo (NCT01552044);
- eplerenone versus placebo (NCT01990677; NCT02153125);
- three doses of PDT (50%, 40%, 30%) (NCT01630863);
- half-dose versus half-fluence PDT (NCT01019668);
- half dose PDT versus micropulse diode laser (NCT01797861).

Note: trial NCT01990677 includes both acute and chronic CSC separately.

Type of CSC not clearly specified:

- micropulse diode laser versus observation (NCT01982383);
- short-term oral mifepristone versus placebo (NCT02354170).

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Risk of bias in included studies

Figure 3 provides a summary of our judgments for each risk of bias domain for the included studies.

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Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

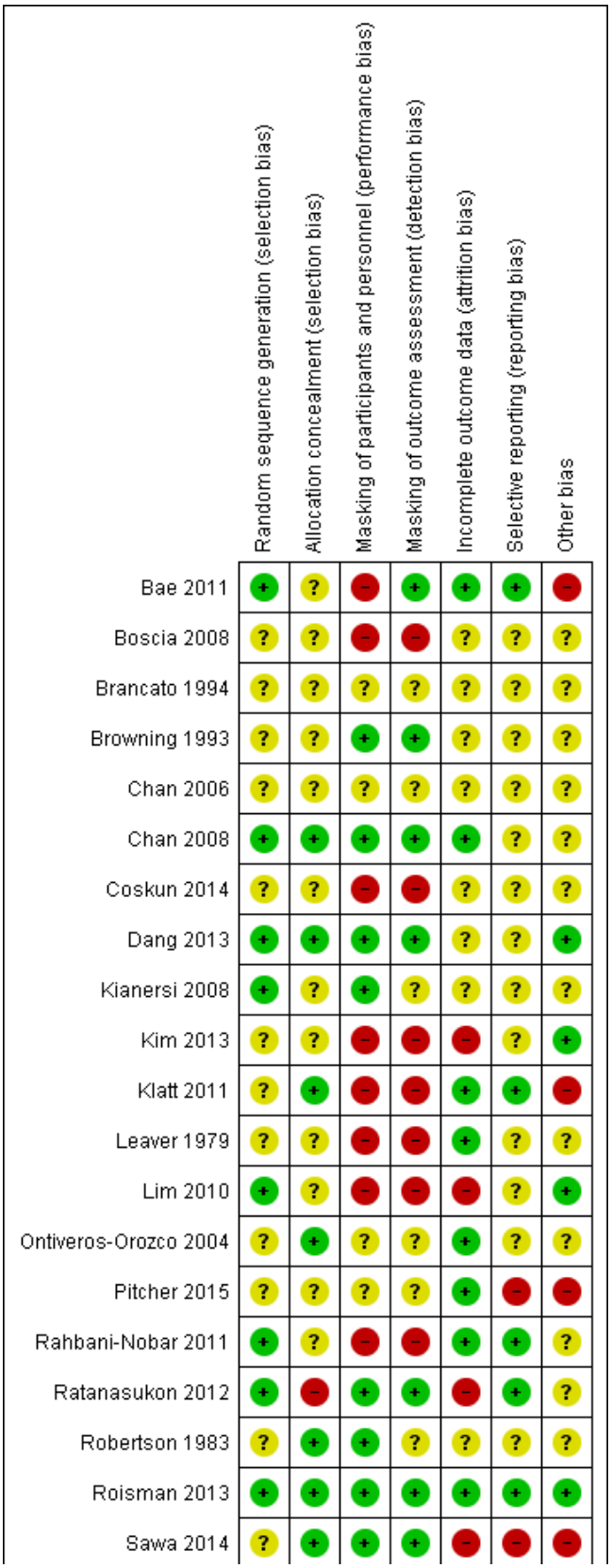

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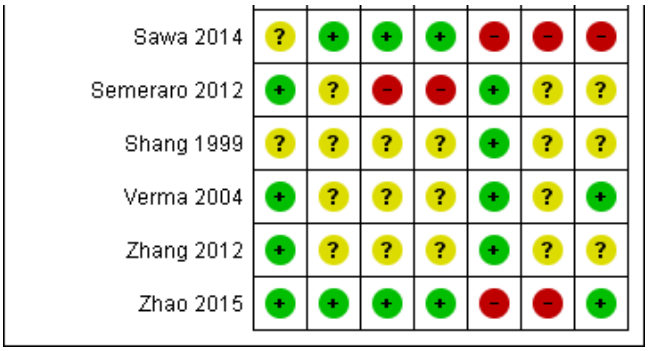
Figure 3. (Continued)



Allocation

We judged 12 of 25 included studies at low risk of bias as the authors explicitly reported the method used to generate a random sequence (e.g. computer-generated, randomization software, random table, random block size design). We judged the remaining 13 studies at unclear risk of bias as the authors did not clearly describe or report the method of randomization. None of the included studies were judged at high risk of bias.

We judged eight of 25 included studies at low risk of bias as the authors explicitly reported appropriate methods to conceal the assignment sequence (e.g. data coordination center, opaque sealed envelope). We judged 16 of 24 included studies at unclear risk of bias as they had an appropriate method of random sequence generation, but did not clearly describe how the random sequence was assigned or stored, or they did not clearly describe how the random sequence was generated or stored. We judged one included study at high risk of bias as one of the investigators was involved in the sequence generation and assignment (Ratanasukon 2012).

Masking of participants and personnel (performance bias)

We judged each study based on the interventions administered to each group; studies had different treatments (e.g. laser versus observation) and studies with similar treatments (e.g. 50% PDT versus 30% PDT). Nine studies compared different treatments (Bae 2011; Boscia 2008; Coskun 2014; Kim 2013; Klatt 2011; Leaver 1979; Lim 2010; Rahbani-Nobar 2011; Semeraro 2012). None of these studies explicitly reported masking and so we judged them at high risk of performance bias.

The remaining 16 studies had similar treatments. Nine of these 16 studies were judged at low risk of bias as the authors had explicitly stated that participants were masked. We judged seven of these 15 studies at unclear risk of bias as there was no information on masking or reported 'double blinded' without explicit description of how they were masked.

Masking of outcome assessors (detection bias)

Eight studies reported that outcome assessors were masked to treatment group and we judged them at low risk of detection bias (Bae 2011; Browning 1993; Chan 2008; Dang 2013; Ratanasukon 2012; Roisman 2013; Sawa 2014; Zhao 2015). Eight studies did not report any masking and the treatments were different and so we judged them at high risk of detection bias (Boscia 2008; Coskun 2014; Kim 2013; Klatt 2011; Leaver 1979; Lim 2010; Rahbani-Nobar 2011; Semeraro 2012). In the remainder, it was unclear in general because the groups were similar but masking was not explicitly reported.

Incomplete outcome data

We judged five studies at high risk of attrition bias. Kim 2013 did not report the number of people randomized and loss to follow-up by group and the final numbers analyzed were identical between treatment and observation group (20/20). Lim 2010 did not follow up 25% of participants and did not report which group they were in. Sawa 2014 excluded 5/39 participants after randomization but did not report which group they were in. Ratanasukon 2012 lost 3/29 participants to follow-up at three months in intervention group and 4/29 in the control group (4/29) but at 12 months, only assessed seven participants in each group. So there was a low risk at three months and high risk for 12 months outcomes. In Zhao 2015, there were different losses to follow-up in each group (13% compared with 6%).

We judged 12 studies at low risk of attrition bias because loss to follow-up was less than 20% and there was no obvious reason why loss to follow-up should be related to outcome (Bae 2011; Chan 2008; Klatt 2011; Leaver 1979; Ontiveros-Orozco 2004; Pitcher 2015; Rahbani-Nobar 2011; Roisman 2013; Semeraro 2012; Shang 1999; Verma 2004; Zhang 2012).

In the remaining studies, it was unclear whether attrition bias was a problem, usually because of a lack of information.

Selective reporting

Only five studies were at low risk of selective reporting, that is, outcomes reported a priori (usually on a trials registry entry) were reported in the published paper (Bae 2011; Klatt 2011; Rahbani-Nobar 2011; Ratanasukon 2012; Roisman 2013). In most cases it was unclear because we did not have access to the trial protocol and the trial was not registered with a publicly available database. For Pitcher 2015, Sawa 2014, and Zhao 2015, there was some evidence of selective reporting. Sawa 2014 measured, but did not report, BCVA and only reported resolution of CSC for the intervention (lutein) group. Pitcher 2015 included additional outcomes that were not specified in the trial registry entry. Zhao 2015 specified the primary outcome at clinicaltrials.gov (NCT01574430) was "change from baseline in BCVA", but primary outcomes specified in the published report were OCT-based improvement rate and FA-based improvement rate at six and 12 months. They did report BCVA, but it was not defined as primary outcome (Zhao 2015).

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Other potential sources of bias

We judged four studies at risk of bias either because they were industry funded or there was a declared conflict of interest (Bae 2011; Klatt 2011; Pitcher 2015; Sawa 2014). Six studies were at low risk of bias because they were non-industry funded or the authors declared they had no conflicts of interest, or both (Dang 2013; Kim 2013; Lim 2010; Roisman 2013; Verma 2004; Zhao 2015). For the remainder of the studies, it was unclear, usually because the studies did not report funding sources and conflicts of interest.

Effects of interventions

See: **Summary of findings for the main comparison** Interventions for central serous chorioretinopathy: direct comparisons

Pairwise meta-analysis (direct comparisons)

Anti-vascular endothelial growth factor versus observation

Two trials compared anti-VEGF therapy to observation; both studies were conducted in South Korea (Kim 2013; Lim 2010). Both studies enrolled participants with acute CSC, which was defined as CSC of less than three months' duration. A total of 82 people (82 eyes) were randomized in these two trials and 64 people were followed up to six months. Both trials were at high risk of performance, detection, and attrition bias.

In Kim 2013, a single dose of ranibizumab (0.5 mg/0.05 mL) was given at baseline and participants followed up for six months. In Lim 2010, a single dose of bevacizumab (1.25 mg/0.05 mL) was given within one week of diagnosis and participants were followed up for six months.

Mean change in best-corrected visual acuity between baseline and 12 months

Both trials reported visual acuity at six months, which was similar in the anti-VEGF and observation groups (MD 0.01 LogMAR, 95% CI -0.02 to 0.03; 64 eyes; $I^2 = 0\%$; Analysis 1.1). We judged this to be low quality evidence downgrading for risk of bias (-1) and indirectness (-1) as the outcome was only measured at six and not 12 months.

Recurrence of central serous chorioretinopathy at 12 months

Neither trial reported recurrence of CSC at 12 months.

Persistent central serous chorioretinopathy at 12 months

Both trials reported that all participants in treatment and control groups (total of 64 eyes) were resolved by six months (i.e. did not have persistent CSC).

Mean change in contrast sensitivity between baseline and 12 months

Neither trial reported mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

Both studies measured central retinal thickness using an OCT. There was no evidence for a difference between the two groups (MD 8.73 µm, 95% CI -18.08 to 35.54; 64 participants; $I^2 = 20\%$; Analysis 1.2) We judged this to be low quality evidence downgrading for risk of bias (-1) and indirectness (-1).

Best-corrected visual acuity 20/40 or better at 12 months

Neither trial reported BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

Neither trial reported BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

Neither trial reported quality of life at 12 months.

Adverse events

Both studies reported that there were no adverse effects of anti-VEGF treatment. Kim 2013 specified that they looked for systemic and ocular adverse events.

Anti-vascular endothelial growth factor versus photodynamic therapy

Two studies compared anti-VEGF to PDT and were conducted in South Korea (Bae 2011) and Italy (Semeraro 2012). Both studies enrolled participants with chronic CSC: in Bae 2011 this was defined as "chronic CSC with visual disturbance persisting for >6 months or recurrent CSC"; in Semeraro 2012 this was defined as "either persistence of subretinal fluid detected on optical coherence topography (OCT) for at least 3 months after diagnosis or more than 3 recurrences in at least 3 months with gravitational RPE atrophy". A total of 54 participants (56 eyes) were randomized in these trials and all were followed up to nine months (Semeraro 2012) and 12 months (Bae 2011). We judged both studies at high risk of performance bias; Semeraro 2012 was also at high risk of detection bias; Bae 2011 was industry funded.

In both studies, PDT was "low fluence", which means that they used a light dose of 25 J/cm^2. In Bae 2011, ranibizumab (0.5 mg/0.05 mL) was given at baseline, one month, and two months; in Semeraro 2012, bevacizumab (1.25 mg) was given at baseline and then as needed after four weeks.

Mean change in best-corrected visual acuity between baseline and 12 months

Visual acuity was similar between the two groups (MD 0.03 logMAR, 95% CI -0.08 to 0.15; 56 eyes; $I^2 = 0\%$; Analysis 2.1). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1) as we cannot exclude a clinically important effect.

Recurrence of central serous chorioretinopathy at 12 months

The two studies had different results for this outcome ($I^2 = 71\%$; Analysis 2.2). In Bae 2011, there was a much higher risk of recurrence in the anti-VEGF group (ranibizumab) compared with the PDT group (RR 19.83, 95% CI 1.19 to 330.50; 21 eyes); in Semeraro 2012 there was also an increased risk of recurrence in the anti-VEGF (bevacizumab) group but the size of the effect was much smaller and the CIs included 1 (i.e. no effect) (RR 1.46, 95% CI 0.59 to 3.58; 22 eyes). Note the denominator in these studies is smaller as only the eyes where CSC had resolved were at risk of recurrence. We judged this to be very low quality of evidence downgrading for risk of bias (-1), imprecision (-1), and inconsistency (-1); we are very uncertain as to the size of the effect.

Persistent central serous chorioretinopathy at 12 months

Only Bae 2011 reported persistent CSC at 12 months. People in the anti-VEGF group (ranibizumab) were more likely to have persistent

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CSC at 12 months (RR 6.19, 95% CI 1.61 to 23.81; 34 eyes; Analysis 2.3). We judged this to be low quality evidence and downgraded for risk of bias (-1) and imprecision (-1).

Mean change in contrast sensitivity between baseline and 12 months

Neither trial reported mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The two studies found different results for central retinal thickness (I^2 = 69%; Analysis 2.4). In Bae 2011, there was a greater reduction in thickness in the PDT group (MD 31.30 µm, 95% CI -3.46 to 66.06); in Semeraro 2012, there was a greater reduction in the anti-VEGF group (bevacizumab) (MD -13.00, 95% CI -46.05 to 20.05). We judged this to be very low quality of evidence downgrading for risk of bias (-1), imprecision (-1), and inconsistency (-1); we are very uncertain as to the size of the effect.

Best-corrected visual acuity 20/40 or better at 12 months

Neither trial reported BCVA 20/40 or better at 12 months.

Central serous chorioretinopathy eyes with best-corrected visual acuity 20/200 or worse at 12 months

Neither trial reported CSC eyes with BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

Neither trial reported quality of life at 12 months.

Adverse events

Both studies reported that no systemic or ocular adverse events related to the drugs or procedures were observed.

Anti-vascular endothelial growth factor plus 50% photodynamic therapy versus 50% photodynamic therapy alone

One study conducted in Turkey compared anti-VEGF (bevacizumab 1.25 mg single dose three days after PDT) plus PDT to PDT alone (Coskun 2014). The PDT was "half dose" (i.e. the dose of verteporfin used was half that usually delivered (3 mg/m^2)). The study enrolled 15 participants with chronic CSC (duration six months) and followed them up for a mean of 12 months in the anti-VEGF plus PDT group and nine months in the PDT alone group. This study was reported in an abstract only and was largely judged at unclear risk of bias apart from performance and detection bias where we judged them at high risk of bias because masking was not mentioned and the treatments were obviously different.

Mean change in best-corrected visual acuity between baseline and 12 months

At follow-up, the mean logMAR visual acuity in the anti-VEGF plus PDT group was 0.36 (standard deviation (SD) 0.25) and in the PDT alone group was 0.06 (SD 0.15). This gives an MD in favor of PDT alone of 0.30 logMAR (95% CI 0.09 to 0.51; Analysis 3.1). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1) as the CIs include clinically unimportant effects.

Recurrence of central serous chorioretinopathy at 12 months

The trial did not report recurrence of CSC at 12 months.

Persistent central serous chorioretinopathy at 12 months

CSC resolved in 7/8 eyes in the anti-VEGF plus PDT group and 6/7 eyes in the PDT alone group (RR 0.88, 95% CI 0.07 to 11.54; Analysis 3.2). We judged this to be very low quality evidence and downgraded for risk of bias (-1) and imprecision (-2) due to very wide CIs. We are very uncertain as to the size of the effect.

Mean change in contrast sensitivity between baseline and 12 months

The trial did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

In the anti-VEGF plus PDT group, the central macular thickness was 203 µm (SD 45) and in the PDT alone group it was 187 µm (SD 15) (MD 16.00 µm, 95% CI -17.10 to 49.10; Analysis 3.3). We judged this to be low quality evidence; we downgraded for risk of bias (-1) and imprecision (-1).

Best-corrected visual acuity 20/40 or better at 12 months

The trial did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The trial did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The trial did not report quality of life at 12 months.

Adverse events

The trial did not report adverse events.

Six-dose anti-vascular endothelial growth factor versus four-dose anti-vascular endothelial growth factor

One study from the US compared two treatment regimens: aflibercept 2.0 mg/0.05 mL administered six times (at baseline, one, two, three, four, and five weeks) versus four times (at baseline, one, two, and four weeks) (Pitcher 2015). The study enrolled 12 participants and followed them for six months. This study was poorly reported with mostly unclear risk of bias and high risk of reporting bias. The study received industry funding.

Mean change in best-corrected visual acuity between baseline and 12 months

There was a similar change in logMAR acuity over six months in the two groups. In the group given six doses, on average visual acuity improved by 0.1 logMAR (SD 0.32) and in the group given four doses it improved by 0.08 logMAR (SD 0.16). This was an MD of 0.02 logMAR units greater improvement (95% CI -0.31 to 0.27) in the six-doses group but with wide CIs (Analysis 4.1). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1).

Recurrence of central serous chorioretinopathy at 12 months

The trial did not report recurrence of CSC at 12 months.

Persistent central serous chorioretinopathy at 12 months

The trial did not report persistent CSC at 12 months.

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Mean change in contrast sensitivity between baseline and 12 months

The trial did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The two groups had similar change in central macular thickness over six months with an MD of 26.50 µm (95% CI -123.41 to 176.41; 12 participants). Both groups experienced a decrease: in the six-dose group of -80 µm (SD 103.7) and in the four-dose group of -103 µm (SD 156). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1).

Best-corrected visual acuity 20/40 or better at 12 months

The trial did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The trial did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The trial did not report quality of life at 12 months.

Adverse events

The trial reported there were no adverse events.

Photodynamic therapy versus observation or sham treatment

Two studies compared PDT to no PDT and were conducted in Italy (Boscia 2008) and China (Hong Kong) (Chan 2008).

Boscia 2008 was reported in an abstract only and there was no information on our review outcomes. We contacted the investigators (twice) for more information but did not receive a reply. In the abstract report of Boscia 2008 no actual data were reported. In the results section, the following statement was made "No significant changes in all parameters were seen in untreated group. An improvement of far and near BCVA were seen in comparison with both baseline (ANOVA, p=0,008 and 0,000), and control group (t-TEST, p=0,010 at p=0,000), with the greatest effect at week 24. In all treated eyes a complete resolution of subretinal fluid was observed, with significant reduction of central macular thickness. On week 24, in treated eyes, a significant improvement in mean fixation stability was also observed (ANOVA, p=0,011). No recurrence and/or adverse event occurred in any of the treated patients during the follow-up".

Therefore, the following review outcomes were only available for Chan 2008.

Chan 2008 enrolled people with acute CSC, which was defined as less than three months' duration. The study enrolled 63 people (63 eyes) and followed up 58 people to 12 months. The study was low risk of bias in most domains and unclear for two domains: selective outcome reporting (where we did not have access to protocol or trials register entry to check this) and other bias (one of the authors declared a conflict of interest but this was only one of five authors and not the first author). Chan 2008 compared 'half dose' PDT (verteporfin 3 mg/m^2) to sham PDT treatment (saline infusion and laser application as for PDT).

Mean change in best-corrected visual acuity between baseline and 12 months

At 12 months, the visual acuity in the PDT group was better than the visual acuity in the sham PDT group (MD -0.10, 95% CI -0.18 to -0.02). We judged this to be low quality evidence, downgrading for imprecision (-1) (as the CIs included a clinically unimportant effect) and risk of bias (-1) (Analysis 5.1).

Recurrence of central serous chorioretinopathy at 12 months

CSC resolved in 38 eyes in the PDT group and one of these 38 eyes had a recurrence by 12 months. In the control group, 15/19 resolved and four of these 15 had a recurrence (RR 0.10, 95% CI 0.01 to 0.81; Analysis 5.2). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1), as there were very few events.

Persistent central serous chorioretinopathy at 12 months

One of 29 eyes had persistent CSC in the PDT group compared with 4/39 eyes in the control group (RR 0.12, 95% CI 0.01 to 1.02; Analysis 5.2). We judged this to be low quality evidence; downgrading for risk of bias (-1) and imprecision (-1).

Mean change in contrast sensitivity between baseline and 12 months

The trial did not report mean change in contrast sensitivity between baseline and 12 months

Mean change in central retinal thickness between baseline and 12 months

The CRT was thinner in the PDT group compared with the sham PDT group at 12 months (MD -117.00 µm, 95% CI -205.71 to -28.29; Analysis 5.3). We judged this to be low quality evidence, downgrading for risk of bias (-1) and imprecision (-1), as the CIs included a clinically unimportant effect.

Best-corrected visual acuity 20/40 or better at 12 months

The trial did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The trial did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The trial did not report quality of life at 12 months.

Adverse events

Chan 2008 reported that no systemic or ocular adverse events related to the PDT procedure were observed.

30% photodynamic therapy compared with 50% photodynamic therapy compared with photodynamic therapy

One study compared 30% PDT, 50% PDT, and PDT (Zhang 2012). This study was conducted in China and enrolled 90 eyes of 90 participants with 30 participants in each group and followed them up to 12 months. The type of CSC was not specified. We largely judged this study to be at unclear risk of bias because of problems with reporting.

One additional study, also conducted in China, compared 30% PDT with 50% PDT (Zhao 2015). This study enrolled 129 participants (129 eyes) and followed 117 participants to 12 months. We judged this study to be at low risk of bias in most domains with the exception

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of attrition bias (6% of the 30% PDT group were lost to follow-up compared to 13% of the 50% PDT group) and selective outcome reporting (primary and secondary outcomes were designated differently on the trial register entry and the published report).

Both studies applied 50 J/cm^2 light energy for 83 seconds but varied the dose of verteporfin: full dose (6 mg/m^2), 50% dose (3 mg/m^2), and 30% dose (2 mg/m^2) (Zhang 2012), and 1.8 mg/m^2 (Zhao 2015).

Mean change in best-corrected visual acuity between baseline and 12 months

30% photodynamic therapy compared with photodynamic therapy

The mean change in visual acuity for the 30% PDT group was 0.03 logMAR (SD 0.02) and the mean change in the PDT group was 0.19 logMAR (SD 0.16). This gives an MD in favor of 30% PDT group (MD -0.16 logMAR, 95% CI -0.22 to -0.10; Analysis 6.1). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

50% photodynamic therapy compared with photodynamic therapy

The mean change in visual acuity for the 50% PDT group was 0.23 logMAR (SD 0.15) and the mean change in the PDT group was 0.19 logMAR (SD 0.16). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1) due to wide CIs. We are uncertain as to the size of the effect (MD 0.04, 95% CI -0.04 to 0.12; Analysis 7.1).

30% photodynamic therapy compared with 50% photodynamic therapy

The MD was favor of 30% PDT group over 50% PDT (MD -0.12, 95% CI -0.15 to -0.08; 177 participants; 2 studies; Analysis 8.1). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

Recurrence of central serous chorioretinopathy at 12 months

30% photodynamic therapy compared with photodynamic therapy

CSC resolved in 30 eyes in the 30% PDT group and 22 of these 30 eyes had a recurrence by 12 months. In the control group, 30 eyes resolved and eight of these 30 had a recurrence (RR 2.75, 95% CI 1.46 to 5.17; Analysis 6.2). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

50% photodynamic therapy compared with photodynamic therapy

CSC resolved in 30 eyes in the 50% PDT group and 10 of these 30 eyes had a recurrence by 12 months. In the PDT group, 30 eyes resolved and eight of these 30 had a recurrence (RR 1.25, 95% CI 0.57 to 2.73; 60 participants; 1 study; Analysis 7.2). We judged this low quality evidence, downgrading for risk of bias (-1) and imprecision (-1).

30% photodynamic therapy compared with 50% photodynamic therapy

The risk of recurrence of CSC for 30% PDT at 12 months was 2.5 times higher than that of 50% PDT group (RR 2.50, 95% CI 1.54 to 4.06; 153 participants; Analysis 8.2). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

Persistent central serous chorioretinopathy at 12 months

30% photodynamic therapy compared with photodynamic therapy

Zhang 2012 did not report 30% PDT compared with PDT.

50% photodynamic therapy compared with photodynamic therapy

Zhang 2012 did not report 50% PDT compared with PDT.

30% photodynamic therapy compared with 50% photodynamic therapy

Data from Zhao 2015 showed that CSC was persistent in 19 of 61 eyes in the 30% PDT group and in four of 56 eyes in the 50% PDT group (RR 4.36, 95% CI 1.58 to 12.04; Analysis 8.3). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

Mean change in contrast sensitivity between baseline and 12 months

Neither study reported mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

30% photodynamic therapy compared with photodynamic therapy

The mean change in central retinal thickness was reduced by 10.8 µm (SD 6.52) in the 30% PDT group and reduced by 52.13 µm (SD 9.06) in the PDT group. This means that on average there was a greater reduction in central retinal thickness in the PDT group (MD 41.33 µm, 95% CI 37.34 to 45.32; 60 participants; Analysis 6.3). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

50% photodynamic therapy compared with photodynamic therapy

The mean change in central retinal thickness was reduced 55.66 µm (SD 0.21) in the 50% PDT group and reduced by 52.13 µm (SD 9.06) in the PDT group. This means that there was a small greater reduction in central retinal thickness in the 50% PDT group (MD -3.53, 95% CI -6.77 to -0.29; Analysis 7.3). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1).

30% photodynamic therapy compared with 50% photodynamic therapy

There was a greater mean reduction in central retinal thickness in the 50% PDT group (MD 44.90, 95% CI 42.57 to 47.23; 177 participants; Analysis 8.4). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

Best-corrected visual acuity 20/40 or better at 12 months

Neither study reported BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

Neither study reported BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

Neither study reported quality of life at 12 months.

Adverse events

Zhang 2012 did not report on adverse events.

Zhao 2015 reported that no ocular adverse event occurred; one participant developed nausea because of an allergic reaction to verteporfin.

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Laser versus observation or sham treatment

Four studies compared laser to observation or sham laser treatment.

Klatt 2011 was conducted in Germany and enrolled 30 eyes with acute CSC (30 participants) in a trial of micropulse laser ("selective retina therapy") compared with observation with follow-up of three months. Selective retina therapy was Q-switched neodymium-doped yttrium lithium fluoride (Nd:YLF) laser with a wavelength of 527 nm. They used a spot diameter of 200 µm and pulse repetition rate of 100 Hz. We judged this study at high risk of performance and detection bias and the authors reported conflict of interest.

Leaver 1979 was conducted in the UK and compared direct argon laser photocoagulation to observation in 67 people with acute CSC. Four participants were lost to follow-up at 12 months. With the exception of two subfoveal leaks, direct treatment was applied using the "Coherent Radiation 800" argon laser to the leaking spot using burns of 50 to 200 µm in diameter. The study was at high risk of performance and detection bias and otherwise was not clearly reported (being quite an old study) and was largely at unclear risk of bias for the other domains.

Robertson 1983 was conducted in the US and enrolled 41 participants (42 eyes) with acute CSC. The study sample was stratified according to the site of leakage. In eyes where the leakage site was in the papillomacular bundle, or within 500 µm of the capillary-free zone of the macula, eyes were randomly assigned either to indirect argon laser photocoagulation or sham treatment. In eyes where the leakage site was outside the papillomacular bundle, and more than 500 µm from the capillary-free zone, eyes were randomly allocated to direct or indirect laser photocoagulation - this comparison is discussed below. Participants receiving indirect laser photocoagulation received three argon laser burns directed to the pigment epithelium in an area remote from the fovea, the papillomacular bundle, and the fluorescein leakage site. The laser beam diameter was 200 µm and the burn duration was 0.2 seconds at a power setting of 80 to 120 mW. In the sham technique, the laser beam was switched in the "off" position. We judged the study at low risk of performance and detection bias but unclear risk for other domains (being an older study relevant aspects were not reported).

Roisman 2013 was conducted in Brazil and compared micropulse diode laser to sham photocoagulation in 15 people with chronic CSC. The laser treatment consisted of subthreshold 810-nm diode micropulse laser. We judged the study to be largely at low risk of bias.

Mean change in best-corrected visual acuity between baseline and 12 months

This outcome was available for only two of the four studies (Klatt 2011; Roisman 2013). In Leaver 1979, Snellen acuities were converted to a numerical scale from 1 (6/4) to 5 (6/12). The mean acuity at six months was 3.1 in the laser group and 2.9 in the control group. In Robertson 1983, mean visual acuity was not reported.

The two studies that reported mean change in BCVA between baseline and 12 months had high statistical heterogeneity (I^2 = 82%) but both were in favor of laser treatment (Analysis 9.1). In Klatt 2011, the difference between treatment and control at three months in improvement in vision was -0.13 logMAR (95% CI -0.24 to -0.01) in favor of selective retina therapy. In Roisman 2013, the difference between final visual acuity at six months was -0.38 logMAR (95% CI -0.56 to -0.20) in favor of micropulse diode laser treatment.

Recurrence of central serous chorioretinopathy at 12 months

One study reported on recurrence of CSC at 12 months (Robertson 1983). Similar numbers of the indirect laser group (5/15) compared with the sham laser group had a recurrence during the study (RR 1.25, 95% CI 0.41 to 3.77; Analysis 9.2). We judged this to be very low quality evidence downgrading for risk of bias (-1) and imprecision (-2).

Persistent central serous chorioretinopathy at 12 months

None of the studies clearly reported persistent CSC at 12 months.

Mean change in contrast sensitivity between baseline and 12 months

None of the studies reported mean change in contrast sensitivity between baseline and 12 months

Mean change in central retinal thickness between baseline and 12 months

None of the studies reported mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

None of the studies reported BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

None of the studies reported BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

None of the studies reported quality of life at 12 months.

Adverse events

Klatt 2011 reported that no adverse effects related to micropulse laser were observed.

Roisman 2013 did not specifically report on adverse events but did note "no evidence of retinal damage induced by the treatment".

Leaver 1979 and Robertson 1983 did not provide any information on adverse effects.

Micropulse diode laser versus argon laser

One trial conducted in India compared micropulse diode laser to argon laser (Verma 2004). The study enrolled 30 people with CSC (not specified whether acute or chronic) and allocated them to 810-nm diode laser or 514-nm argon laser and followed them up for 12 weeks. We judged the trial to be at low/unclear risk of bias.

Mean change in best-corrected visual acuity between baseline and 12 months

This was reported in Snellen decimal acuity.

	Mean (SD) Snellen decimal acuity

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	Micropulse diode laser (15 participants)	Argon laser (15 participants)
Baseline	0.29 (0.14)	0.32 (0.16)
12 weeks	1.06 (0.09)	0.98 (0.14)

Recurrence of central serous chorioretinopathy at 12 months

None of the 30 participants had a recurrence before 12 weeks.

Persistent central serous chorioretinopathy at 12 months

None of the 30 participants had persistent CSC at 12 weeks.

Mean change in contrast sensitivity between baseline and 12 months

	Mean absolute value of contrast sensitivity (Cambridge low contrast gratings)	
	Micropulse diode laser (15 participants)	Argon laser (15 participants)
Baseline	98.4 (24.77)	130.66 (31.95)
12 weeks	306.0 (46.57)	215.33 (23.25)

Mean change in central retinal thickness between baseline and 12 months

The study did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

The study did not report BCVA 20/40 or better at 12 months

Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months

Quality of life at 12 months

The study did not report quality of life at 12 month.

Adverse events

None of the participants developed subretinal neovascularization. No other complications or adverse effects were mentioned.

Indirect argon laser versus direct argon laser

One study compared indirect and direct argon laser (Robertson 1983). This study was conducted in the US and enrolled 41 participants (42 eyes) with acute CSC. In eyes where the leakage site was outside the papillomacular bundle, and more than 500 µm from the capillary-free zone, eyes were randomly allocated to direct or indirect laser photocoagulation. Participants receiving indirect laser photocoagulation received three argon laser burns directed to the pigment epithelium. The laser beam diameter was 200 µm and the burn duration was 0.2 seconds at a power setting of 80 to 120 mW. We judged the study at low risk of performance and detection bias but unclear risk for other domains (being an older study relevant aspects were not reported).

Mean change in best-corrected visual acuity between baseline and 12 months

The study did not report mean change in BCVA between baseline and 12 months.

Recurrence of central serous chorioretinopathy at 12 months

Three of five participants in the indirect group experienced a recurrence by 24 weeks compared with 0/7 in the direct laser group (RR 9.33, 95% CI 0.59 to 148.60; Analysis 10.1). We judged this to be very low quality evidence downgrading for risk of bias (-1) and imprecision (-2); we are very uncertain as to the size of the effect.

Persistent central serous chorioretinopathy at 12 months

The study did not report persistent CSC at 12 months.

Mean change in contrast sensitivity between baseline and 12 months

The study did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The study did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

The study did not report BCVA 20/40 or better at 12 months.

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Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The study did not report quality of life at 12 months.

Adverse events

The study did not report adverse events.

Yellow versus red versus green wavelength laser

One study conducted in China compared yellow, red, and green wavelength laser in 90 participants with CSC of duration longer than eight weeks (Shang 1999). We largely judged the trial to be at unclear risk of bias.

Mean change in best-corrected visual acuity between baseline and 12 months

The study did not report mean change in BCVA between baseline and 12 months.

Recurrence of central serous chorioretinopathy at 12 months

The relative effects of these wavelengths on this outcome were uncertain (Analysis 11.1). We graded these estimates as low quality evidence downgrading for risk of bias (-1) and imprecision (-1).

Yellow compared with red

RR 0.60, 95% CI 0.16 to 2.29; 60 eyes.

Yellow compared with green

RR 0.72, 95% CI 0.18 to 2.96; 59 eyes.

Red compared with green

RR 1.21, 95% CI 0.36 to 4.06; 59 eyes.

Persistent central serous chorioretinopathy at 12 months

The study did not report persistent CSC at 12 months.

Mean change in contrast sensitivity between baseline and 12 months

The study did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The study did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

The study did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The study did not report quality of life at 12 months.

Adverse events

The study did not report adverse events.

Antioxidant supplements versus placebo

Two studies compared antioxidant supplements to placebo.

Ratanasukon 2012 was conducted in Thailand and enrolled 58 participants (58 eyes) with acute CSC (onset within six weeks). These participants were randomly allocated to antioxidants or placebo and followed up at three and 12 months. There was high attrition at 12 months with only 14 people seen at that time point. The antioxidants were supplied as ICaps (Alcon Laboratories) in a version that contained vitamin A (6600 IU), vitamin C (400 mg), vitamin E (150 IU), riboflavin (10 mg), zinc (60 mg), copper (4 mg), selenium (40 mg), manganese (4 mg), and lutein/zeaxanthin (4000 µg). We judged the study at high risk of selection bias and attrition bias.

Sawa 2014 was conducted in Japan and investigated the effects of a lutein supplement (20 mg/day) with follow-up of four months. The type of CSC and the total number of people randomized was not specified. The total number analyzed was 39. We judged the study at high risk of attrition bias and selective outcome reporting bias and it was funded by the manufacturer of the supplement.

The main aim of Sawa 2014 was to examine at changes in macular pigment optical density; none of our review outcomes were reported. The following outcomes are discuss for Ratanasukon 2012.

Mean change in best-corrected visual acuity between baseline and 12 months

Visual acuity at 12 months was similar in the antioxidant and placebo groups (MD 0.01, 95% CI -0.04 to 0.06; 14 participants; Analysis 12.1). We judged this to be low quality evidence downgrading for risk of bias (-2).

Recurrence of central serous chorioretinopathy at 12 months

Only three participants had a recurrence, one in the antioxidant group and two in the control group (RR 0.32, 95% CI 0.03 to 3.19; 36 participants; Analysis 12.2). With so few events, we are very uncertain as to the effect and judged this to be very low quality evidence downgrading for risk of bias (-1) and imprecision (-2).

Persistent central serous chorioretinopathy at 12 months

The paper did not report persistent CSC at 12 months clearly but the number of people with complete resolution was reported. People in the antioxidant group were less likely to have complete resolution (RR 0.35, 95% CI 0.13 to 0.95; 51 participants; Analysis 12.3). We judged this to be low quality evidence downgrading for risk of bias (-1) and indirectness (-1), as it was not precisely the outcome required.

Mean change in contrast sensitivity between baseline and 12 months

The study did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

There was a mean reduction of 180 µm (SD 15.05) in the antioxidant group compared to 186.22 µm reduction in the placebo group (MD -6.22, 95% CI -25.13 to 12.69; 14 participants; Analysis 12.4).

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Best-corrected visual acuity 20/40 or better at 12 months

The study did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The study did not report quality of life at 12 months.

Adverse events

The study reported "no significant side effects" at three months.

Beta-blocker versus placebo

Two studies compared beta-blocker to placebo. They were conducted in US (Browning 1993) and Iran (Kianersi 2008). The studies enrolled a total of 76 eyes (possibly 76 people) and followed them up to four months (Browning 1993) and 12 months (Kianersi 2008).

Browning 1993 looked at the effect of nadolol 40 mg/day in 16 participants and Kianersi 2008 investigated propranolol 40 mg/day delivered as 20 mg twice a day in 60 participants.

We judged both studies at low risk of detection bias because they were placebo controlled, but were largely judged at unclear risk of bias for the other domains because of poor reporting.

Browning 1993 was a short report and did not report any of the review outcomes. The following outcomes are discussed for Kianersi 2008 only (60 eyes).

Mean change in best-corrected visual acuity between baseline and 12 months

Mean visual acuity in the propranolol group at 12 months was 0.98 logMAR (SD 0.13) and in the placebo group was 0.97 logMAR (SD 0.18) (MD 0.01 logMAR, 95% CI -0.07 to 0.09; 60 eyes; Analysis 13.1). We judged this to be moderate quality evidence downgrading for risk of bias (-1).

Recurrence of central serous chorioretinopathy at 12 months

The effect of beta-blocker on recurrence was uncertain (RR 0.60, 95% CI 0.16 to 2.29; 60 eyes; Analysis 13.2). We judged this to be low quality evidence, downgrading for risk of bias (-1) and imprecision (-1).

Persistent central serous chorioretinopathy at 12 months

The study did not report persistent CSC at 12 months.

Mean change in contrast sensitivity between baseline and 12 months

The study did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The study did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

Similar numbers of people in the beta-blocker and placebo groups had visual acuity 20/40 or better at 12 months (RR 1.10, 95% CI 0.81 to 1.49; 60 participants; Analysis 13.3). We judged this to be low quality evidence, downgrading for risk of bias (-1) and imprecision (-1).

Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The study did not report quality of life at 12 months.

Adverse events

The study reported that no adverse events occurred.

Beta-blocker versus calcium antagonist

One study compared beta-blocker (propranolol) to a calcium antagonist in 25 participants affected with acute and chronic CSC (Brancato 1994). The study was reported in abstract form only and the abstract did not include any results. We contacted the trialists twice but received no reply.

Topical carbonic anhydrase inhibitors versus placebo

One study conducted in Mexico enrolled 13 participants with acute CSC (less than 20 days' duration) and randomly allocated them to brinzolamide (2%, twice a day) or placebo (polyvinyl alcohol) with follow-up of six months (Ontiveros-Orozco 2004). We largely judged the trial to be at unclear risk of bias.

Mean change in best-corrected visual acuity between baseline and 12 months

The study did not report mean change in BCVA between baseline and 12 months.

Recurrence of central serous chorioretinopathy at 12 months

One of seven participants in the brinzolamide group had a recurrence compared with 4/6 participants in the placebo group (RR 0.21, 95% CI 0.03 to 1.43; Analysis 14.1). We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1).

Persistent central serous chorioretinopathy at 12 months

None of seven participants in the brinzolamide group had persistent CSC compared with 1/6 participants in the placebo group (RR 0.29, 95% CI 0.01 to 6.07; Analysis 14.1). We judged this to be very low quality evidence downgrading for risk of bias (-1) and imprecision (-2).

Mean change in contrast sensitivity between baseline and 12 months

The study did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The study did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

The study did not report BCVA 20/40 or better at 12 months.

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Best-corrected visual acuity 20/200 or worse at 12 months

The study did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The study did not report quality of life at 12 months.

Adverse events

The study noted no adverse effects of brinzolamide.

Helicobacter pylori treatment versus placebo or observation

Two studies compared *H. pylori* treatment to no treatment in people with acute CSC who also had *H. pylori* infection. Dang 2013 was conducted in China and compared *H. pylori* therapy to placebo in 53 participants with follow-up of 12 weeks. Rahbani-Nobar 2011 was conducted in Iran and compared H. pylori treatment with no treatment in 50 participants with follow-up of 16 weeks. We judged Dang 2013 at low risk of bias in most domains; and Rahbani-Nobar 2011 at high risk of performance and detection bias.

Mean change in best-corrected visual acuity between baseline and 12 months

Visual acuity was slightly better in the *H. pylori*-treated group (MD -0.04 logMAR, 95% CI -0.07 to -0.02; 103 participants; Analysis 15.1) Heterogeneity was high (I^2 = 82%) but the two studies showed similar direction and order of effect. We judged this to be low quality evidence downgrading for risk of bias (-1) and imprecision (-1) as the CIs included a clinically unimportant effect.

Recurrence of central serous chorioretinopathy at 12 months

The studies did not report recurrence of CSC at 12 months.

Persistent central serous chorioretinopathy at 12 months

Fewer people in the *H. pylori*-treated group had persistent CSC at 12 weeks (Dang 2013) or 16 weeks (Rahbani-Nobar 2011) of follow-up (RR 0.67, 95% CI 0.36 to 1.22; 103 participants; Analysis 15.2). We judged this to be low quality evidence, downgrading for risk of bias (-1) and imprecision (-1).

Mean change in contrast sensitivity between baseline and 12 months

The studies did not report mean change in contrast sensitivity between baseline and 12 months.

Mean change in central retinal thickness between baseline and 12 months

The studies did not report mean change in central retinal thickness between baseline and 12 months.

Best-corrected visual acuity 20/40 or better at 12 months

The studies did not report BCVA 20/40 or better at 12 months.

Best-corrected visual acuity 20/200 or worse at 12 months

The studies did not report BCVA 20/200 or worse at 12 months.

Quality of life at 12 months

The studies did not report quality of life at 12 months.

Adverse events

Dang 2013 noted that no systemic or ocular adverse events occurred during follow-up.

Rahbani-Nobar 2011 noted that no systemic adverse effects of medication were observed.

Network meta-analyses (direct and indirect comparisons)

As specified in Types of interventions section, we restricted our network to interventions applied directly to the eye.

We planned to look at three outcomes: visual acuity, recurrence, and adverse events. Almost all studies reported no adverse events, so we are unable to do this analysis.

Visual acuity

Description of network

Figure 4 shows the network plots. With so few trials included in the network it was difficult to assess transitivity (Table 1). It is possible that the inclusion of people with acute or chronic CSC may be different in the different comparisons. This would affect the validity of the network. Overall, there was no evidence for statistical inconsistency (P value = 0.3208). There was only one closed loop (anti-VEGF, PDT, control) and again no evidence for inconsistency (inconsistency factor = 0.073, P value = 0.321). However, the power of these tests will be low and we cannot exclude the possibility of important inconsistency in the network.

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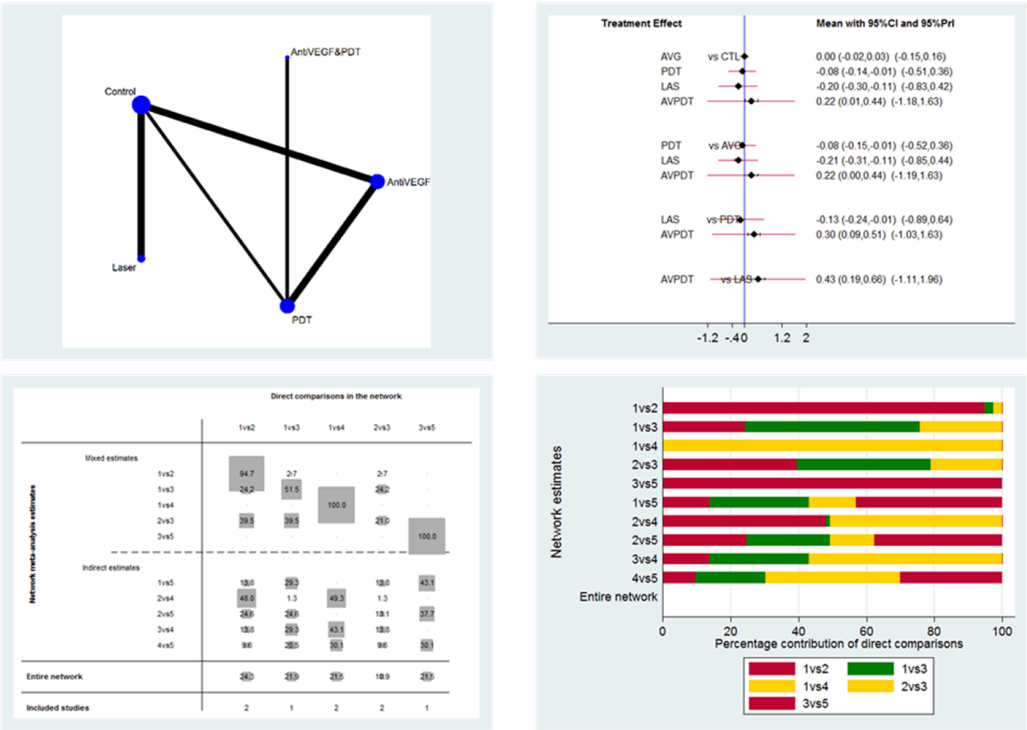
Figure 4. Visual acuity network: network plot, interval plot, contribution matrix and risk of bias. AVG: Anti-VEGF PDT: photodynamic therapy LAS: laser AVPDT: anti-VEGF plus PDT. 1 = control; 2 = anti-VEGF; 3 = PDT; 4 = laser; 5 = anti-VEGF plus PDT.



Comparative effects

Table 2 summarizes the comparative effects. These are plotted in Figure 4.

An alternative formulation of the network based on the specific type of intervention resulted in two disconnected networks and we considered it unwise to proceed further.

Recurrence of central serous chorioretinopathy

Description of network

Figure 5 shows the network plot. There were no closed loops and, therefore, it was not possible to assess consistency. Table 3 shows the assessment of transitivity. Again with few trials it was difficult to assess but type of CSC was a concern.

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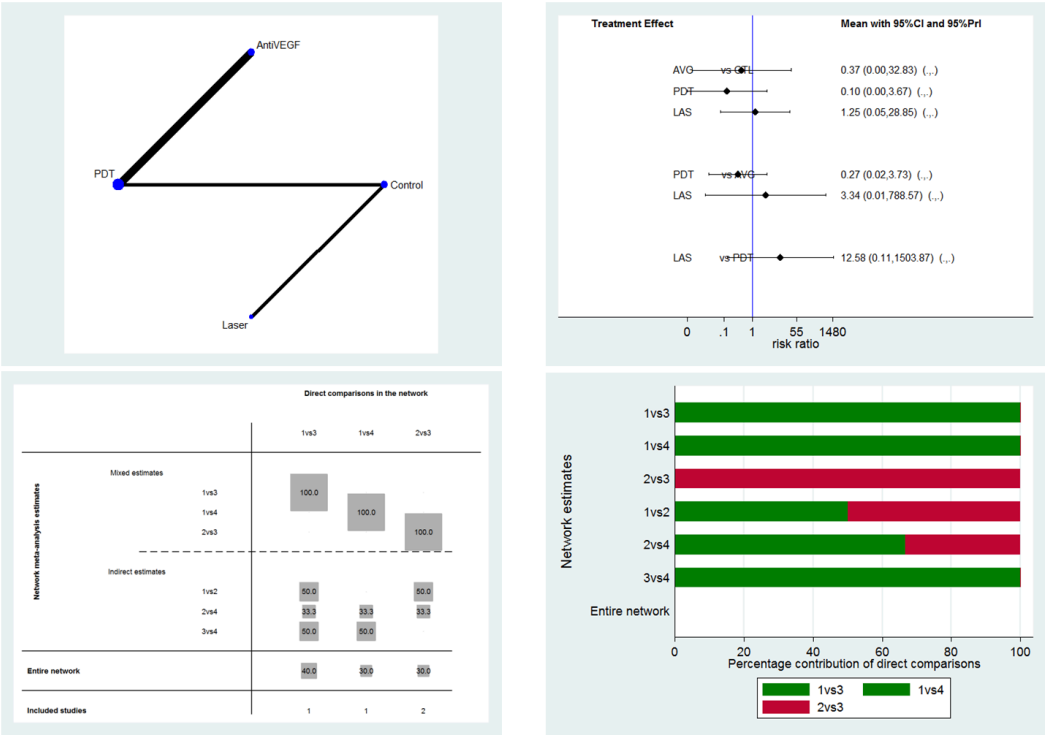
Figure 5. Recurrence CSC network: network plot, interval plot, contribution matrix and risk of bias. AVG: Anti-VEGF; PDT: photodynamic therapy; LAS: laser: CTL: control. 1 = control; 2 = anti-VEGF; 3 = PDT; 4 = laser.



Comparative effects

Table 4 summarizes the comparative effects. These are plotted in Figure 5. All estimates were very uncertain. The contribution matrix shows that all the evidence either came from direct or indirect estimates, reflecting the lack of closed loops in the network (Figure 5).

DISCUSSION

Summary of main results

Given that there were fewer than three studies per treatment comparison, that the available studies generally contained small numbers of participants, and given the methodological limits identified by this method of review, there are at the present time, insufficient data to make robust treatment recommendations. Of note, the present review did not identify a contraindication to observation as an initial management strategy in acute CSC.

Reporting of systemic or ocular adverse events were vague for most included studies. Studies would report "no systemic or ocular adverse events occurred" without reporting which systemic or ocular adverse events were being monitored. Thus, we were unable to make robust conclusions on potential adverse events for each intervention.

A brief summary of the mains results can be found in the Summary of findings for the main comparison.

We also identified 12 ongoing trials. In separate trials of acute CSC, PDT, aflibercept, and eplerenone are being compared to control (observation versus PDT, sham injection versus aflibercept, or placebo versus eplerenone). In separate trials of chronic CSC, spironolactone, eplerenone, and lutein are being compared to placebo, PDT is being compared to micropulse diode laser, and there are several head-to-head comparisons of PDT dose. In two trials, the type of CSC is not clearly specified on the trials register - in these trials, micropulse diode laser is compared to observation and oral mifepristone to placebo.

Overall completeness and applicability of evidence

The present review did not identify a contraindication to current practice, which is observation as an initial management strategy in acute CSC. However, the identified studies do not sufficiently address all of the review objectives as there were too few included studies for each comparison to make robust conclusions. Furthermore, each study identified in this review had varying definitions of acute and chronic CSC, therefore, the review conclusions cannot be isolated to people with either acute or chronic CSC.

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One further difficulty with the applicability of the evidence is that different treatments are indicated for different types of CSC: conventional laser may be directed to extrafoveal well-defined leaks, micropulse laser to juxtafoveal leaks, PDT to subfoveal leaks (but may be less applicable to very large and ill-defined leaking areas). Oral drugs are often used in any long-standing fluid.

Quality of the evidence

Overall, with one or two exceptions, we judged the quality of the evidence to be low or very low. This means that further research is very likely to have an important impact on our confidence in the estimates of effect and is likely to change the estimates.

We included 25 studies that enrolled 1098 participants. In general, these trials were small, with fewer than 50 participants. These studies considered a variety of treatments and, in general, there was only one or two trials contributing data for each comparison. The studies were poorly reported and often it was unclear whether key aspects of the trial, such as allocation concealment, had been done. A substantial proportion of the trials were not masked (nine trials), which may put them at risk of performance and detection bias. Problems with follow-up that may lead to attrition bias was also a potential problem in five trials.

We downgraded for risk of bias and imprecision for most analyses, reflecting the study limitations and imprecise estimates because of the small size of the included studies and few number of trials contributing to the analyses. Network meta-analysis did not help to resolve this uncertainty due to a lack of trials to construct a reliable network and potential problems with intransivity with respect to acute or chronic CSC.

Potential biases in the review process

This review followed standard Cochrane methods and limited any potential biases in the review process.

Agreements and disagreements with other studies or reviews

To our knowledge, there is no systematic review that has included all interventions of CSC. We identified two reviews evaluating isolated comparisons. Specifically, authors of Chung 2013 evaluated the effects of intravitreal bevacizumab injection and reported that their results were inconclusive. The authors of Ma 2014 compared PDT with other therapy or compared different parameters of PDT. Overall, they concluded that "PDT is a promising therapy for CSC patients". They included case series and observational studies, which are at higher risk of bias and uncontrolled confounding, and they did not distinguish trials and citations, leading to some double counting of results.

For outcomes such as adverse effects that may occur infrequently, trial evidence may not be the best source of information. One review of over 200 participants with chronic CSC treated with PDT concluded that adverse effects were rare. RPE atrophy occurred in 4% of participants and acute severe visual decrease occurred in 1.5% (Lim 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Given that there were fewer than three studies per treatment comparison, that the available studies generally contained small numbers of participants, and given the methodological limits identified by this method of review, there are, at the present time, insufficient data to inform treatment decisions. Of note, the present study did not identify a contraindication to observation as an initial management strategy in acute central serous chorioretinopathy (CSC).

Implications for research

Overall, when considering all of the studies reviewed, and the methods applied, the quality of the presently available data is low or very low. This means that further research is very likely to have an important impact on confidence in the estimates of effect, and is also very likely to change the estimates. This finding identifies well-designed, prospectively randomized controlled trials with larger numbers of participants, examining the safety and efficacy of treatments for CSC, as potentially high impact areas of study. Due to the recurrent and chronic nature of CSC, the appropriate treatment is one that can result in visual improvement, shorten the duration of symptoms, and reduce the recurrent rate. The benefit will likely extend to patients, care providers, and funders. The somewhat stronger evidence in the areas of thermal laser for focal leakage and the various photodynamic therapy (PDT) regimens suggests that further work to define their risks and benefits, as well as to identify the pertinent patients and entry points for such interventions, is a logical point of emphasis for future trials. Given the complexity of CSC, the following features could be considered in future trials: duration of symptoms and fluid, extent of retinal pigment epithelium derangement, and number and delimitation of leaks. For laser/PDT whether treatment is applied to leaks or RPE abnormalities or choroidal hyperpermeability should be considered. Future research on CSC would benefit from development of a 'core outcome set' including standardized measures of visual acuity and definition of persistence and recurrence, potentially including these as one outcome.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bae 2011

Methods	**Study design:** parallel randomized controlled trial
	Number randomized:
	16 eyes of NR participants in anti-VEGF group
	18 eyes of NR participants in PDT group
	Exclusions after randomization:
	0 in anti-VEGF group
	0 in PDT group
	Number analyzed:
	16 eyes of NR participants in anti-VEGF group
	18 eyes of NR participants in PDT group
	Unit of analysis: mixed, some participants had 1 eye included, some participants had both eyes included
	Losses to follow-up:

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Bae 2011 *(Continued)*

	2 eyes of participants in anti-VEGF group 0 in PDT group **How were missing data handled?:** NA **Power calculation:** power = 80% and sample size = 34 eyes total (17 eyes in each group)
Participants	**Country:** South Korea **Mean age (SD) (years):** 50.8 (7.7) overall 48.9 (7.5) in anti-VEGF group 51.4 (8.2) in PDT group **Gender (%):** 28 men (82%) and 6 women (18%) in Total group 13 men (81%) and 3 women (19%) in anti-VEGF group 15 men (83%) and 3 women (17%) in PDT group **Participants with chronic CSC were included as defined as:** "chronic CSC with visual disturbance persisting for >6 months or recurrent CSC. Recurrent CSC was defined as the recurrence of serous retinal detachment on optical coherence tomography (OCT) associated with visual symptoms after complete recovery of ocular manifestations; the first episode occurred >6 months before screening and the current episode persisted >3 months with sustained SRF on OCT" **Inclusion criteria:** BCVA 0-1.0 logMAR; presence of SFF persisting for > 3 months on OCT; presence of multifocal/diffuse RPE decompensation with leakage on the FA; and choroidal vascular hyperpermeability and abnormal dilation of the choroidal vasculature on ICGA **Exclusion criteria:** history of treatment including PDT, focal laser photocoagulation, intravitreal injection of steroid or anti-VEGF agent in the study eye; evidence of CNV or polypoidal choroidal vasculopathy; any other ocular diseases that can affect visual acuity, including diabetic retinopathy, retinal vascular occlusion, or ocular inflammatory diseases; media opacity that interferes with adequate image acquisition; history of any intraocular surgery except uncomplicated cataract surgery > 3 months before enrollment; history of systemic steroid or anti-VEGF treatment in the preceding 12 months; uncontrolled glaucoma with intraocular pressure > 21 mm Hg despite treatment; uncontrolled hypertension, diabetes, or history of cerebrovascular accident or myocardial infarction; and pregnancy **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** anti-VEGF (ranibizumab) Dose: 0.5 mg/0.05 mL Frequency: baseline, 1 and 2 months **Control:** low-fluence PDT Light dose: 25 J/cm^2 Verteporfin concentration: 6 mg/m^2
Outcomes	**Length of follow-up:** 12 months **Primary outcome, as defined in study reports:** primary efficacy outcome was proportion of eyes that maintained the complete absorption of SRF until 12 months without any rescue treatment **Secondary outcomes, as defined in study reports:** serial changes from baseline of mean change in logMAR BCVA; mean change in CRT obtained by OCT; proportion of eyes with resolved leakage on FA; proportion of eyes with resolved choroidal hyperpermeability on ICGA; and fluid-free interval, which was defined as the interval between the time when the SRF was completely absorbed without any rescue treatment and when re-accumulation of the fluid occurred **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 3, 6, 9, and 12 months
Notes	**Full study name:** Low-fluence photodynamic therapy versus ranibizumab for chronic central serous chorioretinopathy: one-year results of a randomized trial

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Bae 2011 *(Continued)*

Type of study: published full-text
Funding sources: Novartis Korea, Seoul, Korea
Disclosures of interest: reported explicitly none of the authors had any financial relationship

Trial registry: NCT01325181 (clinicaltrials.gov)
Study period: July 2009 to September 2012 (as reported in the trial registry)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to receive low-fluence PDT or the intravitreal injections of ranibizumab with an equal allocation ratio by means of permuted block randomization" p. 559
Allocation concealment (selection bias)	Unclear risk	"Subjects and the treating ophthalmologist (S.H.B.) were not masked to the treatment modalities" p. 559 Unclear if the allocation was masked before enrollment
Masking of participants and personnel (performance bias)	High risk	"Subjects and the treating ophthalmologist (S.H.B.) were not masked to the treatment modalities" p. 559
Masking of outcome assessment (detection bias)	Low risk	"The investigator (J.H.) and the other examiners for BCVA measurement, OCT, FA, and ICGA were masked to treatment allocation" p. 559
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/34 participants (< 10%) lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes on trial registry entry reported in paper
Other bias	High risk	Received industry funding (Novartis Korea, Seoul, Korea). Stated that "the sponsor or funding organization had no role in the design or conduct of this research. No conflicting relationship exists for any author"

Boscia 2008

Methods	**Study design:** unclear - refers only to eyes **Number randomized:** 8 eyes of NR participants in PDT group 8 eyes of NR participants in observation group **Exclusions after randomization:** not reported **Number analyzed:** NR **Unit of analysis:** unclear **Losses to follow-up:** NR **How were missing data handled?:** NA **Power calculation:** NR
Participants	**Country:** Italy (probably) **Mean age (SD) (years):** NR for overall and by group **Gender (%):** did not report number of men and women overall or by group

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Boscia 2008 *(Continued)*

	Participants with chronic CSC were included as defined as: not defined **Inclusion criteria:** BCVA 0.2-1 logMAR; presence of SRF or serous pigment epithelial detachment on OCT (or both) without regression for ≥ 3 months, RPE leakage on FA and choroidal vascular hyperpermeability on confocal SLO-ICGA **Exclusion criteria:** any previous treatment for CSC; evidence of other chorioretinal disorders; media opacities; and treatment with systemic steroids **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** low-fluence PDT light dose: 25 J/cm^2 Verteporfin concentration: NR **Control:** observation
Outcomes	**Length of follow-up:** 24 weeks **Primary outcome, as defined in study reports:** far BCVA (logMAR, using ETDRS charts) and near BCVA (logMAR, using MNRead Acuity Charts); CMT (OCT3, Zeiss-Humphrey) **Secondary outcomes, as defined in study reports:** macular sensitivity and stability of fixation determined using microperimetry (Nidek MP1) **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 4, 12, and 24 weeks
Notes	**Full study name:** Low fluence photodynamic therapy in chronic central serous chorioretinopathy: blind randomized clinical trial of efficacy and safety **Type of study:** published abstract **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR Contacted study authors and received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	High risk	Different groups and the study described as being "blind" but no information on masking
Masking of outcome assessment (detection bias)	High risk	Different groups and the study described as being "blind" but no information on masking
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

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Brancato 1994

Methods	**Study design:** cross-over randomized controlled trial **Number randomized:** NR eyes of 25 participants in total, By group NR **Exclusions after randomization:** NR **Number analyzed:** NR **Unit of analysis:** unclear **Losses to follow-up:** NR **How were missing data handled?:** NA **Power calculation:** NR **Unusual study design:** "two weeks of treatment with propranolol, then one week of wash-out; two weeks of treatment with nimodizin and again one of wash-out; two weeks of placebo treatment"
Participants	Participants with both acute or chronic CSC were enrolled **Country:** NR **Inclusion criteria:** NR **Equivalence of baseline characteristics:** unclear
Interventions	**Intervention:** beta-blocker (propranolol) Dose: NR Frequency: NR Duration: NR **Control:** calcium antagonist (nimodizin) Dose: NR Frequency: NR Duration: NR
Outcomes	**Length of follow-up:** NR **Primary outcome:** no outcomes defined **Secondary outcomes:** no outcomes defined **Adverse events reported:** no **Intervals at which outcomes assessed:** NR
Notes	**Full study name:** Treatment of central serous chorioretinopathy with beta-blockers and calcium antagonists **Type of study:** published abstract **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR Contacted study authors and received no response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Brancato 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	Both interventions were pills but no information on how similar the pills were
Masking of outcome assessment (detection bias)	Unclear risk	Both interventions were pills but no information on how similar the pills were
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Browning 1993

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** NR eyes of 8 participants in beta-blocker group NR eyes of 8 participants in placebo group **Exclusions after randomization:** NR **Number analyzed:** NR **Unit of analysis:** individual **Losses to follow-up:** NR **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** US **Mean age (SD) (years):** 41.5 (NR) in total 41 (NR) in beta-blocker group 42 (NR) in placebo group **Gender (%):** 9 men (56%) and 7 women (44%) in total 4 men (50%) and 4 women (50%) in beta-blocker group 5 men (63%) and 3 women (38%) in placebo group **Type of CSC not specified** **Inclusion criteria:** "all patients had serous retinal detachments and consistent fluorescein angiograms. no patient had vitreous cells, uncontrolled hypertension, recent pregnancy, or other causes of serous retinal detachment" **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** beta-blocker (nadolol) Dose: 40 mg

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Browning 1993 *(Continued)*

	Frequency: daily Duration: NR **Control:** placebo
Outcomes	**Length of follow-up:** 4 months Primary and secondary outcomes not differentiated **Adverse events reported:** no **Intervals at which outcomes assessed:** 4 months
Notes	**Full study name:** Nadolol in the treatment of central serous retinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"I evaluated the effect of the nonselective beta-blocker nadolol in a prospective, randomized, double-masked trial" p. 770 No further information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Low risk	Placebo-controlled trial
Masking of outcome assessment (detection bias)	Low risk	Placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Chan 2006

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 15 eyes of 15 participants in total By group NR **Exclusions after randomization:** NR **Number analyzed:** NR **Unit of analysis:** individual

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Chan 2006 *(Continued)*

	Losses to follow-up: NR **How were missing data handled?:** NR **Power calculation:** NR
Participants	Type of CSC not specified **Country:** US **Mean age (SD) (years):** Total and by group NR **Gender (%):** total and by group NR **Inclusion criteria:** NR **Equivalence of baseline characteristics:** unclear
Interventions	**Intervention:** low-dose transpupillary thermotherapy **Control:** sham laser
Outcomes	**Length of follow-up:** 3 months Primary and secondary outcomes not differentiated **Outcomes:** proportion of eyes with resolved CSC **Adverse events reported:** no **Intervals at which outcomes assessed:** 3 months
Notes	**Full study name:** Low-dose transpupillary thermotherapy for the treatment of central serous chorioretinopathy **Type of study:** published abstract **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR Contacted study authors who were unable to provide a reference to the full-text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Fifteen eyes of 15 patients with CSR [CSC] were randomly assigned" No further information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	Control group had sham therapy but no details on how this was done
Masking of outcome assessment (detection bias)	Unclear risk	Control group had sham therapy but no details on how this was done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

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Chan 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Chan 2008

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 42 eyes of 42 participants in PDT group 21 eyes of 21 participants in placebo group **Exclusions after randomization:** 0 in PDT group 0 in placebo group **Number analyzed:** 39 eyes of 39 participants in PDT group 19 eyes of 19 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 3 eyes of 3 participants in PDT group 2 eyes of 2 participants in placebo group **How were missing data handled?:** NR **Power calculation:** power = 85% and sample size = yes, power = 85% and sample size = 63 participants total (42 participants in PDT group and 21 participants in placebo group)
Participants	**Participants with acute CSC were included and defined as:** acute symptomatic CSC of ≤ 3 months' duration **Country:** China **Mean age (SD) (years):** 41.0 (6.7) in total 40.3 (5.8) in PDT group 42.4 (8.4) in placebo group **Gender (%):** 54 men (86%) and 9 women (14%) in total 38 men (90%) and 4 women (10%) in PDT group 16 men (76%) and 5 women (24%) in placebo group **Inclusion criteria:** people with BCVA ≥ 20/200; presence of SRF involving the fovea on OCT; presence of active angiographic leakage on FA caused by CSC but not CNV or other diseases; and abnormal dilated choroidal vasculature and other features on ICGA consistent with the diagnosis of CSC **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** 50% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 3 mg/m^2 **Control:** placebo (30 mL normal saline infused instead of verteporfin, and laser applied in the same manner as in the verteporfin group)
Outcomes	**Length of follow-up:** 12 months

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Chan 2008 *(Continued)*

	Primary outcome, as defined in study reports: proportion of eyes with complete absorption of SRF at 12 months **Secondary outcomes, as defined in study reports:** serial changes in logMAR BCVA, OCT CFT, FA, and ICGA, and systemic and ocular complications during the study **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 3, 6, 9, and 12 months
Notes	**Full study name:** Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** "Dr Lai has served as a consultant to an advisory board of Novartis, Inc" **Trial registry:** not registered **Study period:** December 2004 to December 2005, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using a computerized randomization table kept centrally by a research nurse, and the group allocation was performed before drug preparation and infusion" p. 1757
Allocation concealment (selection bias)	Low risk	"The randomization sequence was generated using a computerized randomization table kept centrally by a research nurse, and the group allocation was performed before drug preparation and infusion. All patients and investigators were masked to the treatment allocation group by wrapping the infusion syringes externally with aluminum foil" p. 1757
Masking of participants and personnel (performance bias)	Low risk	"All patients and investigators were masked to the treatment allocation group by wrapping the infusion syringes externally with aluminum foil" p. 1757
Masking of outcome assessment (detection bias)	Low risk	"All patients and investigators were masked to the treatment allocation group by wrapping the infusion syringes externally with aluminum foil" p. 1757
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall 5/58 participants (< 10%) were lost to follow-up; 3/39 PDT group lost to follow-up; 2/19 of placebo group
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Source of funding not reported. A conflict of interest was declared but only for 1 of the 5 authors and not the first author: "Dr Lai has served as a consultant to an advisory board of Novartis, Inc. All other authors have no financial interest to declare"

Coskun 2014

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 8 eyes of 8 participants in anti-VEGF group 7 eyes of 7 participants in PDT group **Exclusions after randomization:** NR

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Coskun 2014 *(Continued)*

	Number analyzed: 8 eyes of 8 participants in anti-VEGF group 7 eyes of 7 participants in PDT group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** NR **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** Turkey **Mean age (SD) (years):** NR in total 46.5 (11.5) in anti-VEGF group 56.1 (7.5) in PDT group **Gender (%):** NR **Participants with chronic CSC were included and defined as:** eyes with symptomatic chronic CSC (duration 6 months) **Inclusion criteria:** eyes with symptomatic chronic CSC **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** 50% PDT + anti-VEGF (bevacizumab) Light dose: 50 J/cm^2 Verteporfin concentration: 3 mg/m^2 Bevacizumab dose: 1.25 mg Bevacizumab duration: single dose, 3 days after PDT **Control:** 50% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 3 mg/m^2
Outcomes	**Length of follow-up:** 12 months Primary and secondary outcomes not differentiated **Outcomes:** time to CSC resolution; BCVA; CMT **Adverse events reported:** no **Intervals at which outcomes assessed:** 1, 3, 6, and 12 months
Notes	**Full study name:** Combined half dose photodynamic therapy with verteporfin and intravitreal bevacizumab for chronic central serous chorioretinopathy **Type of study:** published abstract **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

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Coskun 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	Groups different and no mention of masking
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Dang 2013

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 32 eyes of 32 participants in *Helicobacter pylori* treatment group 32 eyes of 32 participants in placebo group **Exclusions after randomization:** NR **Number analyzed:** 27 eyes of 27 participants in *H. pylori* group 26 eyes of 26 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 5 eyes of 5 participants in *H. pylori* group 6 eyes of 6 participants in placebo group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** China **Mean age (SD) (years):** NR in total 35.66 (5.47) in *H. pylori* group 34.85 (5.53) in placebo group **Gender (%):** 43 men (81%) and 10 women (19%) in total 22 men (81%) and 5 women (19%) in *H. pylori* group 21 men (81%) and 5 women (19%) in placebo group **Participants with chronic CSC were included and defined as:** duration > 12 weeks **Inclusion criteria:** single idiopathic leakage detected by FA excluding any other diseases; SRF confirmed by OCT (3D OCT-2000; TOPCON Corporation, Tokyo, Japan); *H. pylori* infection diagnosed according to a specific protocol 1 pupillary diameter); diffused retinal pigment epitheliopathy; aged < 20 years old and > 70 years old; and pregnancy, steroid use, and any other systemic diseases **Equivalence of baseline characteristics:** NR

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Dang 2013 *(Continued)*

Interventions	**Intervention:** *Helicobacter pylori* treatment Drug (dose): omeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg Frequency: twice a day Duration: 14 days **Control:** placebo
Outcomes	**Length of follow-up:** 12 weeks Primary and secondary outcomes not differentiated **Outcomes:** disappearance rate of SRF; BCVA; and central retinal sensitivity **Adverse events reported:** yes, but not descriptive; "during the follow-up visit, no systemic or ocular adverse events occurred" p. 358 **Intervals at which outcomes assessed:** 2, 4, 8, and 12 weeks
Notes	**Full study name:** The effect of eradicating *Helicobacter pylori* on idiopathic central serous chorioretinopathy patients **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** not registered **Study period:** September 2010 to December 2012, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned through a web-based data entry system maintained at the Data Coordinating Center (The MEDABC Corporation, Zhengzhou, Henan, People's Republic of China), with equal probability of receiving either *H. pylori* eradication (referred to as the active treatment group) or placebo drugs (referred to as the control group) using a permuted-block design with random block sizes" p. 356
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned through a web-based data entry system maintained at the Data Coordinating Center (The MEDABC Corporation, Zhengzhou, Henan, People's Republic of China), with equal probability of receiving either *H. pylori* eradication (referred to as the active treatment group) or placebo drugs (referred to as the control group) using a permuted-block design with random block sizes" p. 356
Masking of participants and personnel (performance bias)	Low risk	"The control group received an identical placebo that was the same color, size, and had the same identification name as the treatment. The placebos were taken in the same manner as the study drugs. Both drugs were also in identical opaque bottles and prepared by one nonclinician research assistant" p. 356
Masking of outcome assessment (detection bias)	Low risk	"The control group received an identical placebo that was the same color, size, and had the same identification name as the treatment. The placebos were taken in the same manner as the study drugs. Both drugs were also in identical opaque bottles and prepared by one nonclinician research assistant" p. 356
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"A total of 64 eyes in 64 patients were enrolled and randomized equally into two groups. Eleven eyes (17.18%) were lost to follow-up or did not yield enough data (five eyes in the active treatment group and six eyes in the control group). A total of 53 eyes (82.81%) were included in the study." p. 357

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Dang 2013 *(Continued)*

		Although similar drop-outs loss to follow-up was approaching 20% and no information on reasons for loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry not available for comparison
Other bias	Low risk	Source of monetary support not reported and conflict of interest was declared: "the authors report no conflicts of interest in this work"

Kianersi 2008

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 30 eyes of 30 participants in beta-blocker group 30 eyes of 30 participants in placebo group **Exclusions after randomization:** 0 in beta-blocker group 0 in placebo group **Number analyzed:** 30 eyes of 30 participants in beta-blocker group 30 eyes of 30 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in beta-blocker group 0 in placebo group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** Iran **Mean age (SD) (years):** 35 (8) in total 34 (7) in beta-blocker group 36 (8) in placebo group **Gender (%):** 44 men (73%) and 16 women (27%) in total 23 men (77%) and 7 women (23%) in beta-blocker group 21 men (70%) and 9 women (30%) in placebo group **The type of CSC was not specified** **Inclusion criteria:** no contraindication for propranolol use; no other eye disease such as cataract, retinal disorders, etc., which causes diminish visual activity; no indication for laser therapy **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** beta-blocker (propranolol) Dose: 20 mg Frequency: twice daily Duration: NR **Control:** placebo
Outcomes	**Length of follow-up:** 12 months Primary and secondary outcomes not differentiated

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Kianersi 2008 *(Continued)*

	Outcomes: psychological tension; subretinal fleck; recurrence of CSC; visual acuity **Adverse events reported:** yes, laser therapy; kidney transplantation; multiple sclerosis; kidney disease caused by steroid use **Intervals at which outcomes assessed:** weekly for 1 year
Notes	**Full study name:** Effects of propranolol in patients with central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** 2003 to 2004, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients met the inclusion criteria were referred to the second author (FF), and according to the table of random numbers, they were assigned randomly in two groups; half of patients received propranolol (treatment group) and the other half received placebo with the shape and color similar to propranolol" p. 104
Allocation concealment (selection bias)	Unclear risk	"Patients met the inclusion criteria were referred to the second author (FF), and according to the table of random numbers, they were assigned randomly in two groups; half of patients received propranolol (treatment group) and the other half received placebo with the shape and color similar to propranolol" p. 104
Masking of participants and personnel (performance bias)	Low risk	"Patients met the inclusion criteria were referred to the second author (FF), and according to the table of random numbers, they were assigned randomly in two groups; half of patients received propranolol (treatment group) and the other half received placebo with the shape and color similar to propranolol" p. 104
Masking of outcome assessment (detection bias)	Unclear risk	"Patients met the inclusion criteria were referred to the second author (FF), and according to the table of random numbers, they were assigned randomly in two groups; half of patients received propranolol (treatment group) and the other half received placebo with the shape and color similar to propranolol" p. 104 This suggests that the research staff may have been unmasked to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Kim 2013

Methods	**Study design:** parallel randomized controlled trial **Number randomized:**

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Kim 2013 *(Continued)*

	25 eyes of 25 participants in anti-VEGF group 25 eyes of 25 participants in placebo group **Exclusions after randomization:** NR **Number analyzed:** 20 eyes of 20 participants in anti-VEGF group 20 eyes of 20 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 5 eyes of 5 participants in anti-VEGF group 5 eyes of 5 participants in placebo group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** South Korea **Mean age (SD) (years):** 43.05 (7.46) in anti-VEGF group 41.40 (7.80) in placebo group **Gender (%):** 22 men (55%) and 18 women (45%) in total 12 men (60%) and 8 women (40%) in anti-VEGF group 10 men (50%) and 10 women (50%) in placebo group **Participants with acute CSC were included and defined as:** < 3 months' duration **Inclusion criteria:** NR **Exclusion criteria:** people who had received any previous treatment, including PDT or focal thermal laser photocoagulation for CSC, or who had evidence of CNV, polypoidal choroidal vasculopathy, or other maculopathy on fundus examination, FA, or ICGA **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** anti-VEGF (ranibizumab) Dose: 0.5 mg/mL Frequency: single dose at baseline **Control:** observation
Outcomes	**Length of follow-up:** 6 months **Primary outcome, as defined in study reports:** time from baseline to complete resolution of neurosensory retinal detachment during follow-up **Secondary outcomes, as defined in study reports:** serial changes in logMAR BCVA, OCT CFT, FA, and ICGA and the systemic and ocular complications during the study **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 2, 3, 4, 5, 6 months
Notes	**Full study name:** Intravitreal ranibizumab for acute central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** 2012 Research Grant from Kangwon National University **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** January 2010 to December 2011, as reported in the full-text article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Kim 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients were randomized into the IVRI [anti-VEGF] group or the observation group at a ratio of 1: 1" p. 153 No details on how the random allocation generated
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	High risk	Masking not reported and treatments different (injection vs. no treatment)
Masking of outcome assessment (detection bias)	High risk	Masking not reported and treatments different (injection vs. no treatment)
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported how many were randomized by group and loss to follow-up by group. Final numbers analyzed identical between treatment and observation group (20/20)
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry not available for comparison
Other bias	Low risk	Funding from non-profit and conflict of interest was not reported. "This study was supported by 2012 Research Grant from Kangwon"

Klatt 2011

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 14 eyes of NR participants in micropulse laser group ("selective retina therapy") 16 eyes of NR participants in placebo group **Exclusions after randomization:** 0 in micropulse laser group ("selective retina therapy") 0 in placebo group **Number analyzed:** 14 eyes of number of participants NR in micropulse laser group ("selective retina therapy") 16 eyes of number of participants NR in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in micropulse laser group ("selective retina therapy") 0 in placebo group **How were missing data handled?:** NR **Power calculation:** power = 80% and sample size = 62 eyes
Participants	**Country:** Germany **Mean age (SD) (years):** 43.8 (5.6) in total 42.8 (5.5) in micropulse laser group ("selective retina therapy") 44.7 (5.7) in placebo group **Gender (%):** 26 men (87%) and 4 women (13%) in total 14 men (100%) and 0 women (0%) in micropulse laser group ("selective retina therapy")

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Klatt 2011 *(Continued)*

	12 men (75%) and 4 women (25%) in placebo group **Participants with acute CSC were included and defined as:** acute symptomatic CSC and a documented disease progression of at least 3 months' duration **Inclusion criteria:** minimum age 18 years; minimum history 3 months of reduced visual acuity; minimum BCVA of 20 ETDRS letters (20/200); presence of SRF on OCT; and presence of active angiographic leakage in FA **Exclusion criteria:** other retinal diseases; glaucoma; cataract or other media opacities, which preclude color fundus photography and FA; previous PDT or continuous wave laser photocoagulation for CSC; systemic corticosteroid treatment, Cushing disease, renal diseases, pregnancy, and breastfeeding **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** micropulse laser ("selective retina therapy") Q-switched neodymium-doped yttrium lithium fluoride (Nd:YLF) laser wavelength: 527 nm spot diameter; 200 µm pulse repetition rate: 100 Hz **Control:** observation
Outcomes	**Length of follow-up:** 3 months **Primary outcome, as defined in study reports:** change of best corrected Early Treatment Diabetic Retinopathy Study visual acuity (BCVA); change in SRF as measured by OCT **Secondary outcomes, as defined in study reports:** rate of complete absorption of SRF; presence of leakage in FA; systemic or ocular adverse effects **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1 and 3 months
Notes	**Full study name:** Selective retina therapy for acute central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** "Johann Roider, Ralf Brinkmann and Reginald Birngruber hold patents on selective retina therapy. Carsten Klatt, Mark Saeger, Till Oppermann, Erk Porksen, Felix Treumer, Jost Hillenkamp and Elfriede Fritzer have no competing interests" **Trial registry:** NCT00987077 (clinicaltrials.gov) **Study period:** April 2007 to June 2008, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, opaque, sealed envelopes were prepared on the basis of the accomplished randomisation" p. 84
Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	"At all visits, BCVA was assessed using ETDRS charts at 4 m distance. The investigator was blinded" p. 84 Masking for other outcomes not reported and visual acuity assessment may be affected by the fact that the patient knew which group they were in

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Klatt 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients kept their follow-up appointment and were included in the analysis" p. 84
Selective reporting (reporting bias)	Low risk	All outcomes reported as stated in the trials registry entry (NCT00987077; clinicaltrials.gov)
Other bias	High risk	Source of monetary support was not reported and conflict of interest was declared: "Johann Roider, Ralf Brinkmann and Reginald Birngruber hold patents on selective retina therapy. Carsten Klatt, Mark Saeger, Till Oppermann, Erk Porksen, Felix Treumer, Jost Hillenkamp and Elfriede Fritzer have no competing interests"

Leaver 1979

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** NR eyes of 35 participants in argon laser group NR eyes of 35 participants in placebo group **Exclusions after randomization:** NR **Number analyzed:** NR eyes of 32 participants in argon laser group NR eyes of 31 participants in placebo group Unit of analysis: participant, 1 eye per person **Losses to follow-up:** NR eyes of 3 participants in argon laser group NR eyes of 4 participants in placebo group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** UK **Mean age (SD) (years):** 40.1 (NR) in total NR in argon laser group NR in placebo group **Gender (%):** 53 men (84%) and 10 women (16%) in total NR in argon laser group NR in placebo group Participants with both acute or chronic CSC were enrolled **Inclusion criteria:** corrected visual acuity ≥ 6/12; retina detached at macula; RPE defects < 1 disc diameter; no symptomatic improvement since onset; no subretinal exudates present; no cystic retinal edema present; no associated ocular disease (e.g. drusen, congenital pit of the disc, generalized RPE dystrophy, etc.); consent to participate in the study after explanation of aims and methods **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** argon laser (direct) **Control:** observation
Outcomes	**Length of follow-up:** 12.1 years Primary and secondary outcomes not differentiated **Outcomes:** time to recovery; visual acuities; hue discrimination

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Leaver 1979 *(Continued)*

	Adverse events reported: no **Intervals at which outcomes assessed:** "weekly intervals for 4 weeks and then at monthly intervals until symptoms improved, the retina flattened, and there was no identifiable leakage on fluoresce in fundus angiography (FFA). Thereafter examinations were carried out at 3- and 6-monthly intervals. Longest follow-up 12 years"
Notes	**Full study name:** Argon laser photocoagulation in the treatment of central serous retinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on how the random allocation generated: "randomised cards from sealed envelopes" p. 675
Allocation concealment (selection bias)	Unclear risk	"...randomised cards from sealed envelopes" (p. 675) but not enough information on how sealed envelopes were prepared e.g. sequentially number? opaque?
Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	Groups different and no mention of masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/70 (10%) missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Lim 2010

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 32 eyes of number of participants NR in total By group NR **Exclusions after randomization:** NR **Number analyzed:** 12 eyes of 12 participants in anti-VEGF group 12 eyes of 12 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 8 eyes of number of participants NR in total; by group NR

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Lim 2010 *(Continued)*

	How were missing data handled?: NR **Power calculation:** NR
Participants	**Country:** South Korea **Mean age (SD) (years):** 43.2 (9.0) in total 45.6 (10.4) in anti-VEGF group 40.7 (7.0) in placebo group **Gender (%):** 20 men (83%) and 4 women (17%) in total 9 men (75%) and 3 women (25%) in anti-VEGF group 11 men (92%) and 1 women (8%) in placebo group **Participants with acute CSC were included and defined as:** "patients with symptomatic CSC of less than a 3-month duration" **Inclusion criteria:** diagnosis of CSC was established by the presence of serous macular detachment on fundus examination and dilated choroidal vasculature and hyperpermeability on ICGA **Exclusion criteria:** participants who had received any previous treatment, including PDT or focal thermal laser photocoagulation for CSC, or who had evidence of CNV, polypoidal choriovasculopathy, or other maculopathy on clinical examination, FA, or ICGA **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** anti-VEGF (bevacizumab) Dose: 1.25 mg/0.05 mL Frequency: single dose injected < 1 week after diagnosis **Control:** observation
Outcomes	**Length of follow-up:** 6 months **Primary outcome, as defined in study reports:** time measured from baseline to complete absorption of SRF during follow-up **Secondary outcomes, as defined in study reports:** serial changes in the logMAR visual acuity and OCT central 1-mm macular thickness **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 2, 3, 4, 5, and 6 months
Notes	**Full study name:** The effect of intravitreal bevacizumab in patients with acute central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** not registered **Study period:** March 2008 to August 2008, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using a computerized randomization table" p. 156
Allocation concealment (selection bias)	Unclear risk	Not reported

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Lim 2010 *(Continued)*

Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	Groups different and no mention of masking
Incomplete outcome data (attrition bias) All outcomes	High risk	8/32 (25%) of participants not followed up and not reported which group they were in
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Low risk	Source of monetary support not reported and conflict of interest declared: "no potential conflict of interest relevant to this article was reported"

Ontiveros-Orozco 2004

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 16 participants were included in the study, but allocation not reported NR eyes of NR participants in carbonic anhydrase inhibitor group NR eyes of NR participants in placebo group **Exclusions after randomization:** 3 **Number analyzed:** Number of eyes NR of 7 participants in carbonic anhydrase inhibitor group Number of eyes NR of 6 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** NR **How were missing data handled?:** NA **Power calculation:** NR
Participants	**Participants with acute CSC were included and define as:** participants with "symptoms for less than 20 days, no previous treatment" **Country:** Mexico **Mean age (SD) (years):** NR in total NR in carbonic anhydrase inhibitors group NR in placebo group **Gender (%):** 9 men (69%) and 4 women (31%) in total 4 men (57%) and 3 women (43%) in carbonic anhydrase inhibitors group 5 men (83%) and 1 women (17%) in placebo group **Inclusion criteria:** CSC idiopathic; fluorangiography showing hyperfluorescence associated with serous retinal pigment epithelial detachment; with 3 months of follow-up after recovery and provide informed consent **Exclusion criteria:** "any patients older than 50 years, patients that had any additional pre-existing ocular pathology or systematic pathology. Any patients were eliminated that did not comply with their appointments, studies, or that had received any medications during their development" **Equivalence of baseline characteristics:** NR

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Ontiveros-Orozco 2004 *(Continued)*

Interventions	**Intervention:** carbonic anhydrase inhibitors (brinzolamide) Dose: 2% Duration: twice daily **Control:** placebo (polyvinyl alcohol)
Outcomes	**Length of follow-up:** 6 months **Primary outcome, as defined in study reports:** time to clinical recovery **Secondary outcomes, as defined in study reports:** "complications: RPE atrophy, recurrence, persistence of subretinal fluid and appearance of neovascular membranes. Each complication received a value according to the severity (from 0 for the absence of complications to 4 for the presence of neovascular membranes)" **Adverse events reported:** reported no adverse effects **Intervals at which outcomes assessed:** weekly for the first month, then monthly for 3 months, and 6 months
Notes	**Full study name:** Brinzolamide for topical treatment coroidorretinopatía idiopathic central serous **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** June 2002 to October 2003, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	The labeling and drug control was done by third person not related with the study p. 134
Masking of participants and personnel (performance bias)	Unclear risk	Similar groups (both groups' treatment were eye drops), but no information on masking
Masking of outcome assessment (detection bias)	Unclear risk	Similar groups (both groups' treatment were eye drops), but no information on masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Pitcher 2015

Methods	**Study design:** parallel randomized controlled trial **Number randomized:**

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Pitcher 2015 *(Continued)*

	6 eyes of 6 participants in 6-dose group 6 eyes of 6 participants in 4-dose group **Exclusions after randomization:** 0 in 6-dose group 0 in 4-dose group **Number analyzed:** 6 eyes of 6 participants in 6-dose group 6 eyes of 6 participants in 4-dose group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in 6-dose group 0 in 4-dose group **How were missing data handled?:** NA **Power calculation:** NR
Participants	**Country:** USA **Mean age (SD) (years):** NR in total 53.50 (9.61) in 6-dose group 53.83 (12.80) in 4-dose group **Gender (%):** all participants were men **Participants with chronic CSC were included as defined as:** "persistent CSCR [CSC] demonstrated by subfoveal fluid (SFF) on optical coherence tomography (OCT) for greater than 3 months" **Inclusion criteria:** age ≥ 18 years; ability to provide informed consent; persistent CSC demonstrated by SFF on OCT for > 3 months; active leakage on FA at the time of enrolment; evidence of hyperpermeability and abnormal dilation of choroidal vasculature on ICGA; BCVA between 20/25 and 20/320. Only 1 eye for each participant was included in participants with bilateral CSC **Exclusion criteria:** concurrent progressive retinal or substantial ocular disease in the study eye; prior treatment for CSC in the study eye (anti-VEGF, PDT, or laser) within 3 months prior to enrolment; presence of CNV or polypoidal choroidal vasculopathy on enrolment imaging; history of intraocular surgery except uncomplicated cataract surgery > 3 months prior to enrolment; prior treatment with systemic anti-VEGF agents or steroid agents within the preceding 12 months; uncontrolled glaucoma; history of cerebrovascular accident or myocardial infarction; pregnancy **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** 6-dose group (aflibercept) Dose: 2.0 mg/0.05 mL Duration: single dose at baseline, 1, 2, 3, 4, and 5 weeks **Control:** 4-dose group (aflibercept) Dose: 2.0 mg/0.05 mL Duration: single dose at baseline, 1, 2, and 4 weeks
Outcomes	**Length of follow-up:** 6 months Primary and secondary outcomes not differentiated **Outcomes listed as:** occurrence of ocular or systemic adverse events; mean change from baseline in ETDRS letter score; percentage of eyes with 20/40 or better vision; percentage of eyes with ≥ 15-letter gain from baseline; percentage of eyes with < 15-letter loss from baseline; mean change in CMT; mean change in SFF manually measured by a masked observer; percentage of eyes with complete resolution of macular fluid on OCT; mean change in subfoveal choroidal thickness as measured via enhanced depth imaging; and percentage of eyes with absence of leakage on FA **Adverse events reported:** yes

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Pitcher 2015 *(Continued)*

	Intervals at which outcomes assessed: 6 months
Notes	**Full study name:** A prospective pilot study of intravitreal aflibercept for the treatment of chronic central serous chorioretinopathy: the CONTAIN study **Type of study:** published full-text **Funding sources:** Regeneron Pharmaceuticals **Disclosures of interest:** "none" **Trial registry:** NCT01710332 (clinicaltrials.gov) **Study period:** November 2012 to May 2013, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to two groups" p. 849 Did not clear describe method of randomization
Allocation concealment (selection bias)	Unclear risk	Did not describe clearly how the sequence generation was assigned/stored
Masking of participants and personnel (performance bias)	Unclear risk	Masking not reported
Masking of outcome assessment (detection bias)	Unclear risk	SFF height was determined by a masked observer using the digital caliper function to measure distance from the hyper-reflective RPE to the photoreceptor outer segments on a b-scan through the foveal center point. Choroidal thickness was determined by a masked observer using the digital caliper to measure distance from the inner border of the choroido-scleral interface to the hyper-reflective RPE
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Did not clearly define the primary and secondary outcomes in the published full-text, while the trial registry had primary and secondary outcomes were clearly defined. Reported 5 additional outcomes not defined in the trial registry: "mean change in CMT; mean change in SFF manually measured by a masked observer; percentage of eyes with complete resolution of macular fluid on OCT; mean change in subfoveal choroidal thickness as measured via enhanced depth imaging; and percentage of eyes with absence of leakage on FA
Other bias	High risk	Industry funding

Rahbani-Nobar 2011

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** NR eyes of 25 participants in *Helicobacter pylori* group NR eyes of 25 participants in placebo group **Exclusions after randomization:** 0 in *H. pylori* group

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Rahbani-Nobar 2011 *(Continued)*

	0 in placebo group **Number analyzed:** NR eyes of 25 participants in *H. pylori* group NR eyes of 25 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in H. pylori group 0 in placebo group **How were missing data handled?:** NA **Power calculation:** NR
Participants	**Participants with acute CSC were included but definition not given** **Country:** Iran **Mean age (SD) (years):** NR in total 32.54 (4.57) in *H. pylori* group 34.24 (4.78) in placebo group **Gender (%):** 41 men (82%) and 9 women (18%) in total 21 men (84%) and 4 women (16%) in *H. pylori* group 20 men (80%) and 5 women (20%) in placebo group **Inclusion criteria:** to accept participation in the study by signing an informed consent; not having been treated with antibiotics, a proton pomp inhibitor, corticosteroids, or sympathomimetic drugs for 3 months before the study; no history of previous ocular surgery **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** *H. pylori* Drugs: metronidazole and amoxicillin Dose: 500 mg Frequency: 3 times daily Duration: 2 weeks Drug: omeprazole Dose: NR Frequency: once daily Duration: 6 weeks **Control:** observation
Outcomes	**Length of follow-up:** 16 weeks Primary and secondary outcomes not differentiated **Outcomes:** average neuroretinal and/or pigment epithelial detachment; number of cases that reached zero subretinal fluid value; subretinal fluid level; subretinal fluid reabsorption time; mean visual acuity **Adverse events reported:** yes **Intervals at which outcomes assessed:** 2, 4, 6, 8, 12, and 16 weeks
Notes	**Full study name:** The effect of *Helicobacter pylori* treatment on remission of idiopathic central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR

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Rahbani-Nobar 2011 *(Continued)*

Disclosures of interest: NR

Trial registry: NCT00817245 (clinicaltrials.gov)

Study period: February 2008 to January 2010, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were divided in two groups using random allocation software" p. 100
Allocation concealment (selection bias)	Unclear risk	"The patients were divided in two groups using random allocation software" p. 100, but no information specifically on allocation concealment
Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	Groups different and no mention of masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Outcomes on clinical trials registry entry (NCT00817245) were reported in the full text
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Ratanasukon 2012

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 29 eyes of 29 participants in antioxidant group 29 eyes of 29 participants in placebo group **Exclusions after randomization:** NR **Number analyzed:** 26 eyes of 26 participants in antioxidant group 25 eyes of 25 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 3 eyes of 3 participants in antioxidant group 4 eyes of 4 participants in placebo group **How were missing data handled?:** NR **Power calculation:** power = 80% and sample size = 58 participants in total (29 participant in each group)
Participants	**Country:** Thailand **Mean age (SD) (years):** 40.4 (NR) in total 41.28 (5.07) in antioxidant group

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Ratanasukon 2012 *(Continued)*

	39.48 (6.95) in placebo group **Gender (%):** 48 men (83%) and 10 women (17%) in total 23 men (79%) and 6 women (21%) in antioxidant group 25 men (86%) and 4 women (14%) in placebo group **Participants with acute CSC were included and defined as:** "onset within 6 weeks" **Inclusion criteria:** people with acute CSC (within 6 weeks of onset), aged 30-50 years, new or recurrent attack (symptom-free ≥ 6 months), FA-confirmed diagnosis with inkblot or smoke-stack leakage, OCT by Status OCT showing definite SRF and the people's ability for proper follow-up **Exclusion criteria:** chronic CSC (> 6 weeks), multiple attacks (> 2 times), large pigment epithelial detachment (> 1 disc diameter), multiple pigment epithelial detachment or diffuse retinal pigment epitheliopathy, younger or older ages, follow-up time < 3 months, complicated CSC such as secondary CNV detected from FA, pregnancy, steroid use and people with contraindication from high-dose antioxidant therapy such as heavy smokers, and people with lung cancer, thyrotoxicosis, renal stones and anemia (hematocrit < 30%) **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** antioxidant (Icaps: vitamin A (6600 IU); vitamin C (400 mg), vitamin E (150 IU); riboflavin (10 mg); zinc (60 mg); copper (4 mg); selenium (40 mg); manganese (4 mg) and lutein/zeaxanthin (4000 µg)) **Control:** placebo
Outcomes	**Length of follow-up:** 3 months planned but 12 months reported (with high attrition) **Primary outcome, as defined in study reports:** change in visual acuity; change in CMT recorded by OCT during every visit **Secondary outcomes, as defined in study reports:** number of participants with SRF at each follow-up time, the number of participants who showed FA leakage at the end of the 3rd month and participants who received additional treatments in each group **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1, 2, 3, 6, and 12 months
Notes	**Full study name:** High-dose antioxidants for central serous chorioretinopathy; the randomized placebo-controlled study **Type of study:** published full-text **Funding sources:** "study and placebo drugs were contributed by Alcon Laboratories (Thailand)" **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** NCT00963131 (clinicaltrials.gov) **Study period:** December 2004 to December 2008, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomly assigned to high-dose antioxidant or placebo drugs. The randomization was computer generated with a 1:1 ratio, block lengths of 4 and random numbers were coded to all bottles. Moreover, the codes were in envelops until the end of the study" p. 2
Allocation concealment (selection bias)	High risk	"The corresponding author generated the allocation sequence, enrolled and assigned the patients to any additional treatments when needed" p. 2
Masking of participants and personnel (performance bias)	Low risk	"The patients were randomly assigned to high-dose antioxidant or placebo drugs. The randomization was computer generated with a 1:1 ratio, block lengths of 4 and random numbers were coded to all bottles. Moreover, the codes were in envelops until the end of the study" p. 2
Masking of outcome assessment (detection bias)	Low risk	"The patients were randomly assigned to high-dose antioxidant or placebo drugs. The randomization was computer generated with a 1:1 ratio, block

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Ratanasukon 2012 *(Continued)*

		lengths of 4 and random numbers were coded to all bottles. Moreover, the codes were in envelops until the end of the study" p. 2
Incomplete outcome data (attrition bias) All outcomes	High risk	3/29 lost to follow-up at 3 months in intervention group and 4/29 lost to follow-up in control group but at 12 months only 7 participants seen in each group. So low risk of bias for 3 months and high risk of bias for 12 months outcomes
Selective reporting (reporting bias)	Low risk	Trial registry entry was available for comparison, and all outcomes were reported as per the trial registry
Other bias	Unclear risk	"Study and placebo drugs were contributed by Alcon Laboratories (Thailand)" but authors reported that none of the authors had any financial relationship

Robertson 1983

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 15 eyes of 15 participants in argon (direct) laser group 15 eyes of 15 participants in sham laser group 7 eyes of 7 participants in argon (direct) laser group 5 eyes of 5 participants in argon (indirect) laser group **Exclusions after randomization:** NR **Number analyzed:** 15 eyes of 15 participants in argon (direct) laser group 15 eyes of 15 participants in sham laser group 7 eyes of 7 participants in argon (direct) laser group 5 eyes of 5 participants in argon (indirect) laser group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** NR **How were missing data handled?:** NR **Power calculation:** NR **Unusual study design:** eyes were divided into 2 groups depending on the site of leakage (determined by FA) "We assigned eyes in which the leakage site was in the papillomacular bundle or within 500 µm of the capillary-free zone of the macula to Group A" "We assigned eyes in which the leakage site was outside the papillomacular bundle and more than 500 µm from the capillary-free zone to Group B"
Participants	**Country:** US **Mean age (SD) (years):** NR in total 39.7 (NR) in argon (direct) laser group NR in sham laser group 41.3 (NR) in argon (direct) laser group 44.8 (NR) in argon (indirect) laser group **Gender (%):** 29 men (69%) and 13 women (31%) in total 10 men (67%) and 5 women (33%) in (direct) laser group 9 men (60%) and 6 women (40%) in sham laser group 5 men (71%) and 2 women (29%) in (direct) laser group 5 men (100%) and 0 women (0%) in (indirect) laser group **Participants with acute CSC were included and defined as:** "central serous chorioretinopathy of recent onset" p. 458

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Robertson 1983 *(Continued)*

	Inclusion criteria: no evidence of previous ocular surgery, trauma, photocoagulation, cloudy media, vitreous inflammation, retinal vessel occlusion, hypertensive or diabetic retinopathy, vitreoretinal traction, congenital optic pits, mass lesion, or any other unusual retinal or choroidal abnormality **Equivalence of baseline characteristics:** NR
Interventions	**Group A intervention:** argon laser (indirect laser photocoagulation) **Group A control:** sham laser **Group B intervention:** argon laser (direct laser photocoagulation) **Group B control:** argon laser (indirect laser photocoagulation
Outcomes	**Length of follow-up:** examined at 6 months recurrences reported to 18 months Primary and secondary outcomes not differentiated **Outcomes:** resolution of CSC as determined by 2 observers by following criteria: subretinal fluid absent on biomicroscopic exam and stereoscopic FA showed no active leakage; visual acuity measured by Sloan chart; visual fields **Adverse events reported:** no **Intervals at which outcomes assessed:** 2 weeks, 6 months, 18 months
Notes	**Full study name:** Direct, indirect, and sham laser photocoagulation in the management of central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** Grant EY0 1709 from the National Eye Institute and by the Mayo Foundation **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** May 1977 to January 1981, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on how the random allocation generated: "After the patient was positioned at the laser, a sealed envelope containing the randomized treatment assignment was opened. The assignments, worked out and kept by the statistician, directed the physician (D.M.R. in all cases) to administer direct, indirect, or sham laser photocoagulation" p. 459
Allocation concealment (selection bias)	Low risk	"After the patient was positioned at the laser, a sealed envelope containing the randomized treatment assignment was opened. The assignments, worked out and kept by the statistician, directed the physician (D.M.R. in all cases) to administer direct, indirect, or sham laser photocoagulation." p. 459
Masking of participants and personnel (performance bias)	Low risk	"The subject did not learn which of the three forms of treatment he or she had received until the study ended six months later" pp. 459-460
Masking of outcome assessment (detection bias)	Unclear risk	Similar groups (both groups' treatment were laser), but no information on masking of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Funded by government sources but conflicts of interest were not reported

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Roisman 2013

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 10 eyes of 10 participants in micropulse diode laser group 5 eyes of 5 participants in placebo group **Exclusions after randomization:** 0 in micropulse diode laser group 0 in placebo group **Number analyzed:** 10 eyes of 10 participants in micropulse diode laser group 5 eyes of 5 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in micropulse diode laser group 0 in placebo group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** Brazil **Mean age (SD) (years):** NR in total 39.5 (7.7) in micropulse diode laser group 44.2 (5.8) in placebo group **Gender (%):** 10 men (67%) and 5 women (33%) in total 7 men (70%) and 3 women (30%) in micropulse diode laser group 3 men (60%) and 2 women (40%) in placebo group **Participants with chronic CSC were included and defined as:** "CSC lasting more than 6 months were enrolled" **Inclusion criteria:** NR **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** micropulse diode laser Wavelength: 810 nm FastPulse laser; Opto, Brazil **Control:** sham laser
Outcomes	**Length of follow-up:** 12 months **Primary outcome, as defined in study reports:** change in visual acuity after 3 months **Secondary outcomes, as defined in study reports:** change in CMT after 3 months **Adverse events reported:** no **Intervals at which outcomes assessed:** 1, 3, 6, and 12 months
Notes	**Full study name:** Micropulse diode laser treatment for chronic central serous chorioretinopathy: a randomized pilot trial **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** NCT01327170 (clinicaltrials.gov) **Study period:** NR

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Roisman 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The 15 patients were randomized 2:1 through double-masked random draw into two groups" p. 466
Allocation concealment (selection bias)	Low risk	"The 15 patients were randomized 2:1 through double-masked random draw into two groups" p. 466
Masking of participants and personnel (performance bias)	Low risk	Double-masked with placebo group
Masking of outcome assessment (detection bias)	Low risk	Double-masked with placebo group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes stated in the trial registry were reported
Other bias	Low risk	Source of monetary funding not reported but the conflict of interest declared: "the authors have no financial or proprietary interest in the materials presented herein"

Sawa 2014

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** Total number randomized was 44 Unclear number in each group **Exclusions after randomization:** 5 people excluded after randomization but not reported to which groups they belonged **Number analyzed:** NR eyes of 20 participants in antioxidant group NR eyes of 19 participants in placebo group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** NR **How were missing data handled?:** NR **Power calculation:** NR
Participants	The type of CSC was not specified **Country:** Japan **Mean age (SD) (years):** 49 (10) in total 51.2 (9) in antioxidant group 46.6 (8.3) in placebo group **Gender (%):** 35 men (90%) and 4 women (10%) in total

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Sawa 2014 *(Continued)*

	19 men (95%) and 1 women (5%) in antioxidant group 16 men (84%) and 3 women (16%) in placebo group **Inclusion criteria:** previous regular intake of lutein or zeaxanthin, or both; corticosteroid treatment; disturbance of ocular media; other retinal disorders such as age-related macular degeneration, polypoidal choroidal vasculopathy, retinal vein occlusion, or diabetic retinopathy **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** antioxidant (lutein) Dose: 20 mg/day **Control:** placebo
Outcomes	**Length of follow-up:** 4 months **Primary outcome, as defined in study reports:** macular pigment optical density and plasma lutein concentration **Secondary outcomes, as defined in study reports:** NR **Adverse events reported:** no **Intervals at which outcomes assessed:** 1 and 4 months
Notes	**Full study name:** Effects of a lutein supplement on the plasma lutein concentration and macular pigment in patients with central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** Santen Pharmaceutical Co., Ltd **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** not registered **Study period:** March 2011 to June 2012, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"The study was a randomized, double-masked, placebo-controlled trial" p. 5239
Masking of participants and personnel (performance bias)	Low risk	"The study was a randomized, double-masked, placebo-controlled trial" p. 5239
Masking of outcome assessment (detection bias)	Low risk	"The study was a randomized, double-masked, placebo-controlled trial" p. 5239
Incomplete outcome data (attrition bias) All outcomes	High risk	5 people excluded after randomization but not reported to which groups they belonged
Selective reporting (reporting bias)	High risk	BCVA measured but not reported. Only reported resolution of CSC for the intervention (lutein) group
Other bias	High risk	Funded by manufacturer of the supplement. Authors reported not having any conflict of interest

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Semeraro 2012

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 12 eyes of 12 participants in anti-VEGF group 10 eyes of 10 participants in PDT group **Exclusions after randomization:** 12 eyes of 12 participants in anti-VEGF group 10 eyes of 10 participants in PDT group **Number analyzed:** 12 eyes of 12 participants in anti-VEGF group 10 eyes of 10 participants in PDT group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in anti-VEGF group 0 in PDT group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Participants with chronic CSC were included and defined as:** "...either persistence of subretinal fluid detected on optical coherence tomography (OCT) for at least 3 months after diagnosis or more than 3 recurrences in at least 3 months with gravitational RPE atrophy" and "The inclusion criteria consisted of presence of CSC with chronic foveal detachment of the neuroepithelium (C3 months) and no previous treatment for CSC" **Country:** Italy **Mean age (SD) (years):** NR in total 35.2 (6) in anti-VEGF group 36 (8) in PDT group **Gender (%):** 13 men (59%) and 9 women (41%) in total 7 men (58%) and 5 women (42%) in anti-VEGF group 6 men (60%) and 4 women (40%) in PDT group **Inclusion criteria:** presence of CSC with chronic foveal detachment of the neuroepithelium (≥ 3 months) and no previous treatment of CSC **Exclusion criteria:** ages > 50 years; chronic systemic disease; pregnancy; any uncontrolled ocular disease; and presence of occult or minimally classic choroidal neovascular lesions, scarring, or atrophy within the lesion **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** anti-VEGF (bevacizumab) Dose: 1.25 mg Duration: single dose at baseline and then as needed after 4 weeks **Control:** low fluence PDT Light dose: 25 J/cm^2 Verteporfin concentration: NR
Outcomes	**Length of follow-up:** 9 months Primary and secondary outcomes not differentiated **Outcomes:** change in macular thickness; the number of eyes with recurrence; stabilization of the lesions; the number of retreatments **Adverse events reported:** no

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Semeraro 2012 *(Continued)*

	Intervals at which outcomes assessed: 9 months
Notes	**Full study name:** Intravitreal bevacizumab versus low-fluence photodynamic therapy for treatment of chronic central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** February 2009 to April 2010, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Enrolled patients were randomly assigned to group 1 or group 2 by random block permutation in accordance with a computer-generated randomization list" p. 609
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	High risk	Groups different and no mention of masking
Masking of outcome assessment (detection bias)	High risk	Groups different and no mention of masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Shang 1999

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** NR eyes of 30 participants in yellow laser group NR eyes of 30 participants in red laser group NR eyes of 30 participants in green laser group **Exclusions after randomization:** 0 in yellow group 0 in red group 0 in green group **Number analyzed:** NR eyes of 30 participants in yellow group NR eyes of 30 participants in red group

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Shang 1999 *(Continued)*

	NR eyes of 30 participants in green group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in yellow group 0 in red group 0 in green group **How were missing data handled?:** NR **Power calculation:** NR
Participants	The type of CSC was not specified **Country:** China **Mean age (SD) (years):** 40.0 (6.3) in total 43.7 (7.6) in yellow group 39.9 (7.0) in red group 39.5 (5.0) in green group **Gender (%):** 79 men (89%) and 10 women (11%) in total NR in yellow group NR in red group NR in green group **Inclusion criteria:** people with CSC validated by eye exam, Amsler chart examine and FFA; duration of the disease > 8 weeks; corrected visual acuity ≤ 0.8; distance between fundus fluorescein leakage point showed by FFA and central fovea of macula > 250 µm **Exclusion criteria:** NR **Equivalence of baseline characteristics:** NR
Interventions	**Intervention 1:** yellow **Intervention 2:** red **Control:** green
Outcomes	**Length of follow-up:** 12 months Primary and secondary outcomes not differentiated **Outcomes:** visual acuity; light sensitivity; recurrent rate; disease course; photocoagulation energy; photocoagulation spot expansion **Adverse events reported:** yes, made mention of protrusion, proliferation/diffusion, RPE complications **Intervals at which outcomes assessed:** 12 months
Notes	**Full study name:** Wavelength selection in management of central serous chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** NR

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Shang 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	No mention of masking
Masking of outcome assessment (detection bias)	Unclear risk	No mention of masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Verma 2004

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** NR eyes of 15 participants in micropulse diode laser group NR eyes of 15 participants in argon laser group **Exclusions after randomization:** 0 in micropulse diode laser group 0 in argon laser group **Number analyzed:** NR eyes of 15 participants in micropulse diode laser group NR eyes of 15 participants in argon laser group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in micropulse diode laser group 0 in argon laser group **How were missing data handled?:** NR **Power calculation:** NR
Participants	**Country:** India **Mean age (SD) (years):** NR in total 34.06 (2.54) in micropulse diode laser group 34.66 (3.23) in argon laser group **Gender (%):** 25 men (83%) and 5 women (17%) in total

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Verma 2004 *(Continued)*

	12 men (80%) and 3 women (20%) in micropulse diode laser group 13 men (87%) and 2 women (13%) in argon laser group The type of CSC was not specified **Inclusion criteria:** ages < 50 years; type I central serous retinopathy with a single leak on FA that was at least 300 µm away from fovea; presence of an indication for laser treatment (recurrence, occupational, history of poor visual outcome in fellow eye); no history of any treatment in the past **Exclusion Criteria:** participants with multiple leak central serous retinopathy; type 2 or type 3 central serous retinopathy or leak at papillomacular bundle or leak within 300 µm from the foveal center; people with ocular pathology such as CNV, choroidal inflammatory, or neoplastic disorder or a congenital optic nerve pit **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** micropulse diode laser Wavelength: 810 nm **Control:** argon laser (NR) Wavelength: 514 nm
Outcomes	**Length of follow-up:** 12 weeks Primary and secondary outcomes not differentiated **Outcomes:** mean BCVA; mean contrast sensitivity **Adverse events reported:** no **Intervals at which outcomes assessed:** 4, 8, and 12 weeks
Notes	**Full study name:** Comparative evaluation of diode laser versus argon laser photocoagulation in patients with central serous retinopathy: a pilot, randomized controlled trial ISRCTN84128484 **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** ISRCTN84128484 (ICTRP) **Study period:** January 1998 to June 2000, as reported in the full-text article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"They were randomly assigned into 2 groups according to the statistical random table using sequence generation" p. 2
Allocation concealment (selection bias)	Unclear risk	"The allocation of patients into 2 groups was done by a person who was not involved in the study and the sequence was concealed until interventions were assigned to prevent bias" p. 2
Masking of participants and personnel (performance bias)	Unclear risk	Similar groups but no information on masking
Masking of outcome assessment (detection bias)	Unclear risk	Similar groups but no information on masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison

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Verma 2004 *(Continued)*

Other bias	Low risk	Source of monetary support not reported and conflict of interest declared: "the author(s) declare that they have no competing interests"

Zhang 2012

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 30 eyes of 30 participants in 30% PDT group 30 eyes of 30 participants in 50% PDT group 30 eyes of 30 participants in PDT group **Exclusions after randomization:** 0 in 30% PDT group 0 in 50% PDT group 0 in PDT group **Number analyzed:** 30 eyes of 30 participants in 30% PDT group 30 eyes of 30 participants in 50% PDT group 30 eyes of 30 participants in PDT group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 0 in 30% PDT group 0 in 50% PDT group 0 in PDT group **How were missing data handled?:** NR **Power calculation:** NR
Participants	The type of CSC was not specified **Country:** China **Mean age (SD) (years):** NR in total 33.8 (5.5) in 30% PDT group 34.2 (5.2) in 50% PDT group 32.0 (4.1) in PDT group **Gender (%):** 25 men (83%) and 5 women (17%) in total 8 men (27%) and 22 women (73%) in 30% PDT group 11 men (37%) and 19 women (63%) in 50% PDT group 9 men (30%) and 21 women (70%) in PDT group **Inclusion criteria:** aged < 45 years with conscious visual distortion of imagery, darkened vision or changes of smaller imagery vision;

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Zhang 2012 *(Continued)*

	anterior segments do not have anything in particular or abnormal. Fundus exam should show macula regions or macula peripheral region gray spots with irregular formation or circular type infection, arching or ring-shaped hemorrhage, including various degrees of retinal edema; through FFA exam, low fluorescent shows in the early exudative lesion focus, hemorrhage spots always cover the fluorescein, but exudative lesion focus and mild bleeding spot could show CNV with typical petal shaped or trochoid shaped high fluorescent. As the time of radiography gets longer, fluorescein leakage could be observed. It is splinter high fluorescent, the scale and scope is similar to the gray exudative lesion focus; excluding external injury related, myopia related, or other established causes of non-age-related macular degeneration CNV; people who have not received laser photocoagulation, intraocular injections, or invasive surgical ocular treatments **Exclusion criteria:** history of penicillin allergy or systemic illnesses or issues with fluorescence or other systems of sexually transmitted disease that could cause intolerance of FFA treatment and PDT treatment; serious corneal illness, cataracts, blood volume, light opacity interfering mediums that can disturb the treatment plan and examination plan of the study; corneal endothelial cell scarring, shows FA has not created leakage; poor participant compliance with those who cannot complete follow-up times **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** 30% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 2 mg/m^2 **Intervention:** 50% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 3 mg/m^2 **Control:** PDT Light dose: 50 J/cm^2 Verteporfin concentration: 6 mg/m^2
Outcomes	**Length of follow-up:** 12 months Primary and secondary outcomes not differentiated **Outcomes:** BCVA value change; number of eyes show CNV change; CFT value change; number of treatments; recurrence of CSC **Adverse events reported:** no **Intervals at which outcomes assessed:** 3, 6, and 12 months, but not all participants had 12 month
Notes	**Full study name:** Different doses of verteporfin photodynamic therapy for central exudative chorioretinopathy **Type of study:** published full-text **Funding sources:** NR **Disclosures of interest:** NR **Trial registry:** not registered **Study period:** January 2006 to December 2009, as reported in the full-text article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Zhang 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization sequence specified and outlined in methods. Low risk of random sequence generation. The study used a number sequence table to assign proper randomization for groups. They used a verified and structured numbering sequence of 1-90 that was aligned for row and column and considered from smallest value to largest. They then randomized and recorded each randomly generated assignment figure
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	Similar groups but no information on masking
Masking of outcome assessment (detection bias)	Unclear risk	Similar groups but no information on masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol and trial registry entry not available for comparison
Other bias	Unclear risk	Conflict of interest and source of funding not reported

Zhao 2015

Methods	**Study design:** parallel randomized controlled trial **Number randomized:** 65 eyes of 65 participants in 30% PDT group 64 eyes of 64 participants in 50% PDT group **Exclusions after randomization:** 0 in 30% PDT group 0 in 50% PDT group **Number analyzed:** 61 eyes of 61 participants in 30% PDT group 56 eyes of 56 participants in 50% PDT group **Unit of analysis:** participant, 1 eye per person **Losses to follow-up:** 4 eyes of 4 participants in 30% PDT group 9 eyes of 9 participants in 50% PDT group **How were missing data handled?:** NR **Power calculation:** power = 80% and sample size = 112 participants (56 participants in each group)
Participants	**Country:** China **Mean age (SD) (years):** NR in total 42.5 (5.6) in 30% PDT group

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Zhao 2015 *(Continued)*

	43.1 (5.3) in 50% PDT group **Gender (%):** 87 men (74%) and 30 women (26%) in total 47 men (77%) and 14 women (23%) in 30% PDT group 40 men (71%) and 16 women (29%) in 50% PDT group **Participants with acute CSC were included and defined as:** "symptoms occurred for the first time, as an episode duration of less than 6 months, or there was a medical record that could prove the presence of subretinal fluid (SRF) for less than 6 months if the patient was asymptomatic" **Inclusion criteria:** symptoms occurred for the first time, as an episode duration of < 6 months, or there was a medical record that could prove the presence of SRF for < 6 months if the participant was asymptomatic; ages 18-50 years; presence of SRF involving the macula and detected using OCT; active fluorescein leakage during FA and abnormal dilated choroidal vasculature detected using ICGA **Exclusion criteria:** previous PDT, focal photocoagulation, intravitreal injections of anti-VEGF, or ocular surgery; other macular abnormalities such as CNV or polypoidal choroidal vasculopathy; choroidopathy that may affect choroidal thickness; any retinal vascular disease that may have fluorescein leakage during FA; history of porphyria or photosensitivity; severe impaired kidney or liver function or unstable heart condition (or a combination of these); pregnancy; inability to obtain photographs or to perform FA or ICGA; use of steroid systemically or topically in the last 6 months **Equivalence of baseline characteristics:** NR
Interventions	**Intervention:** 30% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 1.8 mg/m^2 **Control:** 50% PDT Light dose: 50 J/cm^2 Verteporfin concentration: 3 mg/m^2
Outcomes	**Length of follow-up:** 12 months **Primary outcome, as defined in study reports:** proportion of eyes with complete absorption of SRF; proportion of eyes with complete disappearance of fluorescein leakage at 6 and 12 months **Secondary outcomes, as defined in study reports:** SRF recurrent rate; the fluorescein leakage recurrent rate at 12 months; mean BCVA; the retinal thickness of the foveal center; the maximum retinal thickness at each scheduled visit **Adverse events reported:** yes **Intervals at which outcomes assessed:** 2 weeks, 1, 3, 6, and 12 months
Notes	**Full study name:** A 50% vs 30% dose of verteporfin (photodynamic therapy) for acute central serous chorioretinopathy: one-year results of a randomized clinical trial **Type of study:** published full-text **Funding sources:** Capital Health Research and Development of Special Funding grant D101100050010026 and National Science and Technology Major Project grant 2011ZX09302-007-02 **Disclosures of interest:** reported explicitly none of the authors has any financial relationship **Trial registry:** NCT01574430 (clinicaltrials.gov) **Study period:** March 2011 to February 2012, as reported in the full-text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using a computerized randomization table" p. 334

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Zhao 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	"All patients, examiners, investigators, and research assistants at the reading centers were masked to the treatment allocation group" p. 334
Masking of participants and personnel (performance bias)	Low risk	"All patients, examiners, investigators, and research assistants at the reading centers were masked to the treatment allocation group" p. 334
Masking of outcome assessment (detection bias)	Low risk	"All patients, examiners, investigators, and research assistants at the reading centers were masked to the treatment allocation group" p. 334
Incomplete outcome data (attrition bias) All outcomes	High risk	Level of lost to follow-up was not the same in each group: 4/65 (6%) participants in 30% PDT group and 8/64 (13%) participants 50% PDT group
Selective reporting (reporting bias)	High risk	Primary outcome reported at clinicaltrials.gov (NCT01574430) was change from baseline in BCVA, but study primary outcome were OCT-based improvement rate and FA-based improvement rate at 6 and 12 months. BCVA was reported, but not defined as primary outcome
Other bias	Low risk	Reported no conflicts of interest and non-industry funded

anti-VEGF: anti-vascular endothelial growth factor; BCVA: best-corrected visual acuity; CFT: central foveal thickness; CMT: central macular thickness; CNV: choroidal neovascularization; CRT: central retinal thickness; CSC: central serous chorioretinopathy; FA: fluorescein angiography; FFA: fundus fluorescein angiography; ICGA: indocyanine green angiography; logMAR: logarithm of the minimal angle of resolution; NA: not applicable as no missing data or unclear if there is missing data; NR: not reported; OCT: optical coherence tomography; p: page; PDT: photodynamic therapy; RPE: retinal pigment epithelium; SD: standard deviation; SFF: subfoveal fluid; SRF: subretinal fluid; SLO-ICGA: scanning laser indocyanine green angiography.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ainiwaer 2014	Wrong treatment arms and included traditional Chinese medicine; compared Argon laser to xueshuantong
Arevalo 2013	Not RCT
Aydin 2013	Not RCT
Beger 2012	Not RCT
Behnia 2013	Not RCT
Bi 2000	Not RCT
Boscia 2007	Not RCT
Bruha 1972	Not RCT
Cervera 2008	Not RCT
Chrapek 2015	Not RCT; randomization not clearly described
Demirel 2014	Not RCT

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Study	Reason for exclusion
Di 2013	Wrong treatment arms and included traditional Chinese medicine; compared argon laser to traditional medication (vitamin C, E, inosine, rutin, xueshuantong, difrarel)
Earl 2014	Not RCT
Fang 2013	Wrong treatment arms and included traditional Chinese medicine; compared jolethin combined with argon laser (argon laser and oral jolethin, vitamin B1, inosine and venoruton tablets) to traditional medication (oral lecithin complex iodine, vitamin B1, inosine, venoruton tablets)
Feily 2009	Not RCT
Haas 2004	Not RCT
Heinrich 1974	Not RCT
Huang 2006	Wrong treatment arms and included traditional Chinese medicine; compared argon laser and iodine treatment to argon laser
Khosla 1997	Not RCT
Koss 2012	Not RCT
Kurimoto 1969	Not RCT
Lee 2011	Not RCT
Li 2010	Not RCT
Lim 2011	Not RCT
Liu 2009	Not RCT
Long 2011	Wrong treatment arms and included traditional Chinese medicine; compared krypton laser combined with danshen and inosine to krypton laser combined with anisodine
Lyons 1977	Not RCT
Mackowiakowa 1987	Not RCT
Miyashita 1971	Not RCT
NCT01256580	Wrong participants. RCT enrolled participants with age-related macular degeneration
NCT01585441	This study was terminated early due to lack of enrollment
Novak 1987	Not RCT
Okamoto 2015	Not RCT
Ozdemir 2014	Not RCT
Peng 2010	Not RCT
Radian 1984	Not RCT

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Study	Reason for exclusion
Sanchez-Pacheco 2010	Not RCT
Takagi 1965	Not RCT
Tewari 1986	Not RCT; randomization not clearly described
Wang 2009a	Not RCT
Wang 2009b	Wrong treatment arms and included traditional Chinese medicine; compared therapeutic alliance group (injected subcutaneously compound anisodine injection 2 mL combined with joletion tablets taking) to joletion tablets group
Watzke 1974	Wrong participants
Watzke 1979	Wrong participants
Wu 2010	Wrong treatment arms and included traditional Chinese medicine; compared jolethin combined with argon laser to argon laser
Xu 2013	Not RCT
Xu 2014	Wrong treatment arms and included traditional Chinese medicine; compared anisodine injection to traditional medication (oral medication such as adenosine triphosphate, inosine, vitamin)
Ye 2013	Wrong treatment arms and included traditional Chinese medicine; compared argon laser combined with xueshuantong (laser combined with compound xueshuantong capsule) to argon laser
Zhang 2014	Not RCT
Zheng 2013	Wrong treatment arms and included traditional Chinese medicine; compared hyperbaric oxygen and iodized lecithin to hyperbaric oxygen

RCT: randomized controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2009-017959-98-NL

Trial name or title	Early Treatment of Patients with Central Serous Retinopathy: a Randomized Controlled Trial - CSR & PDT
Methods	**Study design:** parallel group RCT
Participants	**Population age:** adults, elderly **Gender:** men and women "Poor prognostic acute CSR [CSC]"
Interventions	NR PDT versus observation
Outcomes	**Primary outcomes:** visual acuity (BCVA ETDRS) at 1 year of follow-up **Secondary outcomes:** NR
Starting date	25 March 2010

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EUCTR2009-017959-98-NL *(Continued)*

Contact information	NR
Notes	**Sponsor name:** Rotterdam Eye Hospital

JPRN-UMIN000005372

Trial name or title	Study on the Effects of Supplements Containing Lutein on Chronic Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** ≤ 40 years **Gender:** male and female
Interventions	**Intervention 1:** multivitamins, minerals, and lutein **Control:** placebo
Outcomes	**Primary outcomes:** rate of spontaneous resolution of CSC, changes in macular volume measured by OCT **Secondary outcomes:** NR BCVA
Starting date	NR
Contact information	Tsutomu Yasukawa Nagoya City University Graduate School of Medical Sciences Department of Ophthalmology and Visual Science
Notes	**Sponsor name:** Nagoya City University Graduate School of Medical Sciences **Source of funding:** Santen Pharmaceutical Co., Ltd

NCT01019668

Trial name or title	Central Serous Chorioretinopathy Treated by Modified Photodynamic Therapy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 18-75 years **Gender:** men and women
Interventions	**Intervention 1:** verteporfin PDT, half-dose **Intervention 2:** verteporfin PDT, half-fluence
Outcomes	**Primary outcomes:** effectiveness of both modification for the treatment of chronic CSC, fluorescent leakage as regards to BCVA OCT changes

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NCT01019668 *(Continued)*

	Secondary outcomes: detrimental influence on choroidal perfusion, represented by the decrease of fluorescent intensity in ICGA
Starting date	November 2008
Contact information	Cheng-Kuo Cheng, MD Assistant Professor and Attending Physician of Ophthalmology Shin-Kong Wu Ho-Su Memorial Hospital, School of Medicine, Fu-Jen Catholic University
Notes	**Sponsor name:** Shin Kong Wu Ho-Su Memorial Hospital **Source of funding:** NR

NCT01552044

Trial name or title	Effect of Spironolactone in Treating Chronic Non-Resolutive Central Serous Chorioretinitis
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 18-60 years **Gender:** male and female
Interventions	**Intervention 1:** spironolactone 25 mg/day **Intervention 2:** placebo
Outcomes	**Primary outcomes:** change in central macular thickness at 1 and 3 months, subretinal fluid decrease of 40 microns or more **Secondary outcomes:** NR
Starting date	January 2012
Contact information	Francine Behar-Cohen, MD, PhD Hotel-Dieu of Paris, France
Notes	**Sponsor name:** Institut National de la Santé Et de la Recherche Médicale, France **Source of funding:** NR

NCT01630863

Trial name or title	The Safe Effective Light Dose of Photodynamic Therapy for Chronic Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 20-70 years **Gender:** men and women

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NCT01630863 *(Continued)*

Interventions	**Intervention 1:** 50% group (power of PDT is applied to the participants at 50% of the full energy based on TAP study) **Intervention 2:** 40% group (power of PDT is applied to the participants at 40% of the full energy based on TAP study) **Intervention 3:** 30% group (power of PDT is applied to the participants at 30% of the full energy based on TAP study)
Outcomes	**Primary outcomes:** change in BCVA at 1, 3, 6 and months **Secondary outcomes:** change in central retinal thickness, success rate, recurrence rate, and complications at 1, 3, and 6 months
Starting date	June 2012
Contact information	Min Sagong Yeungnam University College of Medicine Daegu, Republic of Korea
Notes	**Sponsor name:** Yeungnam University College of Medicine **Source of funding:** NR

NCT01797861

Trial name or title	Prospective Randomized Controlled Treatment Trial for Chronic Central Serous Chorioretinopathy (PLACE)
Methods	**Study design:** parallel group RCT
Participants	**Population age:** ≥ 18 years **Gender:** men and women
Interventions	**Intervention 1:** half-dose PDT "In the PDT treatment arm, all patients will receive an intravenous drip through which half-dose (3 mg/m2) verteporfin (Visudyne ®) is administered, with an infusion time of 10 minutes. At 15 minutes after the start of the infusion, PDT laser treatment is performed with standard 50 J/cm^2 fluency, a wavelength of 689 nm, and a treatment duration of 83 seconds. If there still is subretinal fluid on OCT scan at Evaluation Visit 1 (6-8 weeks after Treatment Visit 1 / the first treatment with half-dose PDT), a second treatment with half-dose PDT will be performed (Treatment Visit 2)" **Intervention 2:** micropulse laser (ML) treatment ML treatment with an 810 nm diode laser will be performed of the areas identified on mid-phase ICG angiography. Multiple laser spots will be applied, covering the leakage area on mid-phase ICG angiography. The area(s) that has to be treated is determined based on those hyperfluorescent area(s) on mid-phase (approximately 10 minutes) ICG-angiography that correspond to subretinal fluid accumulation in the macula on the OCT scan and hyperfluorescent "hot spots" on the mid-phase (3 minutes) fluorescein angiogram. If there still is subretinal fluid on OCT scan at Evaluation Visit 1 (6-8 weeks after Treatment Visit 1 / the first ML treatment), a second ML treatment will be performed (Treatment Visit 2)
Outcomes	**Primary outcomes:** absence of subretinal fluid on OCT scan

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NCT01797861 *(Continued)*

	Secondary outcomes: BCVA
Starting date	December 2013
Contact information	Camiel JF Boon, MD PhD FEBO Leiden University Medical Center, Netherlands Myrte Breukink, MD Radboud University Nijmegen Medical Centre, Institute of Ophthalmology, Netherlands
Notes	**Sponsor name:** Radboud University **Source of funding:** NR

NCT01971190

Trial name or title	Efficacy and Safety of Intravitreal Aflibercept Injection for Subacute Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 18-60 years **Gender:** men and women
Interventions	**Intervention 1:** aflibercept (Eylea) 2 mg intravitreal injection at baseline, 1 and 2 months **Control:** sham injection at baseline, 1 and 2 months
Outcomes	**Primary outcomes:** change in central subfield thickness from baseline to 1, 2, 3, 4, 5, and 6 months **Secondary outcomes:** percentage of eyes achieving complete resolution of subretinal fluid at 6 months, percentage of eyes achieving 20/20 vision at 6 months, number of aflibercept injections needed to achieve a complete resolution at 6 months, change in subfoveal choroidal thickness from baseline using EDI-OCT at 1, 2, 3, 4, 5, and 6 months, adverse effects of intravitreal aflibercept (Eylea) injection up to 6 months
Starting date	October 2013
Contact information	Young Hee Yoon, MD Asan Medical Center, Republic of Korea
Notes	**Sponsor name:** Asan Medical Center **Source of funding:** NR

NCT01982383

Trial name or title	Study on the Use of Micropulse Laser to Treat Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 30-60 years

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NCT01982383 *(Continued)*

	Gender: men and women "New diagnosis of CSC"
Interventions	**Intervention 1:** micropulse laser treatment "Patient's randomized to ML treatment would be treated with the following settings: 200 micron spot size, 0.2 second duration, 15% duty cycle, and 300 milliWatt power. Their eyes would be dilated prior to treatment with standard mydriatic medications, including Tropicamide and Phenylephrine" **Control:** no treatment "Patients randomized to this treatment arm, will not receive treatment for CSC. They will continue to be observed at month 1 and month 3. If any worsening of pathology is found during the follow-up visits, the patient will be removed from the study and given appropriate standard of care by the attending"
Outcomes	**Primary outcomes:** resolution of fluid build-up within 1 week to 3 months after the laser procedure is completed **Secondary outcomes:** NR
Starting date	November 2012
Contact information	Khadijah Abdallah, MPH George Washington University, District of Columbia, United States
Notes	**Sponsor name:** George Washington University **Source of funding:** NR

NCT01990677

Trial name or title	Eplerenone for the Treatment of Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** ≥ 18 years **Gender:** men and women
Interventions	**Intervention 1:** eplerenone 25 mg - chronic CSC diagnosis "Dosing will begin at 25mg Eplerenone taken orally , one time, each day for 58 days. Throughout the 58 day treatment period dosage will be adjusted. The adjustment will be based on serum potassium and creatine levels from blood draws done at Day 12 and Day 33. From the 25 mg starting dosage, the dosage will either be increased to 50 mg a day or reduced to placebo, one time, each day" **Intervention 2:** placebo - chronic CSC diagnosis "Dosing will begin with placebo and will stay as placebo throughout the study. The placebo pills will be taken orally, once daily, for 58 days. The placebo pills will be compounded to be of similar composition to the eplerenone tablets, without the active ingredient" **Intervention 3:** eplerenone 25 mg - acute CSC diagnosis

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NCT01990677 *(Continued)*

	"Dosing will begin at 25mg Eplerenone taken orally , one time, each day for 28 days. Throughout the 28 day treatment period, dosage will be adjusted based on serum potassium and creatine levels from blood draws done on Day 12. From the 25 mg starting dosage, the dosage will either be increased to 50 mg a day or reduced to placebo, one time, each day" **Intervention 4:** placebo - acute CSC diagnosis "Dosing will begin with placebo and will stay as placebo throughout the study. The placebo pills will be taken orally, once daily, for 28 days. The placebo pills will be compounded to be of similar composition to the eplerenone tablets, without the active ingredient"
Outcomes	**Primary outcomes:** absence of subfoveal (retinal) fluid based on spectral domain OCT measurement at 1 month in acute CSC and 2 months in chronic CSC participants **Secondary outcomes:** mean change in subfoveal fluid height based on OCT measurement at 1 month in acute CSC and 2 months in chronic CSC participants
Starting date	October 2013
Contact information	Brian Burke, MPH Wills Eye Hospital
Notes	**Sponsor name:** Wills Eye Hospital, Philadelphia, United States **Source of funding:** NR

NCT02153125

Trial name or title	Eplerenone for the Treatment of Chronic Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** 18-65 years **Gender:** men and women
Interventions	**Intervention 1:** eplerenone 25 mg given daily for 1 week, followed by 50 mg given for a total of 3 months since commencement of treatment **Intervention 2:** placebo
Outcomes	**Primary outcomes:** decrease of at least 10% in subretinal fluid thickness as measured by OCT at 6 months **Secondary outcomes:** NR
Starting date	April 2014
Contact information	Michaella Goldstein, MD Tel Aviv Souraski Medical Center, Israel
Notes	**Sponsor name:** Tel-Aviv Sourasky Medical Center **Source of funding:** NR

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NCT02215330

Trial name or title	A Study of the Beneficial Effects of Eplerenone on Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** ≥ 21 years **Gender:** men and women
Interventions	**Intervention:** eplerenone 25 mg pills triturated and filled into capsules **Control:** sugar pill (maltodextrin filled into capsules)
Outcomes	**Primary outcomes:** difference in the number of successful treatments after 16 weeks, defined as complete absence of subretinal fluid on SD-OCT **Secondary outcomes:** change in visual acuity between eplerenone and placebo at 16 weeks, change in retinal thickness between eplerenone and placebo at 16 weeks, change in retinal volume between eplerenone and placebo at 16 weeks
Starting date	October 2014
Contact information	Oliver Findl, MD, Prof, MBA Vienna Institute for Research in Ocular Surgery, Department of Ophthalmology Hanusch Hospital Vienna, Vienna, Austria
Notes	**Sponsor name:** Oliver Findl, MD, Prof, MBA **Source of funding:** NR

NCT02354170

Trial name or title	Short-Term Oral Mifepristone for Central Serous Chorioretinopathy
Methods	**Study design:** parallel group RCT
Participants	**Population age:** ≥ 18 years **Gender:** men and woman
Interventions	**Intervention 1:** 1 x 300 mg mifepristone tablet, taken once daily for 4 weeks **Intervention 2:** 3 x 300 mg mifepristone tablets (900 mg dose), taken once daily for 4 weeks **Control:** placebo taken once daily for 4 weeks
Outcomes	**Primary outcomes:** resolution of sub-retinal fluid at 4 weeks after treatment, presence or absence of subretinal fluid on spectral-domain OCT after 4 weeks of treatment with mifepristone 300 or 900 mg daily, compared with placebo **Secondary outcomes:** change in subretinal fluid or intraretinal fluid (or both) at weeks 1, 2, 4, and 8, BCVA at weeks 1, 2, 4, and 8, change in ETDRS BCVA compared with baseline at weeks 1, 2, 4, and 8, change in macular thickness at weeks 1, 2, 4, and 8, change in foveal thickness at weeks 1, 2, 4, and 8, change compared with baseline in thickness of subretinal fluid under the fovea on OCTat weeks 1, 2, 4, and 8, change in choroidal thickness at weeks 1, 2, 4, and 8, dye leakage in vascula-ture at week 4 and 8, change in OCT characteristics in the fellow eye at week 8, proportion of acute

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NCT02354170 *(Continued)*

	versus chronic CSC participants at week 8, proportion of acute versus chronic CSC participants as determined at baseline, with the above outcomes analyzed for each subgroup; safety and tolerability characteristics at week 8
Starting date	January 2015
Contact information	Roger A Goldberg, MD, MBA Bay Area Retina Associates Walnut Creek, California, United States Jeffery S Heier, MD Ophthalmic Consultants of Boston Boston, Massachusetts, United States
Notes	**Sponsor Name:** Roger Goldberg, MD, MBA **Source of funding:** Bay Area Retina Associates, Ophthalmic Consultants of Boston

BCVA: best-corrected visual acuity; CSC: central serous chorioretinopathy (also known as CSR: central serous retinopathy); ETDRS: Early Treatment Diabetic Retinopathy Study; ICGA: indocyanine green angiography; NR: not reported; OCT: optical coherence tomography; PDT: photodynamic therapy; RCT: randomized controlled trial.

DATA AND ANALYSES

Comparison 1. Anti-VEGF versus observation

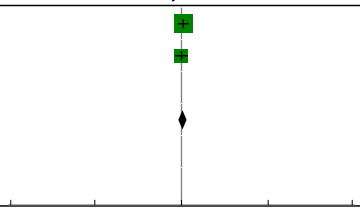
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	2	64	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.02, 0.03]
2 Mean change in CRT at 12 months	2	64	Mean Difference (IV, Fixed, 95% CI)	8.73 [-18.08, 35.54]

Analysis 1.1. Comparison 1 Anti-VEGF versus observation, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	Anti-VEGF N	Anti-VEGF Mean(SD)	Observation N	Observation Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kim 2013	20	0.2 (0.1)	20	0.2 (0)		56.79%	0.01[-0.02,0.04]
Lim 2010	12	0 (0)	12	0 (0.1)		43.21%	0[-0.04,0.04]
Total ***	**32**		**32**			**100%**	**0.01[-0.02,0.03]**

Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%

Test for overall effect: Z=0.47(P=0.64)



Favors anti-VEGF — Favors observation

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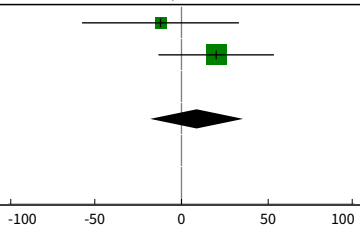
Analysis 1.2. Comparison 1 Anti-VEGF versus observation, Outcome 2 Mean change in CRT at 12 months.

Study or subgroup	Anti-VEGF N	Anti-VEGF Mean(SD)	Observation N	Observation Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kim 2013	20	218 (81)	20	230.1 (64)		35.12%	-12.1[-57.34,33.14]
Lim 2010	12	207 (50)	12	187 (31)		64.88%	20[-13.29,53.29]
Total ***	**32**		**32**			**100%**	**8.73[-18.08,35.54]**

Heterogeneity: Tau^2=0; Chi^2=1.25, df=1(P=0.26); I^2=20.3%

Test for overall effect: Z=0.64(P=0.52)



Comparison 2. Anti-VEGF versus low fluence PDT

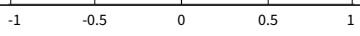
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	2	56	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.08, 0.15]
2 Recurrence of CSC at 12 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mean change in CRT at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Anti-VEGF versus low fluence PDT, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	Anti-VEGF N	Anti-VEGF Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bae 2011	16	-0.2 (0.2)	18	-0.3 (0.2)		71.31%	0.07[-0.07,0.21]
Semeraro 2012	12	0.8 (0.3)	10	0.9 (0.2)		28.69%	-0.06[-0.28,0.16]
Total ***	**28**		**28**			**100%**	**0.03[-0.08,0.15]**

Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%

Test for overall effect: Z=0.55(P=0.58)



Analysis 2.2. Comparison 2 Anti-VEGF versus low fluence PDT, Outcome 2 Recurrence of CSC at 12 months.

Study or subgroup	Anti-VEGF n/N	PDT n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bae 2011	3/5	0/16		19.83[1.19,330.5]
Semeraro 2012	7/12	4/10		1.46[0.59,3.58]

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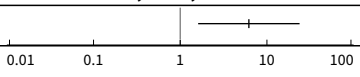
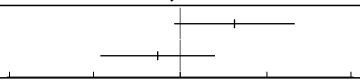
Analysis 2.3. Comparison 2 Anti-VEGF versus low fluence PDT, Outcome 3 Persistent CSC at 12 months.

Study or subgroup	Anti-VEGF n/N	PDT n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bae 2011	11/16	2/18		6.19[1.61,23.81]



Analysis 2.4. Comparison 2 Anti-VEGF versus low fluence PDT, Outcome 4 Mean change in CRT at 12 months.

Study or subgroup	Anti-VEGF N	Anti-VEGF Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bae 2011	14	-71.1 (55)	18	-102.4 (42.1)		31.3[-3.46,66.06]
Semeraro 2012	12	-127 (36)	10	-114 (42)		-13[-46.05,20.05]



Comparison 3. Anti-VEGF plus 50% PDT versus 50% PDT

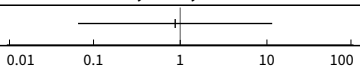
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mean change in CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Anti-VEGF plus 50% PDT versus 50% PDT, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	Anti-VEGF + 50% PDT N	Anti-VEGF + 50% PDT Mean(SD)	50% PDT N	50% PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Coskun 2014	8	0.4 (0.3)	7	0.1 (0.2)		0.3[0.09,0.51]

Analysis 3.2. Comparison 3 Anti-VEGF plus 50% PDT versus 50% PDT, Outcome 2 Persistent CSC at 12 months.

Study or subgroup	Anti-VEGF + 50% PDT n/N	50% PDT n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Coskun 2014	1/8	1/7		0.88[0.07,11.54]



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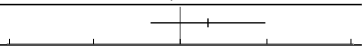
Analysis 3.3. Comparison 3 Anti-VEGF plus 50% PDT versus 50% PDT, Outcome 3 Mean change in CRT at 12 months.

Study or subgroup	Anti-VEGF + 50% PDT N	Anti-VEGF + 50% PDT Mean(SD)	50% PDT N	50% PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Coskun 2014	8	203 (45)	7	187 (15)		16[-17.1,49.1]

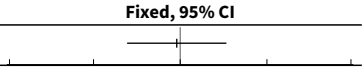


Comparison 4. Six-dose anti-VEGF versus four-dose anti-VEGF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Mean change in CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

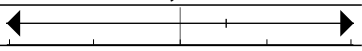
Analysis 4.1. Comparison 4 Six-dose anti-VEGF versus four-dose anti-VEGF, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	Six- dose anti-VEGF N	Six- dose anti-VEGF Mean(SD)	Four- dose a nti-VEGF N	Four- dose a nti-VEGF Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pitcher 2015	6	-0.1 (0.3)	6	-0.1 (0.2)		-0.02[-0.31,0.27]



Analysis 4.2. Comparison 4 Six-dose anti-VEGF versus four-dose anti-VEGF, Outcome 2 Mean change in CRT at 12 months.

Study or subgroup	Six -dose a nti-VEGF N	Six -dose a nti-VEGF Mean(SD)	Four -dose a nti-VEGF N	Four -dose a nti-VEGF Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pitcher 2015	6	-80.3 (103.7)	6	-106.8 (156)		26.5[-123.41,176.41]



Comparison 5. 50% PDT versus sham treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Recurrence/persistence CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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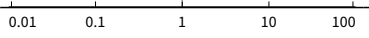
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mean CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 50% PDT versus sham treatment, Outcome 1 Mean BCVA at 12 months.

Study or subgroup	50% PDT N	50% PDT Mean(SD)	Sham N	Sham Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Chan 2008	39	-0 (0.1)	19	0.1 (0.2)		-0.1[-0.18,-0.02]

Analysis 5.2. Comparison 5 50% PDT versus sham treatment, Outcome 2 Recurrence/persistence CSC at 12 months.

Study or subgroup	50% PDT n/N	Sham n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Recurrence of CSC at 12 months				
Chan 2008	1/38	4/15		0.1[0.01,0.81]
5.2.2 Persistent CSC at 12 months				
Chan 2008	1/39	4/19		0.12[0.01,1.02]



Analysis 5.3. Comparison 5 50% PDT versus sham treatment, Outcome 3 Mean CRT at 12 months.

Study or subgroup	50% PDT N	50% PDT Mean(SD)	Sham N	Sham Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Chan 2008	39	161 (65)	19	278 (192)		-117[-205.71,-28.29]

Comparison 6. 30% PDT versus PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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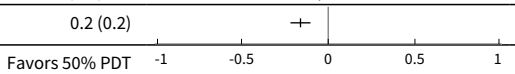
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mean change in CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

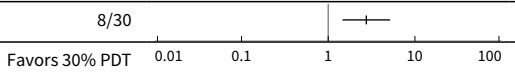
Analysis 6.1. Comparison 6 30% PDT versus PDT, Outcome 1 Mean BCVA at 12 months.

Study or subgroup	30% PDT N	30% PDT Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Zhang 2012	30	0 (0)	30	0.2 (0.2)		-0.16[-0.22,-0.1]



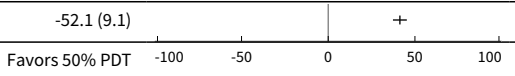
Analysis 6.2. Comparison 6 30% PDT versus PDT, Outcome 2 Recurrence of CSC at 12 months.

Study or subgroup	30% PDT n/N	PDT n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Zhang 2012	22/30	8/30		2.75[1.46,5.17]



Analysis 6.3. Comparison 6 30% PDT versus PDT, Outcome 3 Mean change in CRT at 12 months.

Study or subgroup	30% PDT N	30% PDT Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Zhang 2012	30	-10.8 (6.5)	30	-52.1 (9.1)		41.33[37.34,45.32]



Comparison 7. 50% PDT versus PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mean change in CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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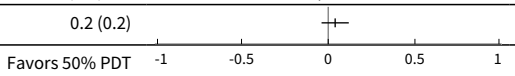
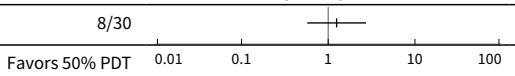
Analysis 7.1. Comparison 7 50% PDT versus PDT, Outcome 1 Mean BCVA at 12 months.

Study or subgroup	50% PDT N	50% PDT Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Zhang 2012	30	0.2 (0.2)	30	0.2 (0.2)		0.04[-0.04,0.12]



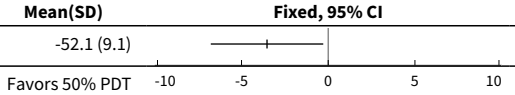
Analysis 7.2. Comparison 7 50% PDT versus PDT, Outcome 2 Recurrence of CSC at 12 months.

Study or subgroup	50% PDT n/N	PDT n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Zhang 2012	10/30	8/30		1.25[0.57,2.73]



Analysis 7.3. Comparison 7 50% PDT versus PDT, Outcome 3 Mean change in CRT at 12 months.

Study or subgroup	50% PDT N	50% PDT Mean(SD)	PDT N	PDT Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Zhang 2012	30	-55.7 (0.2)	30	-52.1 (9.1)		-3.53[-6.77,-0.29]



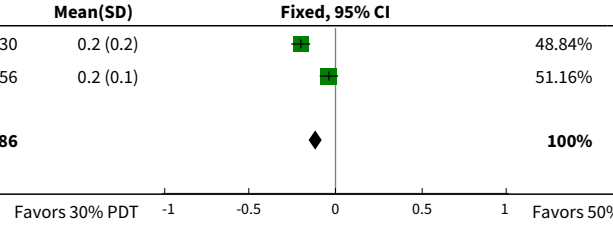
Comparison 8. 30% PDT versus 50% PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	2	177	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.15, -0.08]
2 Recurrence of CSC at 12 months	2	153	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.54, 4.06]
3 Persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mean change in CRT at 12 months	2	177	Mean Difference (IV, Fixed, 95% CI)	44.90 [42.57, 47.23]

Analysis 8.1. Comparison 8 30% PDT versus 50% PDT, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	30% PDT N	30% PDT Mean(SD)	50% PDT N	50% PDT Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Zhang 2012	30	0 (0)	30	0.2 (0.2)		48.84%	-0.2[-0.25,-0.15]
Zhao 2015	61	0.1 (0.2)	56	0.2 (0.1)		51.16%	-0.04[-0.09,0.01]
Total ***	**91**		**86**			**100%**	**-0.12[-0.15,-0.08]**

Heterogeneity: Tau^2=0; Chi^2=17.59, df=1(P<0.0001); I^2=94.31%



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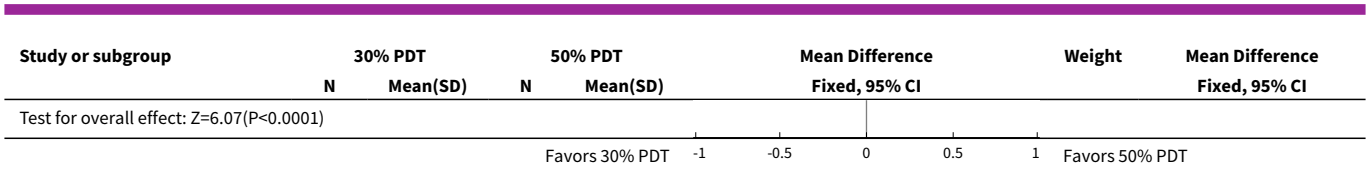
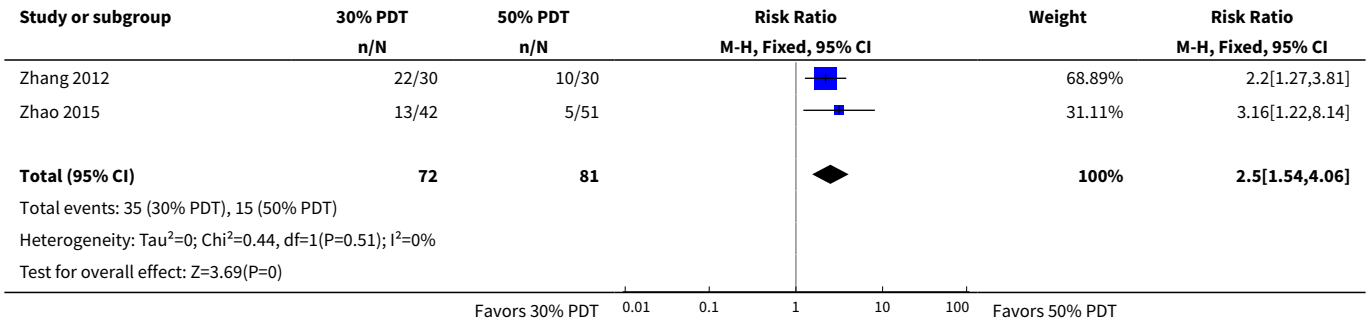
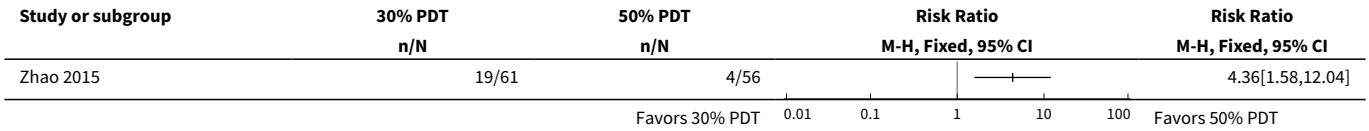


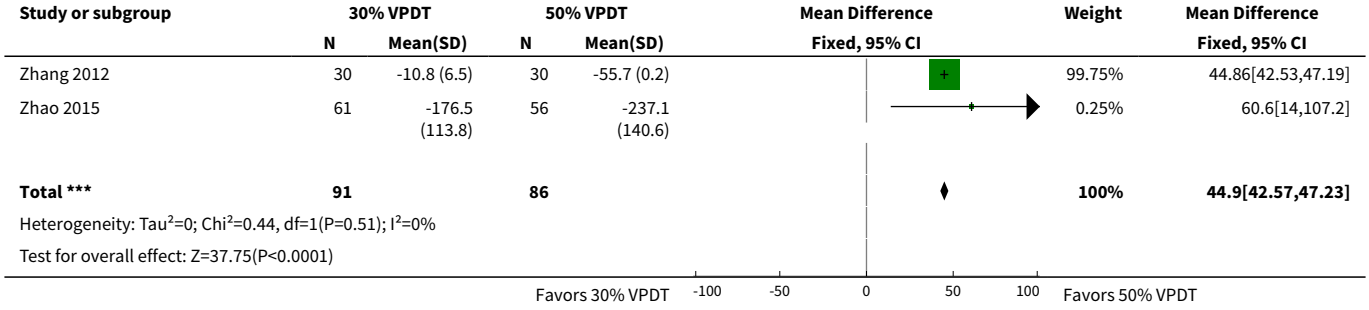
Analysis 8.2. Comparison 8 30% PDT versus 50% PDT, Outcome 2 Recurrence of CSC at 12 months.



Analysis 8.3. Comparison 8 30% PDT versus 50% PDT, Outcome 3 Persistent CSC at 12 months.



Analysis 8.4. Comparison 8 30% PDT versus 50% PDT, Outcome 4 Mean change in CRT at 12 months.



Comparison 9. Laser versus observation or sham treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in BCVA at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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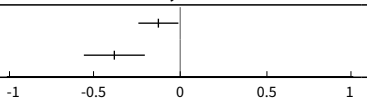
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mean change in CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Laser versus observation or sham treatment, Outcome 1 Mean change in BCVA at 12 months.

Study or subgroup	Laser N	Laser Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Klatt 2011	14	-0.3 (0.1)	16	-0.1 (0.2)		-0.13[-0.24,-0.01]
Roisman 2013	10	0.1 (0.1)	5	0.5 (0.2)		-0.38[-0.56,-0.2]

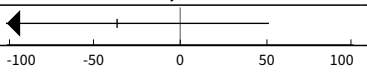


Analysis 9.2. Comparison 9 Laser versus observation or sham treatment, Outcome 2 Recurrence of CSC at 12 months.

Study or subgroup	Laser n/N	Sham n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Robertson 1983	5/15	4/15		1.25[0.41,3.77]

Analysis 9.3. Comparison 9 Laser versus observation or sham treatment, Outcome 3 Mean change in CRT at 12 months.

Study or subgroup	Laser N	Laser Mean(SD)	Observation N	Observation Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Roisman 2013	10	247.2 (105.4)	5	283.6 (66.5)		-36.4[-123.95,51.15]



Comparison 10. Indirect argon laser versus direct argon laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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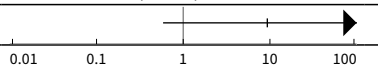
Analysis 10.1. Comparison 10 Indirect argon laser versus direct argon laser, Outcome 1 Recurrence of CSC at 12 months.

Study or subgroup	Indirect argon laser n/N	Direct argon laser n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Robertson 1983	3/5	0/7		9.33[0.59,148.6]

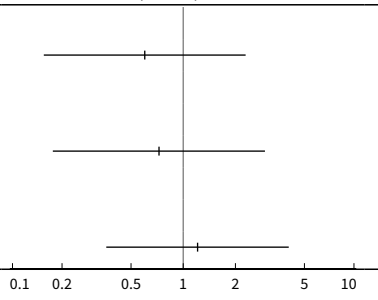


Comparison 11. Comparison of different laser wavelengths

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Yellow compared with red	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Yellow compared with green	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Red compared with green	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 Comparison of different laser wavelengths, Outcome 1 Recurrence of CSC at 12 months.

Study or subgroup	Intervention n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Yellow compared with red				
Shang 1999	3/30	5/30		0.6[0.16,2.29]
11.1.2 Yellow compared with green				
Shang 1999	3/30	4/29		0.73[0.18,2.96]
11.1.3 Red compared with green				
Shang 1999	5/30	4/29		1.21[0.36,4.06]



Comparison 12. Antioxidant supplements versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Recurrence at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Persistence at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 CRT at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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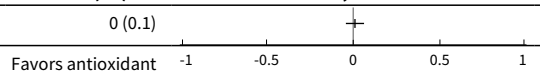
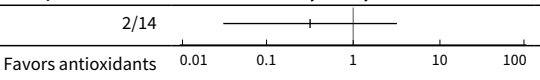
Analysis 12.1. Comparison 12 Antioxidant supplements versus placebo, Outcome 1 BCVA at 12 months.

Study or subgroup	Antioxidant supplements N	Antioxidant supplements Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Ratanasukon 2012	7	0 (0.1)	7	0 (0.1)		0.01[-0.04,0.06]



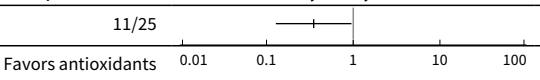
Analysis 12.2. Comparison 12 Antioxidant supplements versus placebo, Outcome 2 Recurrence at 12 months.

Study or subgroup	Antioxidant supplements n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ratanasukon 2012	1/22	2/14		0.32[0.03,3.19]



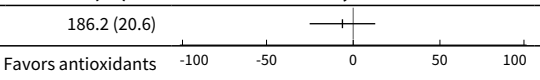
Analysis 12.3. Comparison 12 Antioxidant supplements versus placebo, Outcome 3 Persistence at 12 months.

Study or subgroup	Antioxidant supplements n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ratanasukon 2012	4/26	11/25		0.35[0.13,0.95]



Analysis 12.4. Comparison 12 Antioxidant supplements versus placebo, Outcome 4 CRT at 12 months.

Study or subgroup	Antioxidant supplements N	Antioxidant supplements Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Ratanasukon 2012	7	180 (15.1)	7	186.2 (20.6)		-6.22[-25.13,12.69]



Comparison 13. Beta-blocker versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean BCVA at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 BCVA ≥ 20/40 at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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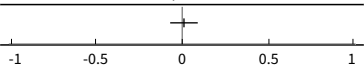
Analysis 13.1. Comparison 13 Beta-blocker versus placebo, Outcome 1 Mean BCVA at 12 months.

Study or subgroup	Beta-blocker N	Beta-blocker Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Kianersi 2008	30	1 (0.1)	30	1 (0.2)		0.01[-0.07,0.09]

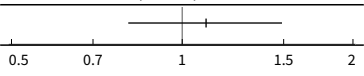


Analysis 13.2. Comparison 13 Beta-blocker versus placebo, Outcome 2 Recurrence of CSC at 12 months.

Study or subgroup	Beta-blocker n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kianersi 2008	3/30	5/30		0.6[0.16,2.29]

Analysis 13.3. Comparison 13 Beta-blocker versus placebo, Outcome 3 BCVA ≥ 20/40 at 12 months.

Study or subgroup	Beta-blocker n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kianersi 2008	23/30	21/30		1.1[0.81,1.49]

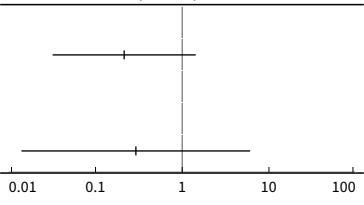


Comparison 14. Carbonic anhydrase inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent/persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Recurrence of CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Persistent CSC at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 Carbonic anhydrase inhibitors versus placebo, Outcome 1 Recurrent/persistent CSC at 12 months.

Study or subgroup	Brinzolamide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
14.1.1 Recurrence of CSC at 12 months				
Ontiveros-Orozco 2004	1/7	4/6		0.21[0.03,1.43]
14.1.2 Persistent CSC at 12 months				
Ontiveros-Orozco 2004	0/7	1/6		0.29[0.01,6.07]



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Comparison 15. *Helicobacter pylori* treatment versus placebo or observation

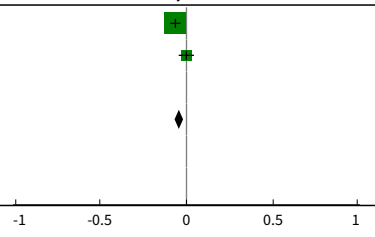
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean BCVA at 12 months	2	103	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.07, -0.02]
2 Persistent CSC at 12 months	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.36, 1.22]

Analysis 15.1. Comparison 15 *Helicobacter pylori* treatment versus placebo or observation, Outcome 1 Mean BCVA at 12 months.

Study or subgroup	H. pylori treatment N	H. pylori treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dang 2013	27	0.1 (0.1)	26	0.1 (0.1)		68.63%	-0.06[-0.09,-0.03]
Rahbani-Nobar 2011	25	0 (0.1)	25	0 (0.1)		31.37%	-0[-0.04,0.04]
Total ***	**52**		**51**			**100%**	**-0.04[-0.07,-0.02]**

Heterogeneity: Tau^2=0; Chi^2=5.45, df=1(P=0.02); I^2=81.64%

Test for overall effect: Z=3.53(P=0)



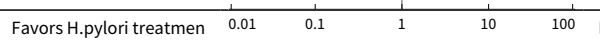
Analysis 15.2. Comparison 15 *Helicobacter pylori* treatment versus placebo or observation, Outcome 2 Persistent CSC at 12 months.

Study or subgroup	H. pylori treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dang 2013	10/27	13/26		81.53%	0.74[0.4,1.38]
Rahbani-Nobar 2011	1/25	3/25		18.47%	0.33[0.04,2.99]
Total (95% CI)	**52**	**51**		**100%**	**0.67[0.36,1.22]**

Total events: 11 (H. pylori treatment), 16 (Control)

Heterogeneity: Tau^2=0; Chi^2=0.49, df=1(P=0.48); I^2=0%

Test for overall effect: Z=1.31(P=0.19)



ADDITIONAL TABLES

Table 1. Assessment of transitivity across treatment comparisons: visual acuity

Treatment comparison	Study	Type of CSC	Date study conducted	Industry sponsored
Anti-VEGF vs. PDT	Bae 2011	Chronic	2009-2012	Yes
	Semeraro 2012	Chronic	2009-2010	NR

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Table 1. Assessment of transitivity across treatment comparisons: visual acuity *(Continued)*

PDT vs. no treatment	Chan 2008	Acute	2004-2005	NR
Laser vs. no treatment	Robertson 1983	Acute	1977-1981	No

One additional study for the comparison PDT vs. no treatment was reported in abstract form only and no data on outcome so was not included in the network meta-analysis (Boscia 2008).
anti-VEGF: anti-vascular endothelial growth factor; CSC: central serous chorioretinopathy; NR: not reported; PDT: photodynamic therapy.

Table 2. Comparative effects of ocular interventions for central serous chorioretinopathy: visual acuity

Anti-VEGF	-0.08 (-0.14 to -0.01)	-0.20 (-0.30 to -0.11)	0.00 (-0.02 to 0.03)	0.22 (0.01 to 0.44)
0.08 (0.01 to 0.14)	**PDT**	-0.13 (-0.24 to -0.01)	0.08 (0.01 to 0.15)	0.30 (0.09 to 0.51)
0.20 (0.11 to 0.30)	0.13 (0.01 to 0.24)	**Laser**	0.21 (0.11 to 0.31)	0.43 (0.19 to 0.66)
-0.00 (-0.03 to 0.02)	-0.08 (-0.15 to -0.01)	-0.21 (-0.31 to -0.11)	**Anti-VEGF and PDT**	0.22 (0.00 to 0.44)
-0.22 (-0.44 to -0.01)	-0.30 (-0.51 to -0.09)	-0.43 (-0.66 to -0.19)	-0.22 (-0.44 to -0.00)	**Control (no treatment or sham treatment)**

Effect estimate is the mean difference (95% confidence interval). Negative values favor the first intervention. In the lower left hand triangle, the first intervention is anti-VEGF, PDT, laser etc. In the upper right hand triangle, the first intervention is control, anti-VEGF and PDT, laser etc. So, for example, visual acuity with anti-VEGF was 0.22 logMAR units better than control 95% CI 0.44 better to 0.01 better.
anti-VEGF: anti-vascular endothelial growth factor; logMAR: logarithm of the minimal angle of resolution; PDT: photodynamic therapy.

Table 3. Assessment of transitivity across treatment comparisons: recurrence

Treatment comparison	Study	Type of CSC	Date study conducted	Industry spon-sored
Anti-VEGF vs. no treatment	Kim 2013	Acute	2010-2011	No
	Lim 2010	Acute	2008	No
Anti-VEGF vs. PDT	Bae 2011	Chronic	2009-2012	Yes
	Semeraro 2012	Chronic	2009-2010	NR
Anti-VEGF + PDT vs. PDT alone	Coskun 2014	Chronic	NR (published 2014)	NR
PDT vs. no treatment	Chan 2008	Acute	2004-2005	NR
Laser vs. no treatment	Klatt 2011	Acute	2007-2008	NR
	Robertson 1983	Acute	1977-1981	No
	Roisman 2013	Chronic	NR (published 2013)	NR

One additional study for the comparison PDT vs no treatment was reported in abstract form only and no data on outcome so was not included in the network meta-analysis (Boscia 2008).
anti-VEGF: anti-vascular endothelial growth factor; CSC: central serous chorioretinopathy; NR: not reported; PDT: photodynamic therapy.

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Table 4. Comparative effects of ocular interventions for CSC: recurrence

Anti-VEGF	0.27 (0.02 to 3.73)	3.34 (0.01 to 788.57)	2.67 (0.03 to 234.08)
3.77 (0.27 to 52.94)	**PDT**	12.58 (0.11 to 1503.87)	10.07 (0.27 to 371.91)
0.30 (0.00 to 70.79)	0.08 (0.00 to 9.50)	**Laser**	0.80 (0.03 to 18.46)
0.37 (0.00 to 32.83)	0.10 (0.00 to 3.67)	1.25 (0.05 to 28.85)	**Control**

Effect estimate is the risk ratio (95% CI).
anti-VEGF: anti-vascular endothelial growth factor; logMAR: logarithm of the minimal angle of resolution; PDT: photodynamic therapy.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Central Serous Chorioretinopathy] explode all trees
#2 central serous near/2 (retinopath* or chorioretinopath*)
#3 retinitis near/3 (angiospastic* or serosa or capillarospastic or capillarospastic or angiosplastic)
#4 retinopath* near/3 (angiospastic* or serosa or capillarospastic or capillarospastic or angiosplastic)
#5 central* near/3 (retinitis or serosa)
#6 #1 or #2 or #3 or #4 or #5

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Central Serous Chorioretinopathy/
14. (central serous adj2 (retinopath$ or chorioretinopath$)).tw.
15. (retinitis adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw.
16. (retinopath$ adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw.
17. (central$ adj3 (retinitis or serosa)).tw.
18. or/13-17
19. 12 and 18

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10

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12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. central serous retinopathy/
34. (central serous adj2 (retinopath$ or chorioretinopath$)).tw.
35. (retinitis adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw.
36. (retinopath$ adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw.
37. (central$ adj3 (retinitis or serosa)).tw.
38. or/33-37
39. 32 and 38

Appendix 4. ISRCTN search strategy

(central serous retinopathy) OR (central serous chorioretinopathy)

Appendix 5. ClinicalTrials.gov search strategy

central serous retinopathy OR central serous chorioretinopathy

Appendix 6. ICTRP search strategy

"central serous retinopathy"

"central serous chorioretinopathy"

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	· **Parallel group RCT** *i.e. people randomized to treatment* · **Within-person RCT** *i.e. eyes randomized to treatment* · **Cluster RCT** *i.e. communities randomized to treatment* · **Cross-over RCT** *i.e. people randomized to sequence of treatment* · Other, specify	Exclusions after randomization Losses to follow-up Number randomized/analyzed How were missing data handled? *e.g., available case analysis, imputation methods*
Unit of randomization/unit of analysis	· **One eye included in study**, *specify how eye selected*	

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(Continued)

	· **Two eyes included in study, both eyes received same treatment**, *briefly specify how* analyzed*(best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	Reported power calculation (Y/N)*, if yes, sample size and power* Unusual study design/issues
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/N)
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.*	
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=)	· Number of people randomized to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	
Outcomes		
Primary and secondary outcomes *as defined in study reports*	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up

CONTRIBUTIONS OF AUTHORS

Each author has undertaken all of the following tasks listed:

- conceived or designed the study, or both;
- drafted the review or commented on it critically for intellectual content;
- provided final approval of the document to be published.

MS, AL, and JE performed study screening and data extraction.

DECLARATIONS OF INTEREST

None known.

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following amendments to our protocol (Salehi 2015).

- We excluded trials of traditional Chinese medicine. This is because we did not have a clear rationale for these treatments and these interventions may not be applicable to the settings covered by this review.
- We restricted the network to interventions applied directly to the eye (ocular interventions) because we felt that a key assumption of the network - participants should be equally likely to be randomized to any of the interventions - would be unlikely to hold otherwise.
- We did not consistently contact trial investigators for clarification of risk of bias as 'unclear' based on unreported or poorly reported information: some of the studies were completed many years ago and we took the judgment that the information was unlikely to be forthcoming.

We omitted to describe the GRADE assessment and 'Summary of findings' table in our protocol and have included that in the review methods.

The following methods set out in our protocol were not done due to lack of data. They may be applicable in future editions of the review.

Unit of analysis

If any studies enroll bilateral CSC cases and randomize eyes in participants to intervention versus comparator (within-person study), we will refer to Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* as a guide for analysis of matched data (Higgins 2011b).

Assessing reporting bias

When future versions of this review's meta-analysis include 10 or more studies, we will investigate small-study effects using a funnel plot. The funnel plot will have the effect estimate on the horizontal axis and the standard error on the vertical axis for each trial. We will conduct a qualitative interpretation of funnel plot asymmetry using guidance from Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Carbonic Anhydrase Inhibitors [therapeutic use]; Central Serous Chorioretinopathy [*therapy]; Helicobacter Infections [drug therapy]; Helicobacter pylori; Laser Therapy [methods]; Photochemotherapy [methods]; Propranolol [therapeutic use]; Randomized Controlled Trials as Topic; Remission, Spontaneous; Treatment Outcome; Vascular Endothelial Growth Factor A [antagonists & inhibitors]; Visual Acuity; Watchful Waiting

MeSH check words

Humans

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