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Monotherapy laser photocoagulation for diabetic macular oedema (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	8
OBJECTIVES	9
METHODS	9
RESULTS	11
Figure 1.	12
Figure 2.	14
Figure 3.	15
DISCUSSION	19
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	20
REFERENCES	21
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	61
Analysis 1.1. Comparison 1 Laser versus no intervention, Outcome 1 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.	61
Analysis 1.2. Comparison 1 Laser versus no intervention, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 24 months.	62
Analysis 1.3. Comparison 1 Laser versus no intervention, Outcome 3 Worsening of best-corrected visual acuity (≥ 15 letters) at 36 months.	62
Analysis 1.4. Comparison 1 Laser versus no intervention, Outcome 4 Anatomic measures: partial to complete resolution of the macular oedema at 36 months.	62
Analysis 2.1. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months.	63
Analysis 2.2. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.	64
Analysis 2.3. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 3 Continuous best-corrected visual acuity (logMAR) at 12 months.	64
Analysis 2.4. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 4 Contrast sensitivity (log unit).	64
Analysis 2.5. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 5 Anatomic measures: partial to complete resolution of macular oedema at 12 months.	65
Analysis 2.6. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 6 Central macular thickness (μm) at 12 months.	65
Analysis 3.1. Comparison 3 Type of laser devices: argon versus others, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) within 12 months.	66
Analysis 3.2. Comparison 3 Type of laser devices: argon versus others, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) within 12 months.	67
Analysis 3.3. Comparison 3 Type of laser devices: argon versus others, Outcome 3 Anatomic measures: partial to complete resolution of macular oedema within 6 months.	68
Analysis 3.4. Comparison 3 Type of laser devices: argon versus others, Outcome 4 Anatomic measures: partial to complete resolution of macular oedema within 12 months.	68
Analysis 4.1. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months.	69
Analysis 4.2. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.	69
Analysis 4.3. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 3 Continuous best-corrected visual acuity (logMAR) at 12 months (change).	70
Analysis 4.4. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 4 Central macular thickness (μm) at 12 months.	70

Analysis 5.1. Comparison 5 Yellow versus infrared micropulse laser, Outcome 1 Continuous best-corrected visual acuity (logMAR) at 12 months.	70
Analysis 5.2. Comparison 5 Yellow versus infrared micropulse laser, Outcome 2 Contrast sensitivity (log unit).	70
Analysis 5.3. Comparison 5 Yellow versus infrared micropulse laser, Outcome 3 Central macular thickness (µm) at 12 months. .	71
APPENDICES	71
CONTRIBUTIONS OF AUTHORS	73
DECLARATIONS OF INTEREST	73
SOURCES OF SUPPORT	73
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	74
INDEX TERMS	74

[Intervention Review]

Monotherapy laser photocoagulation for diabetic macular oedema

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ABSTRACT

Background

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy and one of the most common causes of visual impairment in people with diabetes. Clinically significant macular oedema (CSMO) is the most severe form of DMO. Intravitreal antiangiogenic therapy is now the standard treatment for DMO involving the centre of the macula, but laser photocoagulation is still used in milder or non-central DMO.

Objectives

To access the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema.

Search methods

We searched CENTRAL, which contains the Cochrane Eyes and Vision Trials Register; MEDLINE; Embase; LILACS; the ISRCTN registry; ClinicalTrials.gov and the WHO ICTRP. The date of the search was 24 July 2018.

Selection criteria

We included randomised controlled trials (RCTs) comparing any type of focal/grid macular laser photocoagulation versus another type or technique of laser treatment and no intervention. We did not compare laser versus other interventions as these are covered by other Cochrane Reviews.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcomes were gain or loss of 3 lines (0.3 logMAR or 15 ETDRS letters) of best-corrected visual acuity (BCVA) at one year of follow-up (plus or minus six months) after treatment initiation. Secondary outcomes included final or mean change in BCVA, resolution of macular oedema, central retinal thickness, quality of life and adverse events, all at one year. We graded the certainty of the evidence for each outcome using the GRADE approach.

Main results

We identified 24 studies (4422 eyes). The trials were conducted in Europe (nine studies), USA (seven), Asia (four) and, Africa (one), Latin America (one), Europe-Asian (one) and Oceania (one). The methodological quality of the studies was difficult to assess as they were poorly reported, so the predominant classification of bias was unclear.

At one year, people with DMO receiving laser were less likely to lose BCVA compared with no intervention (risk ratio (RR) 0.42, 95% confidence interval (CI) 0.20 to 0.90; 3703 eyes; 4 studies; $I^2 = 71\%$; moderate-certainty evidence). There were also favourable effects observed at two and three years. One study (350 eyes) reported on partial or complete resolution of clinically significant DMO and found moderate-certainty evidence of a benefit at three years with photocoagulation (RR 1.55, 95% CI 1.30 to 1.86). Data on visual improvement, final BCVA, central macular thickness and quality of life were not available. One study related minor adverse effects on the central visual field and another reported one case of iatrogenic premacular fibrosis.

Nine studies compared subthreshold versus standard macular photocoagulation (517 eyes). Subthreshold treatment was achieved with different methods of photocoagulation: non-visible conventional (two studies), micropulse (four) or nanopulse (one).

Only one small study (29 eyes) reported on improvement or worsening of BCVA and estimates were very imprecise (improvement: RR 0.31, 95% CI 0.01 to 7.09; worsening: RR 0.93, 95% CI 0.15 to 5.76; very low-certainty evidence). All studies reported on continuous BCVA at one year; there was low-certainty evidence of no important difference between subthreshold and standard photocoagulation (mean difference (MD) in logMAR BCVA -0.02 , 95% CI -0.07 to 0.03 ; 385 eyes; 7 studies; $I^2 = 42\%$), and were possibly different for different techniques ($P = 0.07$ and $I^2 = 61.5\%$ for subgroup heterogeneity), with better results achieved with micropulse photocoagulation (MD -0.08 logMAR, 95% CI -0.16 to 0.0) as compared to the results achieved with nanopulse (MD 0.0 logMAR, 95% CI -0.06 to 0.06) and non-visible conventional (MD 0.04 logMAR, 95% CI -0.03 to 0.11), all of them compared to the standard lasers. One study reported partial to complete resolution of macular oedema at one year. There was low-certainty evidence of some benefit with standard photocoagulation, but estimates of effect were imprecise (RR 0.47, 95% CI 0.21 to 1.03; 29 eyes; 1 study). Studies also reported on the change in central macular thickness at one year and found moderate-certainty evidence of no important difference between subthreshold and standard photocoagulation (MD -9.1 μm , 95% CI -26.2 to 8.0 ; 385 eyes; 7 studies; $I^2 = 0\%$). There were no important adverse effects recorded in the studies.

Nine studies compared argon laser versus another type of laser (997 eyes). There was moderate-certainty evidence of a small reduction or no difference between the interventions, with respect to improvement (RR 0.87, 95% CI 0.62 to 1.22; 773 eyes; 6 studies) and worsening of BCVA (RR 0.83, 95% CI 0.57 to 1.21; 773 eyes; 6 studies). Three studies reported few cases of subretinal fibrosis and neovascularization with argon laser and one study found subretinal fibrosis in the krypton group.

One study (323 eyes) compared the modified ETDRS (mETDRS) grid technique with the mild macular grid (MMG), which uses mild, widely spaced burns throughout the macula. There was low-certainty evidence of an increased chance of visual improvement with MMG, but the estimate was imprecisely measured and the CIs include an increased risk or decreased risk of visual improvement at one year (RR 1.43, 95% CI 0.56 to 3.65; visual worsening: RR 1.40, 95% CI 0.64 to 3.05; change of logMAR visual acuity: MD -0.04 logMAR, 95% CI -0.01 to 0.09). There was a more significant reduction of central macular thickness with the mETDRS compared to the MMG technique (MD -34.0 μm , -59.8 to -8.3) in the MMG group. The study did not record important adverse effects.

Authors' conclusions

Laser photocoagulation reduces the chances of visual loss and increases those of partial to complete resolution of DMO compared to no intervention at one to three years. Subthreshold photocoagulation, particularly the micropulse technique, may be as effective as standard photocoagulation and RCTs are ongoing to assess whether this minimally invasive technique is preferable to treat milder or non-central cases of DMO.

PLAIN LANGUAGE SUMMARY

Single therapy laser photocoagulation for diabetic macular oedema

What is the aim of this review?

The aim of this Cochrane Review was to find out if laser photocoagulation is helpful for treatment of diabetic macular oedema. Cochrane researchers collected and analysed all relevant studies to answer this question and found 24 studies.

Key messages

The review showed that laser photocoagulation could reduce the chance of vision loss. Newer (lighter) types of laser photocoagulation may also work better than standard laser. Studies of these newer types of laser are ongoing.

What was studied in the review?

Diabetes is a condition where a person's blood sugar is too high. Some people with diabetes may develop problems with their eyes due to diabetic retinopathy. This is because diabetes affects the small blood vessels at the back of the eye (retina). People with diabetic retinopathy can develop swelling in the central part of the back of eye: this is known as diabetic macular oedema. It is important to treat diabetic macular oedema because it can lead to vision loss.

Eye doctors can treat the back of the eye with small laser burns with the aim of reducing the chance of vision loss from diabetic macular oedema. This is known as laser photocoagulation. In newer types of laser photocoagulation, known as subthreshold, the laser burns are applied using less energy and potentially cause less damage. Different types of laser can be used. The main types of laser are argon or diode laser.

What are the main results of the review?

Cochrane researchers found 24 relevant studies. Nine of these studies were from Europe, seven from the USA and four from Asia. The rest were from Africa, Australia, South America, and one study took place in Europe and Asia. Some of these studies compared laser photocoagulation with no photocoagulation for people with diabetic macular oedema. Other studies compared different intensity of laser, for example, comparing subthreshold laser with standard laser. Other studies compared different types of laser (mainly argon and diode).

Cochrane researchers assessed how certain the evidence was for each review finding. They looked for factors that could make the evidence less certain, such as problems with the way the studies were done, very small studies and inconsistent findings across studies. They also looked for factors that could make the evidence more certain, including very large effects. They graded each finding as very low-, low-, moderate- or high-certainty.

The review showed that:

- people with diabetic macular oedema who received laser were less likely to lose vision compared with no laser over one to three years (moderate-certainty evidence). They were also more likely to have improvements in signs of diabetic macular oedema at the back of the eye;
- low-certainty evidence suggested that subthreshold laser may be similar, or possibly better than standard laser. Studies of subthreshold laser are currently ongoing;
- there was no clear evidence of any difference between the different types of laser (in particular argon and diode);
- there were no important adverse effects after laser treatment.

How up-to-date is this review?

Cochrane researchers searched for studies that had been published up to 24 July 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Laser photocoagulation versus no intervention for diabetic macular oedema

Laser photocoagulation versus no intervention for diabetic macular oedema

Participant or population: diabetic macular oedema

Settings: hospitals

Intervention: laser

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Macular laser	No intervention				
Improvement of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR) Follow-up: 12 months	None of the included studies reported this outcome.					
Worsening of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR) Follow-up: 12 months	116 per 1000	67 fewer per 1000 (93 fewer to 12 fewer)	RR 0.42 (0.20 to 0.90)	3703 eyes (4 studies)	⊕⊕⊕⊖ Moderate	Assumed risk taken from ETDRS 1985 study. ^a Limitation due to incomplete outcome data (-1).
Continuous BCVA on the logMAR scale (lower logMAR scores represent better visual acuity)	None of the included studies reported this outcome.					
Anatomic measures: partial to complete resolution of the macular oedema with stereoscopic fundus photography or biomicroscopy; leakage on fluorescein angiography (IVFA); and, if available, retinal macular thickness with OCT Follow-up: 36 months	460 per 1000	253 more per 1000 (138 more to 396 more)	RR 1.55 (1.30 to 1.86)	350 (1 study)	⊕⊕⊕⊖ Moderate	Limitation due to incomplete outcome data (-1).

Clinically significant macular oedema	
Central retinal thickness (µm)	None of the included studies reported this outcome.
Quality of life measures	None of the included studies reported this outcome.
Adverse events	ETDRS 1985 observed very few adverse effects of focal photocoagulation (not statistically significant) on central visual fields and no adverse effects on colour vision. Olk 1986 reported 1 case of premacular fibrosis possibly due to "too heavy" laser burns in the macula.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** confidence interval; **ETDRS:** Early Treatment of Diabetic Retinopathy Study; **IVFA:** intravenous fluorescein angiography; **logMAR:** logarithm of the minimal angle of resolution; **OCT:** optical coherence tomography; **RR:** risk ratio.

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aThe assumed risk was taken from the study that provided the most evidence, i.e. had the largest weight in the meta-analysis.

Summary of findings 2. Subthreshold versus standard macular photocoagulation for diabetic macular oedema

Subthreshold versus standard macular photocoagulation for diabetic macular oedema

Participant or population: diabetic macular oedema

Settings: hospitals

Intervention: subthreshold

Comparison: standard macular photocoagulation

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
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	Assumed risk	Corresponding risk				
	Standard macular photocoagulation	Subthreshold photocoagulation				
Improvement of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR, recorded at 12 months (plus or minus 6 months)).	71 per 1000	49 fewer per 1000 (70 fewer to 432 more)	RR 0.31 (0.01 to 7.09)	29 (1)	⊕⊕⊕⊕ Very low	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study. ^a Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (-2).
Worsening of BCVA defined as ≥ 15 ETDRS letters (i.e. 3 ETDRS lines or 0.3 logMAR, recorded at 12 months (plus or minus 6 months)). Follow-up: 12 months	142 per 1000	10 fewer per 1000 (121 fewer to 676 more)	RR 0.93 (0.15 to 5.76)	29 (1)	⊕⊕⊕⊕ Very low	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study. ^a Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (-2).
Continuous BCVA: final (or change of) visual acuity Follow-up: 12 months Overall (lower logMAR scores represent better visual acuity)	The mean change in continuous BCVA was -0.03 logMAR (change 0.04 to -0.08 logMAR and final BCVA 0.3 to 0.55 logMAR)	The mean change in continuous BCVA in the intervention group was on mean -0.02 logMAR better (-0.07 better to 0.03 worse)	-	385 (7)	⊕⊕⊕⊕ Low	Standard, micropulse and nanopulse laser used for subthreshold photocoagulation. Limitation due to unclear risk of bias (-1). Limitation due to heterogeneity (-1). Micropulse laser was possibly better than standard laser: -0.08 logMAR (95% CI -0.16 to 0.0), and also better as compared to the subgroup analysis on nanopulse and non-visible conventional subthreshold lasers (change 0.0 and 0.04 logMAR respectively, P = 0.07 for subgroup differences).
Anatomic measures: partial to complete resolution of the macular oedema with stereoscopic fundus photography or biomicroscopy; retinal macular thickness with OCT and	714 per 1000	378 fewer per 1000 (564 fewer to 21 more)	RR 0.47 (0.21 to 1.03)	29 (1)	⊕⊕⊕⊕ Low	Conventional laser used for subthreshold photocoagulation. Assumed risk taken from Bandello 2005 study. ^a Limitation due to unclear risk of bias (-1) Serious limitation due to imprecision (-2).

leakage on fluorescein angiography (IVFA)						
Follow-up: 12 months						
Final (or change of) central retinal thickness (µm):	The mean change in central retinal thickness was -126 µm	The mean difference in central retinal thickness was on average -9.1 µm thinner (-26.2 thinner to 8.0 thicker)	-	385 (7)	⊕⊕⊕⊖ Moderate	Conventional, micropulse and nanopulse laser used for subthreshold photocoagulation.
Follow-up: 12 months						Assumed risk from Lavinsky 2011 .
Overall	(change -129 to 43 µm and final 289 to 310 µm)					Limitation related to unclear risk of bias (-1). A thickness change of more than 10% or 50 µm is considered clinically important.
Quality of life measures	None included studies reported this outcome.					
Adverse events	Bandello 2005 found no central 10° visual loss using perimetry for both subthreshold and standard macular photocoagulation. Vujosevic 2010 used microperimetry and found no decrease in central sensitivity with micropulse laser, but a significant decrease in the standard photocoagulation group.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** confidence interval; **IVFA:** intravenous fluorescein angiography; **logMAR:** logarithm of the minimal angle of resolution; **NA:** not available; **OCT:** optical coherence tomography; **RR:** risk ratio.

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aThe assumed risk was taken from the study that presented the bigger weight in the meta-analysis.

BACKGROUND

Description of the condition

Diabetes mellitus is a condition characterised by abnormal secretion of insulin, and high blood glucose levels in various organs causing damage mainly to the vessels of the kidney and retina as well as the loss of nerve fiber (DCCT Research Group 1995). Data from the International Diabetes Federation showed that more than 425 million people worldwide were living with diabetes in 2017 and this number is estimated to reach 629 million in 2045 (IDF Diabetes Atlas).

Diabetic retinopathy has become the leading cause of vision loss and blindness in working-age adults in both high- and low-income countries (Neubauer 2007). Vision loss results especially from the leaking of fluid from blood vessels within the macula (the central portion of the retina) (Neubauer 2007; Porta 2004).

Diabetic macular oedema (DMO) is an important complication of diabetic retinopathy and one of the most common causes of significant loss of visual function in people with diabetes (Ciulla 2003). DMO can be assessed by slit-lamp biomicroscopy or by stereoscopic macular photographs. Non-invasive imaging techniques such as optical coherence tomography (OCT) are also of value for the diagnosis of DMO and provide both qualitative and quantitative data (Reznicek 2013). Clinically significant macular oedema (CSMO) is the most severe form of DMO and is applied to eyes that have any one or a combination of the following:

- retinal thickening involving or within 500 µm of the centre of the macula;
- hard exudates at, or within, 500 µm of the centre of the macula, if associated with thickening of adjacent retina;
- a zone or zones of retinal thickening in one disc area, or larger in size, any part of which was within one disc diameter of the centre of the macula (ETDRS 1985; ETDRS 1987a).

Diffuse macular oedema is defined as a diffuse fluorescein leakage, by at least two regions, from the macular capillary bed and involving some portion of the foveal avascular zone (ETDRS 1985; ETDRS 1987a).

Description of the intervention

Therapeutic retinal photocoagulation has been practiced for more than 50 years. Since Meyer-Schwickerath's research, the thermal laser was initially directed at treatment of proliferative diabetic retinopathy and later adapted to treatment of DMO (Laursen 2004).

In 1985, the Early Treatment of Diabetic Retinopathy Study (ETDRS) established that focal and grid argon laser decreases the baseline risk of severe diminished vision in eyes with CSMO by 50% (ETDRS 1985). However, a small percentage of participants showed some positive change in visual acuity after photocoagulation and 15% of participants continued to have visual loss despite laser treatment (Aiello 2010; ETDRS 1985; ETDRS 1987a; ETDRS 1995).

Moreover, eyes with diffuse macular oedema have a poor prognosis and do not respond well to treatment (Bresnick 1986; Ladas 1993). The need for successive sessions of laser in refractory cases increases the risk of complications related to laser such as visual field reduction, growth of abnormal new blood vessels and

formation of fibrous tissue under the retina (Han 1992; Lewis 1990; Schatz 1991).

Thus, in the last few years, it has become essential to test new wavelengths and therapies that might improve the morphological and functional outcomes for people with DMO.

The way the laser is applied and the type of laser used can increase the effectiveness of treatment, reducing the damage caused by retinal photocoagulation, especially the peripheral visual field loss and changes in contrast sensitivity and vision of colours (ETDRS 1991). Diode laser has been used as an alternative approach as it might be more efficacious when the macular oedema is found in the foveal avascular zone because it does considerably less damage (Akduman 1997; McHugh 1990). It remains unclear which is the best form of laser application, the precise amount of energy that must be used and the effect of the combination of laser with other therapies.

The use of micropulse photocoagulation has been an alternative to the traditional form of laser application and is less destructive and has a more favourable risk-benefit ratio, justifying the earlier treatment and allowing for the improvement or stabilisation of visual function (Dare 2007); Grigorian 2004 and Laursen 2004 used the micropulse diode laser technique to show that its efficacy is similar to the argon laser for continuous wave for treatment of DMO in terms of visual acuity and reduced oedema.

In severe cases where macular oedema does not respond to laser, vitrectomy with removal of posterior hyaloid membrane can be beneficial. A vitrectomy is effective for releasing vitreous macular traction, increasing oxygenation and diluting vitreous factors that alter vascular permeability (Lewis 1992; Pendergast 2000). Despite advances, there are still doubts about the effectiveness of surgical intervention in cases of macular oedema.

The advent of intravitreal corticosteroids and antivascular endothelial growth factor (VEGF) drugs has opened up a new era in the management of DMO. The laser has been mostly replaced by these drugs, at least in high- and middle-income settings, though the economic burden and long-term need of injections makes combined therapies of interest (Virgili 2014).

Photocoagulation technique

The photocoagulation treatment is prescribed for all microaneurysms and other focal leakage sites in the macula area (i.e. between 500 µm and 3000 µm of the fovea) with a spot size of 50 µm to 100 µm and 0.1 seconds of duration (ETDRS 1985). Repeated burns are sometimes needed, mainly for microaneurysms greater than 40 µm (ETDRS 1987b). Lesions located between 300 µm and 500 µm of the fovea can be treated when visual acuity is less than or equal to 20/40 unless there is perifoveal capillary dropout. Groups of microaneurysms located within 750 µm of the fovea can be treated confluent, with spot size higher, between 200 µm and 500 µm (ETDRS 1985; ETDRS 1987a).

The diffuse oedema is treated in a grid pattern. The aim of the treatment is to produce a burn of light to moderate intensity, with sights of the 50 µm to 200 µm spot size, on areas of diffuse leakage or capillary non-perfusion. Space one burn wide is left between each lesion. The burns can be placed in the papillomacular bundle but no closer than 500 µm from the centre of the macula. Treatment

may be repeated again if there is no clinical improvement after three months (Blankenship 1979; Olk 1990).

The technique of modified grid photocoagulation was proposed by Olk in 1990 and consists of the application of laser in the areas of diffuse leakage followed by applications on focal microaneurysms within and outside the area of diffuse oedema (Olk 1990). Their results are as effective as the original technique proposed by the ETDRS (ETDRS 1985).

In the technique of micropulse laser, a train of repetitive short laser pulses delivers the laser energy within an 'envelope' whose width is typically 0.1 seconds to 0.5 seconds. The normal length of each pulse is 100 μ seconds to 300 μ seconds (Dorin 2003). The 'envelope' includes 'on' time, which is the duration of each micropulse, and 'off' time, which is the time between the micropulses. This treatment was named subthreshold because there is no visible scarring and the individual burns remain below the threshold of observability (Scholz 2017).

How the intervention might work

The exact mechanism of action of laser photocoagulation is still unknown. The improvement in visual acuity has been attributed to a reduction in oedema and ischaemic areas. The microaneurysms can be closed directly by focal photocoagulation. The obstruction of blood flow may be a result of intravascular coagulation and thrombosis induced by laser, or it might occur after necrosis, scarring and contraction of the vessel induced by heat (Weiter 1980). The mechanism of action of grid photocoagulation is even more controversial. It is believed that laser promotes anatomical and functional changes in the blood- retinal barrier internally and externally (Ingolf 1984).

Why it is important to do this review

Recently, photocoagulation has been mostly replaced by intravitreal antiangiogenic therapy, but there is still an interest in newer subthreshold techniques, specifically micropulse laser treatment, to achieve the same effect as standard photocoagulation with no or minimal retinal tissue destruction. Although, the laser has been mostly replaced by these drugs, at least in high- and middle-income settings, the economic burden and long-term need of injections makes need for an alternative therapy. This systematic review aimed to contribute to this field to identify the true effect of laser and its consequences in this new DMO therapeutic era.

OBJECTIVES

To access the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in this systematic review.

Types of participants

We included adults (aged 18 years or older) diagnosed with type I or II diabetes mellitus with macular oedema as defined by the ETDRS Research Group (ETDRS 1985), regardless of gender and ethnicity.

We excluded people previously treated with laser within six months.

Types of interventions

Intervention of interest: any type of focal/grid macular laser photocoagulation (i.e. argon, diode, micropulse) as monotherapy. We considered trials where comparisons had been made between laser treatment and no intervention or sham treatment.

We also compared the effects of different types of laser/ wavelengths (e.g. argon blue/green versus krypton red) and subthreshold (e.g. micropulse, non-visible conventional) versus standard macular photocoagulation.

We did not compare laser versus the following: anti-VEGF alone (Virgili 2014); vitrectomy (review underway) and steroids alone (Grover 2008), as these are covered by other Cochrane Reviews. We excluded studies focusing on the additive effect of drugs on top of laser (i.e. anti-VEGF plus laser, steroids plus laser or cyclo-oxygenase-2 inhibitor plus laser) versus laser alone. In addition, we did not access drugs plus laser versus drugs as this was not the scope of our review.

Types of outcome measures

Primary outcomes

- Improvement or worsening of best-corrected visual acuity (BCVA) defined as gain or loss of 3 lines (0.3 logMAR or 15 ETDRS letters) of BCVA, recorded at 12 months (plus or minus six months) and then yearly.

Secondary outcomes

- Continuous BCVA on the logMAR scale (more negative was better; ETDRS letter visual acuity was converted to logMAR).
- Anatomic measures: partial to complete resolution* of macular oedema with stereoscopic fundus photography or biomicroscopy; retinal macular thickness with OCT (thinner was better) and leakage on fluorescein angiography (intravenous fluorescein angiography - IVFA).
- Contrast sensitivity.
- Quality of life measures: any validated measurement scale which aimed to measure the impact of visual function loss on participants' quality of life.
- Local or systemic adverse events or both.
- Economic data: we performed comparative cost analyses when data were available.

Secondary outcomes were also extracted and analysed at 12 months (plus or minus six months) and then yearly.

*post-hoc (see [Differences between protocol and review](#)).

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 24 July 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 24 July 2018) ([Appendix 1](#)).
- MEDLINE Ovid (1946 to 24 July 2018) ([Appendix 2](#)).
- Embase Ovid (1980 to 24 July 2018) ([Appendix 3](#)).
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 24 July 2018) ([Appendix 4](#)).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 24 July 2018) ([Appendix 5](#)).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 24 July 2018) ([Appendix 6](#)).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip; searched 24 July 2018) ([Appendix 7](#)).

Searching other resources

We checked the reference lists of potentially relevant studies to identify further additional trials. We also contacted specialists in the field and the main authors of included trials for unpublished data; however, none of the authors replied to us by the date of this publication.

Data collection and analysis

Selection of studies

Two review authors (ELJ and RED) independently assessed the titles and abstracts of all reports. We obtained full-text hard copies for studies that appeared to meet the selection criteria and for studies where there was some doubt whether they fulfilled the selection criteria. We resolved any discrepancies by discussion. When consensus was not reached, we did not include data from the trial in question unless or until the authors of the trial resolved the contentious issues.

Data extraction and management

Two review authors (ELJ and RED) independently extracted data. We resolved any discrepancies by discussion. Review authors underwent calibration exercises and used standardised pilot tested screening forms. We then used a standard data extraction form to extract the following information: characteristics of the study (design, methods of randomisation); participants; interventions and outcomes (types of outcome measures, adverse events). Both review authors independently entered all data into Review Manager 5 ([Review Manager 2014](#)), and checked for errors before submission.

Assessment of risk of bias in included studies

For the assessment of study quality, we referred to Chapter 8 of the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2017](#)). We assessed the following criteria: random

sequence generation, allocation concealment, blinding (masking), incomplete outcome data and other bias (i.e. eyes, rather than participant, unit of analysis without adjustment for correlated data). We also assessed the study to see if it was free from any suggestion of selective outcome reporting. For performance bias, we only evaluated the participants, and for detection bias we evaluated the assessors.

In a first step, information relevant to making a judgment on a criterion were copied from the original publication into an assessment table. When additional information was available from the study authors, this was also entered into the table along with an indication that it was unpublished information. Two review authors independently made a judgment as to whether the risk of bias for each criterion was considered to be 'low', 'unclear' or 'high'. We resolved disagreements by discussion.

We considered trials that were classified as low risk of bias in sequence generation, allocation concealment, masking, incomplete data and selective outcome reporting as low risk of bias trials. We recorded this information for each included trial in 'Risk of bias' tables in Review Manager 5 ([Review Manager 2014](#)), and summarised the risk of bias for each study in a summary 'Risk of bias' figure and graph.

Measures of treatment effect

Dichotomous outcomes

For our primary outcome, the proportion of participants with at least 15 letters improvement and proportion of participants with at least 15 letters worsening in visual acuity, we used risk ratio (RR) as the effect measure with 95% confidence intervals (CI). When the included studies reported macular oedema as binary data, we defined it as present or absent on clinical examination, IVFA or OCT or both, and we also generated RRs and 95% CIs. Local and systemic adverse events were treated as dichotomous data.

Continuous outcomes

For continuous data such as BCVA and macular thickness, we presented the results as mean differences (MD) with 95% CIs. We considered visual acuity either on the logMAR or the ETDRS scales. There were no apparent skewness issues regarding continuous outcome measures (logMAR BCVA, contrast sensitivity, and retinal thickness), such as when standard deviations (SDs) were larger than the means and a natural ceiling or floor boundary exists.

Unit of analysis issues

Data were prioritised to be extracted with eyes as the unit of analysis. However, we planned that studies reporting data only for participants, not eyes, would be included as if data were for individual eyes. In this original review, all included studies reported both participants and eyes. [Figueira 2009](#) was a paired, within-person study randomising one eye to standard photocoagulation and the other to micropulse photocoagulation and we considered eyes as if they were independent, which underestimates the precision of this study.

Dealing with missing data

We contacted trial investigators to clarify any missing data. For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data.

Assessment of heterogeneity

We looked for clinical heterogeneity by examining study details, and then we tested for statistical heterogeneity between trial results using the χ^2 test and the I^2 value as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017). We classified heterogeneity using the following I^2 values:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We planned to assess publication bias through visual inspection of funnel plots for each outcome in which we identified 10 or more eligible studies; however, we found an insufficient number of studies to allow for this assessment.

Data synthesis

We used the random-effects model to analyse data from three or more studies. We used a fixed-effect model where there were two studies.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis comparing the effects according to different laser sources (e.g. argon versus other) and photocoagulation techniques (e.g. micropulse versus non-visible conventional).

'Summary of findings' tables

We prepared 'Summary of findings' tables for two key comparisons: laser photocoagulation versus no intervention and subthreshold versus standard macular photocoagulation. We used the principles of the GRADE system to assess the certainty of the body of evidence associated with specific outcomes (improvement or worsening of BCVA, continuous BCVA, anatomic measures, central retinal thickness, quality of life, adverse events) (GRADEpro GDT). The GRADE approach considers within-study risk of bias

(methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias. The certainty of the evidence for a specific outcome was downgraded by one level according to the level of concern with respect to these five factors.

- **High-certainty evidence:** no concerns for any of the GRADE parameters. Further research is unlikely to change the estimate or our confidence in the results.
- **Moderate-certainty evidence:** downgraded one level. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low-certainty evidence:** downgraded two levels. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low-certainty evidence:** downgraded three or more levels. We are very uncertain about the results.
- **No evidence:** no RCTs addressed this outcome.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#) tables.

Results of the search

The electronic searches yielded 3070 records ([Figure 1](#)). After 802 duplicates were removed, the Cochrane Information Specialist (CIS) screened the remaining 2268 records and removed 1360 records which were clearly not relevant to the scope of the review. We screened the remaining 908 records and obtained the full-text reports of 61 records for further assessment. We included 28 reports of 24 studies, see [Characteristics of included studies](#) table. We excluded 25 studies, see [Characteristics of excluded studies](#) table for further information. One study requires translation and is currently awaiting classification ([Ludwig 1991](#)). We identified seven ongoing studies, which are potentially relevant and we will assess these studies when data become available, see [Characteristics of ongoing studies](#) table for details.

Figure 1. Study flow diagram.

Included studies

The individual trials are described in the [Characteristics of included studies](#) table.

We included 24 studies (28 reports) with 2650 randomised participants (4416 eyes) in this review (Akduman 1997; Bandello 2005; Blankenship 1979; Casson 2012; Casswell 1990; DRCRNET 2007; ETDRS 1985; Figueira 2009; Freyler 1990; Karacorlu 1993; Khairallah 1996; Ladas 1993; Laursen 2004; Lavinsky 2011; Olk 1986; Olk 1990; Pei-Pei 2015; Rutllan Civit 1994; Striph 1988; Tewari 1998; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015; Xie 2013) (Figure 1).

Design

All included studies were parallel RCTs, except for Figueira 2009, which randomised one eye to standard macular photocoagulation and the fellow eye to subthreshold micropulse photocoagulation.

Sample size

Twenty of the included studies did not report any details relating to sample size calculation. Sample sizes ranged from 23 eyes (Laursen 2004) to 2244 eyes (ETDRS 1985).

Setting

The trials took place in a variety of settings:

- nine in Europe (Bandello 2005; Casswell 1990; Figueira 2009; Freyler 1990; Ladas 1993; Laursen 2004; Rutllan Civit 1994; Vujosevic 2010; Vujosevic 2015);
- seven trials took place in the USA (Akduman 1997; Blankenship 1979; DRCRNET 2007; ETDRS 1985; Olk 1986; Olk 1990; Striph 1988);
- four in Asia: two in China (Pei-Pei 2015; Xie 2013), and two in India (Tewari 1998; Venkatesh 2011);
- one in Europe-Asian (Turkey) (Karacorlu 1993);
- one in Latin America (Lavinsky 2011);
- one in Africa (Khairallah 1996);
- one in Oceania (Casson 2012).

Participants and duration of trials

Fifteen studies followed participants for 12 months or less (Akduman 1997; Bandello 2005; Casson 2012; DRCRNET 2007; Figueira 2009; Karacorlu 1993; Khairallah 1996; Laursen 2004; Lavinsky 2011; Pei-Pei 2015; Rutllan Civit 1994; Tewari 1998; Venkatesh 2011; Vujosevic 2010; Xie 2013). Six studies followed participants for more than 12 months (Blankenship 1979; Casswell 1990; ETDRS 1985; Ladas 1993; Olk 1986; Olk 1990). One study did not report the follow-up (Striph 1988), and one study presented a follow-up of six to 24 months (Freyler 1990).

Types of intervention

Four studies randomised participants to macular grid/focal argon laser or no intervention (Blankenship 1979; ETDRS 1985; Ladas 1993; Olk 1986).

Nine studies randomised participants to either argon or other types of laser (Akduman 1997; Casswell 1990; Freyler 1990; Karacorlu 1993; Khairallah 1996; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998). Two studies compared argon versus diode laser (Akduman 1997; Tewari 1998); four studies compared argon versus

krypton laser (Casswell 1990; Khairallah 1996; Olk 1990; Striph 1988); and three studies compared argon versus dye laser (Freyler 1990; Karacorlu 1993; Rutllan Civit 1994).

One study compared standard modified ETDRS grid technique with a mild macular grid (MMG) technique (DRCRNET 2007). The standard modified ETDRS grid technique consisted of treating leaking microaneurysms with mild-grey laser burns and a grid laser with barely visible spots applied to all areas with diffuse leakage or non-perfusion within the area considered for grid treatment. The MMG technique consisted of barely visible spots applied to the entire area considered for grid treatment (including unthickened retina). Because laser spots of similar intensity were applied in both treatment arms, and the difference was either in treating microaneurysms (standard) or in the area to be treated (larger in MMG), we did not include this study when different intensities of the visible versus invisible laser spots were compared.

Nine studies compared treatment strategies that adopted laser spots of different intensity to explore whether barely visible or invisible laser spots (subthreshold photocoagulation), obtained with either standard laser or with micropulse laser, were similarly effective to standard argon macular laser with visible, usually mild-grey, laser spot on the retina. Two studies used a standard macular, continuous-wave laser to achieve subthreshold photocoagulation (Bandello 2005; Pei-Pei 2015). Six studies obtained subthreshold macular laser treatment with a micropulse photocoagulator, in which a series of very short duration impulses are delivered consecutively (typically with 5% to 15% laser duty-cycle) and no visible spot can be seen on the retina, with the aim of causing minimal or no retinal tissue destruction (Figueira 2009; Laursen 2004; Lavinsky 2011; Venkatesh 2011; Vujosevic 2010; Xie 2013). Among studies using micropulse photocoagulation, Lavinsky 2011 evaluated three groups: both normal and high-density micropulse diode, and standard macular photocoagulation. Based on the reports, effects on the visual acuity and the interpretation of other studies as well as personal communication (Chen 2016a; ISRCTN17742985; Luttrull 2012), we decided to select the high-density group compared to standard macular photocoagulation. One study, Casson 2012 compared 3-ms nanopulse retina treatment (2RT) with standard photocoagulation, both delivered with an Integre 532 nm laser (Ellex Medical Lasers Ltd, Adelaide, Australia). 2RT applications were delivered with a spot size of 400 µm at an energy setting that produced nil reaction or a barely discernible retinal reaction (approximately 0.3 mJ), and slightly lower energy was then selected for treatment. The applications were advanced to thickened retinal regions, and applied in a grid pattern, one 'burn' width apart to thickened areas of retina at least 500 µm from the foveal centre.

One study compared subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser (Vujosevic 2015).

Conflict of interest

Conflict of interest was an issue in two studies (Akduman 1997; Casson 2012).

Types of outcome measures

Eleven studies measured improvement/remained the same on change in visual acuity (Akduman 1997; Bandello 2005; Blankenship 1979; Casswell 1990; DRCRNET 2007; Ladas 1993; Karacorlu 1993; Khairallah 1996; Olk 1986; Olk 1990; Tewari 1998).

Eight studies reported on mean BCVA (Casson 2012; DRCRNET 2007; Figueira 2009; Lavinsky 2011; Pei-Pei 2015; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015). The proportion of participants with improvement/remained the same on change in visual acuity was used as the primary outcome data were not available.

Twelve studies measured worse or change in visual acuity (Akduman 1997; Bandello 2005; Blankenship 1979; Casson 2012; Casswell 1990; ETDRS 1985; Karacorlu 1993; Khairallah 1996; Ladas 1993; Olk 1986; Olk 1990; Tewari 1998).

Nine studies reported continuous BCVA (Bandello 2005; Casson 2012; DRCRNET 2007; Figueira 2009; Lavinsky 2011; Pei-Pei 2015; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015).

Sixteen studies reported on anatomic measures (Akduman 1997; Bandello 2005; Casson 2012; Casswell 1990; DRCRNET 2007; ETDRS 1985; Figueira 2009; Karacorlu 1993; Khairallah 1996; Lavinsky 2011; Olk 1990; Pei-Pei 2015; Tewari 1998; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015).

Two studies assessed local complications (Casswell 1990; Khairallah 1996), and four studies measured sensitivity contrast (Bandello 2005; Figueira 2009; Venkatesh 2011; Vujosevic 2015).

Excluded studies

We excluded 25 studies mainly due to them being non-RCTs and case series (Akduman 1999; Arévalo 2013; Berger 2015; Chen 2016b; Dong 2001; Dosso 1994; Fang 2016; Fernandez-Vigo 1989; Gaudric 1984; Huang 2016; Inagaki 2015; Ishibashi 2015; Ivanisević 1992; Lacava 1995; Lai 1996; Lee 1981; Lee 2000; Lingyan 2001; Marcus 1977; Okuyama 1995; Reeser 1981; Sinclair 1999; Taylor 1977; Tomasetto 2007; Yan 2016).

Studies awaiting classification

One study requires translation and is currently awaiting classification (Ludwig 1991).

Ongoing studies

Eight studies are currently ongoing and will be added to the review when they are published (CTRI/2015/03/005628; ISRCTN17742985; ISRCTN66877546; NCT01045239; NCT01928654; NCT02309476; NCT03641144; NCT03519581). See Characteristics of ongoing studies table for further information.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other Bias
Akduman 1997	+	?	?	?	+	?	-
Bandello 2005	?	?	?	+	+	?	?
Blankenship 1979	?	+	?	+	-	?	?
Casson 2012	?	+	?	+	+	+	-
Casswell 1990	+	?	?	?	?	?	?
DRCRNET 2007	+	?	?	+	+	+	?
ETDRS 1985	?	?	?	+	-	+	?
Figueira 2009	+	?	?	+	+	+	+
Freyler 1990	?	?	?	?	?	?	?
Karacorlu 1993	?	?	?	?	+	?	?
Khairallah 1996	?	+	?	?	+	?	?
Ladas 1993	?	?	?	+	+	?	?
Laursen 2004	?	?	?	?	+	?	?
Lavinsky 2011	+	+	+	+	+	+	+
Olk 1986	+	?	?	+	-	?	?
Olk 1990	+	?	?	+	-	?	?
Pei-Pei 2015	?	?	?	?	+	+	+
Rutllan Civit 1994	?	?	?	?	-	?	?
Striph 1988	?	?	?	+	?	?	?
Tewari 1998	+	?	?	+	?	?	?

Figure 3. (Continued)

Tewari 1998	+	?	?	+	?	?	?
Venkatesh 2011	?	?	?	?	+	?	+
Vujosevic 2010	?	?	?	?	+	?	+
Vujosevic 2015	?	?	?	?	+	?	+
Xie 2013	?	?	?	?	+	?	?

Allocation

Sixteen studies did not report on how allocation was generated and therefore were at unclear risk of bias for this domain (Bandello 2005; Blankenship 1979; Casson 2012; ETDRS 1985; Freyler 1990; Karacorlu 1993; Khairallah 1996; Ladas 1993; Laursen 2004; Pei-Pei 2015; Rutllan Civit 1994; Striph 1988; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015; Xie 2013).

However, the generation of allocation was rated as low risk of bias as some of the studies used coin toss (Akduman 1997; Casswell 1990; Olk 1990; Tewari 1998); generation obtained from the DRCR.net website (DRCRNET 2007); randomisation table (Figueira 2009); computer-generated randomisation list (Lavinsky 2011); and cards drawn from an envelope (Olk 1986).

Twenty studies did not report the allocation concealment and were at unclear risk of bias (Akduman 1997; Bandello 2005; Casswell 1990; DRCRNET 2007; ETDRS 1985; Figueira 2009; Freyler 1990; Karacorlu 1993; Ladas 1993; Laursen 2004; Olk 1986; Olk 1990; Pei-Pei 2015; Rutllan Civit 1994; Striph 1988; Tewari 1998; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015; Xie 2013).

Four studies used sealed opaque cards, therefore, they were at low risk of bias (Blankenship 1979; Casson 2012; Khairallah 1996; Lavinsky 2011).

Blinding

Ten studies did not report whether there was masking of personnel, participants or outcome assessors, therefore they were at unclear risk of bias (Akduman 1997; Casswell 1990; Karacorlu 1993; Khairallah 1996; Laursen 2004; Pei-Pei 2015; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015; Xie 2013). The authors of 13 studies did not report whether there was masking of personnel or participants, and we ranked the studies at unclear risk of bias for these domains; however, the outcome assessment, a masked observer made the comparisons and so this domain was at low risk of bias (Bandello 2005; Blankenship 1979; Casson 2012; DRCRNET 2007; ETDRS 1985; Figueira 2009; Freyler 1990; Ladas 1993; Olk 1986; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998).

One study reported that the investigators, ophthalmic examinations and the participants were masked, therefore, it was at low risk of bias (Lavinsky 2011).

Incomplete outcome data

Fourteen studies reported withdrawals and they were all less than 20% of the total number of participants, therefore they were at low risk of bias for this domain (Akduman 1997; Bandello 2005; Casson

2012; DRCRNET 2007; Figueira 2009; Karacorlu 1993; Khairallah 1996; Ladas 1993; Laursen 2004; Lavinsky 2011; Pei-Pei 2015; Venkatesh 2011; Vujosevic 2010; Xie 2013). One study reported that all participants completed the study, therefore they were also ranked as at low risk of bias for this domain (Vujosevic 2015).

Five studies were at high risk of bias because they reported withdrawals higher than 20% of the number of participants (Blankenship 1979; ETDRS 1985; Olk 1986; Olk 1990; Rutllan Civit 1994).

Four studies did not report either the withdrawals or the dropouts, therefore they were ranked as at unclear risk of bias (Casswell 1990; Freyler 1990; Striph 1988; Tewari 1998).

Selective reporting

There was selective reporting in six included studies (Casson 2012; DRCRNET 2007; ETDRS 1985; Figueira 2009; Lavinsky 2011; Pei-Pei 2015), therefore they were ranked at low risk of bias for this domain. In other 18 studies (Akduman 1997; Bandello 2005; Blankenship 1979; Casswell 1990; Freyler 1990; Karacorlu 1993; Khairallah 1996; Ladas 1993; Laursen 2004; Olk 1986; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998; Venkatesh 2011; Vujosevic 2010;

Vujosevic 2015; Xie 2013) there was no evidence of selective reporting, however they were ranked at unclear risk of bias because there was no protocol available.

Other potential sources of bias

The authors of six studies had disclosed no relevant financial relationships and there was no evidence of other biases in any of these studies, therefore, they were at low risk of other bias (Figueira 2009; Lavinsky 2011; Pei-Pei 2015; Venkatesh 2011; Vujosevic 2010; Vujosevic 2015).

Sixteen studies did not report conflict of interest and were ranked as unclear risk of bias (Bandello 2005; Blankenship 1979; Casswell 1990; DRCRNET 2007; ETDRS 1985; Freyler 1990; Karacorlu 1993; Khairallah 1996; Ladas 1993; Laursen 2004; Olk 1986; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998; Xie 2013).

In two studies, an author was a consultant of medical instruments and had also been reimbursed for travel expenses, due to this we classified the study as high risk of other bias (Akduman 1997; Casson 2012).

Effects of interventions

See: **Summary of findings for the main comparison** Laser photocoagulation versus no intervention for diabetic macular

oedema; **Summary of findings 2** Subthreshold versus standard macular photocoagulation for diabetic macular oedema

We sent an email to the trial investigators for [Laursen 2004](#) to clarify whether they evaluated only argon versus diode or treatment combination of argon with or without diode laser; however, the authors have not replied. Therefore it was not possible to use their data.

1. Laser versus no intervention

Four studies (1295 participants, 3703 eyes) compared laser versus no intervention ([Blankenship 1979](#); [ETDRS 1985](#); [Ladas 1993](#); [Olk 1986](#)). See [Summary of findings for the main comparison](#).

Outcome: functional outcomes - improvement or worsening of best-corrected visual acuity (BCVA)

There were no data regarding visual improvement. Macular photocoagulation with argon laser prevented the worsening of BCVA at 12 months' follow-up compared to no intervention (RR 0.42, 95% CI 0.20 to 0.90; 3703 eyes; 4 studies; $I^2 = 71\%$; [Analysis 1.1](#); moderate-certainty evidence). Although the studies were heterogeneous, all were in the direction of benefit with laser and were pooled.

Compared to no intervention, macular argon laser prevented visual impairment at 24 months' follow-up (RR 0.63, 95% CI 0.53 to 0.74; 3421 eyes; 3 studies; $I^2 = 60\%$; [Analysis 1.2](#)) and at 36 months' follow-up (RR 0.68, 95% CI 0.58 to 0.79; 3194 eyes; 2 studies; $I^2 = 0\%$; [Analysis 1.3](#)).

Outcome: functional outcomes - continuous BCVA on the logMAR scale

None of the included studies reported on this outcome.

Outcome: anatomic measures

Macular laser improved the chances of partial or complete resolution of macular thickening at 36 months' follow-up compared to no intervention in eyes with CSMO (RR 1.55, 95% CI 1.30 to 1.86; 350 eyes; 1 study; [Analysis 1.4](#); moderate-certainty of evidence). However, we were uncertain on whether laser reduced the occurrence of retinal thickening with the centre of the macula in eyes without CSMO, in which thickening did not affect the central retina (RR 1.12, 95% CI 0.98 to 1.27; 254 eyes; 1 study; [Analysis 1.4](#); low-certainty evidence due to imprecision and high risk of bias related to incomplete outcome data).

Outcome: contrast sensitivity

None of the included studies reported on this outcome.

Outcome: quality of life

None of the included studies reported on this outcome.

Outcome: local or systemic adverse effects or both

[ETDRS 1985](#) wrote that "very few adverse effects of focal photocoagulation have been observed to date" with "only minor adverse effects (not statistically significant) on central visual fields and no adverse effects on colour vision." [Olk 1986](#) reported one case or premacular fibrosis possibly due to "too heavy" laser burns in the macula.

None of the included studies reported on systemic adverse effects.

Outcome: economic data

None of the included studies reported on this outcome.

2. Subthreshold versus standard laser photocoagulation

Nine studies investigated the effect of subthreshold photocoagulation versus standard macular photocoagulation (444 participants, 517 eyes). Seven studies (337 participants, 385 eyes) evaluated three categories of subthreshold photocoagulation: non-visible conventional ([Bandello 2005](#); [Pei-Pei 2015](#): 71 eyes), micropulse laser ([Figueira 2009](#); [Lavinsky 2011](#); [Venkatesh 2011](#); [Vujosevic 2010](#): 276 eyes) and nanopulse laser ([Casson 2012](#): 38 eyes). See [Summary of findings 2](#).

Studies variably used and reported methods to document a difference in retinal function in the treated area surrounding the fovea that could prove additional benefit, or less damage, with subthreshold versus standard macular laser.

Outcome: functional measures - improvement or worsening of best-corrected visual acuity (BCVA)

Only [Bandello 2005](#), a small study on 29 eyes, reported our dichotomous functional primary outcomes comparing standard macular photocoagulation with subthreshold photocoagulation obtained by halving the laser power with a standard macular photocoagulation. Estimates of effects were very imprecise, which made it difficult to assess any benefit regarding both BCVA improvement and BCVA worsening (improvement: RR 0.31, 95% CI 0.01 to 7.09; worsening: RR 0.93, 95% CI 0.15 to 5.76; very low-certainty evidence; [Analysis 2.1](#); [Analysis 2.2](#)).

Outcome: functional outcomes - continuous BCVA on the logMAR scale

Seven studies (385 eyes) reported on final (or change of) logMAR BCVA. There was low-certainty evidence of no important difference between subthreshold photocoagulation and standard photocoagulation (MD -0.02, 95% CI -0.07 to 0.03; 385 eyes; 7 studies; $I^2 = 42\%$; [Analysis 2.3](#)). There was subgroup heterogeneity among standard, micropulse and nanopulse subthreshold lasers ($P = 0.07$ and $I^2 = 61.5\%$ for subgroup heterogeneity). Four studies using micropulse laser found a benefit compared to standard photocoagulation, but estimates were very imprecise (MD -0.08, 95% CI -0.16 to 0.00; 276 eyes; 4 studies; $I^2 = 22\%$). This evidence was of low-certainty because of unclear risk of bias in most studies and subgroup heterogeneity.

Two studies (130 eyes) comparing micropulse with standard photocoagulation reported contrast sensitivity at 12 months, but yielded inconsistent results, with [Figueira 2009](#) showing no difference and [Venkatesh 2011](#) favouring micropulse laser, but not to a statistically significant extent ([Analysis 2.4](#)).

Outcome: anatomic measures

Seven studies reported central macular thickness at 12 months. Pooled estimates suggested moderate-certainty evidence of no large difference between subthreshold and standard macular photocoagulation (MD -9.1 μm , 95% CI -26.2 to 8.0; 385 eyes; 7 studies; $I^2 = 0\%$; [Analysis 2.6](#)). In this analysis, there was no subgroup inconsistency between micropulse, nanopulse and non-

visible conventional photocoagulation ($P = 0.81$; $I^2 = 0\%$). One study reported a partial or complete regression of CSMO (Bandello 2005). There was low-certainty evidence of some benefit with standard photocoagulation but estimates of effect were imprecise (RR 0.47, 95% CI 0.21 to 1.03; 29 eyes; 1 study) (Analysis 2.5).

Outcome: contrast sensitivity

Macular photocoagulation can cause focal scotoma and the aim of subthreshold laser is to avoid this potential complication, especially using micropulse laser.

Bandello 2005 found little change in central retinal sensitivity, as Humphrey perimeter Mean Deviation, from baseline to 12 months for standard and conventional subthreshold ("light") macular laser photocoagulation (-0.04 dB (SD 1.39) with standard versus 0.03 dB (SD 1.84) with conventional subthreshold; $P = 0.99$).

Regarding micropulse versus standard macular laser, Figueira 2009 found the masked grader detected laser scars in 6/43 (13.9%) eyes from the micropulse group compared with 23/39 (59.0%) eyes from standard laser group ($P = 0.001$) in participants with good-quality colour photographs at 12 months. Lavinsky 2011 reported similar favourable outcomes with micropulse laser anecdotally. Venkatesh 2011 used multifocal electroretinography and reported a surrogate measure such as implicit time, which slightly improved for both micropulse and standard laser. Vujosevic 2010 used microperimetry and found mean central retinal sensitivity significantly increased at 12-month follow-up in the micropulse group (mean increase 0.87 dB (SD 1.89); Student's t -test; $P = 0.0075$), whereas it significantly decreased in the standard macular photocoagulation group (mean decrease 21.69 dB (SD 2.45); Student's t -test; $P = 0.0026$).

Outcome: quality of life

None of the included studies reported on this outcome.

Outcome: local or systemic adverse effects or both

None of the included studies reported on this outcome.

Outcome: economic data

None of the included studies reported on this outcome.

3. Types of laser devices

Nine studies compared argon laser versus another type of lasers (diode, dye, krypton) (595 participants, 997 eyes) (Akduman 1997; Casswell 1990; Freyler 1990; Karacorlu 1993; Khairallah 1996; Olk 1990; Rutllan Civit 1994; Striph 1988; Tewari 1998).

Outcome: functional outcomes - improvement or worsening of best-corrected visual acuity (BCVA)

Six studies (490 participants, 773 eyes) reported data for this comparison. We found no difference in the effect of macular argon laser as compared to other types of lasers both regarding improvement (RR 0.87, 95% CI 0.62 to 1.22; 773 eyes; 6 studies; $I^2 = 0\%$; Analysis 3.1) and worsening (RR 0.83, 95% CI 0.57 to 1.21; 773 eyes; 6 studies; $I^2 = 0\%$; Analysis 3.2). This evidence was of moderate-certainty since most studies were at unclear risk of bias. There was no suggestion of subgroup differences for subgroups of argon versus diode, dye or krypton laser both for improvement and

worsening of BCVA (test for subgroup differences: improvement: $P = 0.85$, $I^2 = 0\%$; worsening: $P = 0.39$, $I^2 = 0\%$).

Outcome: functional outcomes - continuous BCVA on the logMAR scale

None of the included studies reported on this outcome.

Outcome: anatomic measures

Data on partial or complete resolution of DMO were consistent with the primary outcomes at six and 12 months (6 months: RR 1.36, 95% CI 0.98 to 1.90; 80 eyes; 1 study; Analysis 3.3; 12 months: RR 1.01, 95% CI 0.98 to 1.05; 773 eyes; 6 studies; $I^2 = 0\%$; Analysis 3.4).

Outcome: contrast sensitivity

None of the included studies reported on this outcome.

Outcome: quality of life

None of the included studies reported on this outcome.

Outcome: local or systemic adverse effects or both

Regarding adverse events of grid laser that caused visual loss, Casswell 1990 reported that two participants developed subretinal neovascularisation at a laser burn in the argon group and Khairallah 1996 found a similar complication, subretinal fibrosis, in the argon group, with both studies finding no such cases in the krypton group. Olk 1990 reported one case of subretinal fibrosis in the krypton groups and one of subretinal neovascularization in the argon group.

Outcome: economic data

None of the included studies reported on this outcome.

4. Types of laser technique

One study compared standard modified ETDRS grid technique with a mild macular grid (MMG) technique (DRCRNET 2007).

Outcome: functional outcomes - improvement or worsening of best-corrected visual acuity (BCVA)

One study (263 participants, 323 eyes) compared the MMG with the modified ETDRS (mETDRS) grid technique (see Types of interventions section) (DRCRNET 2007). The MMG was no better than the mETDRS technique for visual outcomes at one year: visual improvement: RR 1.43 (95% CI 0.56 to 3.65, Analysis 4.1); and visual worsening RR 1.40 (95% CI 0.64 to 3.05, Analysis 4.2). The evidence for the primary outcomes was of low-certainty since the study was at unclear risk of bias and effect estimates were imprecise.

Outcome: functional outcomes - continuous BCVA on the logMAR scale

The MMG was no better than the mETDRS technique for visual outcomes at one year: visual improvement: change of logMAR visual acuity: -0.04 logMAR in the mETDRS group and MD worse by 0.04 logMAR (95% CI -0.01 to 0.09 , Analysis 4.3) in the MMG group, which are both consistent with little change of vision from baseline at one year.

Outcome: anatomic measures

There was a greater reduction of central macular thickness with the mETDRS compared to the MMG technique, since final retinal

thickness in the mETDRS group was 290 μ m and it was 34.0 μ m worse (95% CI 8.3 to 59.8; [Analysis 4.4](#)) in the MMG group. This evidence was of low quality due to unclear risk of bias and imprecision.

Outcome: contrast sensitivity

The included study do not reported on this outcome.

Outcome: quality of life

The included study do not reported on this outcome.

Outcome: local or systemic adverse effects or both

The authors of [DRCRNET 2007](#) did not report significant adverse effects and found no difference between treatments, in relation to the damage caused by retinal photocoagulation.

Outcome: economic data

The included study do not reported on this outcome.

The study authors recommended no further research on MMG as an alternative technique.

5. Yellow versus diode subthreshold micropulse photocoagulation

One study compared subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser ([Vujosevic 2015](#)).

Outcome: functional outcomes - improvement or worsening of best-corrected visual acuity (BCVA)

The included study do not reported on this outcome.

Outcome: functional outcomes - continuous BCVA on the logMAR scale

[Vujosevic 2015](#) (53 participants, 53 eyes) compared yellow (26 eyes) and diode (27 eyes) micropulse laser to treat DMO. At 12 months, they found no statistically significant difference regarding continuous final BCVA ([Analysis 5.1](#)).

Outcome: anatomic measures

At 12 months, they found no statistically significant difference regarding central macular thickness ([Analysis 5.3](#)), but estimates were too imprecise to draw any conclusion and the evidence was of very low-certainty.

Outcome: contrast sensitivity

At 12 months, they found no statistically significant difference regarding contrast sensitivity ([Analysis 5.2](#)), but estimates were too imprecise to draw any conclusion and the evidence was of very low-certainty.

Outcome: quality of life

The included study do not reported on this outcome.

Outcome: economic data

The included study do not reported on this outcome.

DISCUSSION

Summary of main results

Macular grid laser treatment has been used for decades as the only treatment for DMO until antiangiogenic therapy became available ([Virgili 2014](#)). Laser photocoagulation is effective in reducing the risk of visual loss and increasing the resolution of retinal thickening at one year, compared to no intervention, when used as monotherapy for people with DMO, particularly for CSMO. The evidence was of very low to moderate quality due to unclear risk of bias in studies conducted many years ago, some which were regarded as landmark trials in ophthalmology ([ETDRS 1985](#)).

Direct comparisons between different types of laser (argon versus others) showed that there was not change of the beneficial effect of photocoagulation on visual acuity and macular oedema.

We found low-certainty evidence that non-visible, subthreshold photocoagulation, obtained using different lasers techniques, achieves similar visual and anatomic effects compared to visible, standard photocoagulation. There was a suggestion of subgroup differences in relation to the type of laser used, and effects may possibly be better for subthreshold micropulse diode laser (a new novel laser modality using very short duration impulses) that was developed to minimise scar formation and prevent tissue damage and early visual loss.

None of the studies reported major adverse effect, and only five included studies reported local complications ([Casswell 1990](#); [ETDRS 1985](#); [Khairallah 1996](#); [Olk 1986](#); [Olk 1990](#)).

Overall completeness and applicability of evidence

Because of our comprehensive search strategy and contact with experts in the field, we are confident that we have mapped most clinical trials comparing laser versus no treatment as monotherapy for DMO as well as the comparison of different types of laser.

With regards the effectiveness of antiangiogenic drugs, one Cochrane Review concluded that there is also high-quality evidence with the use of anti-VEGF compared to laser ([Virgili 2014](#)). However, the high cost of these drugs limits their use in developing countries. Therefore, macular laser can still be used in selected cases of DMO. There are several ongoing trials ([Characteristics of ongoing studies](#) table) and the results of these studies will clearly be important in informing this review, especially regarding the efficacy of new retinal phototherapeutic techniques.

Quality of the evidence

Methodological rigour of included studies was hard to judge because of poor reporting so that the predominant classification of risk of bias was unclear. Methodological aspects of seven studies had a high risk of introducing bias: incomplete outcome data ([Blankenship 1979](#); [ETDRS 1985](#); [Olk 1986](#); [Olk 1990](#); [Rutllan Civit 1994](#)); and other bias (conflict of interest; [Akduman 1997](#); [Casson 2012](#)). These limitations may be due to some included studies being published in the 1980s and 1990s, and this may also explain the fact that patient-relevant outcomes were missing, such as quality of life and economic data.

Potential biases in the review process

We followed standard methods expected by Cochrane. All changes from protocol are documented in the [Differences between protocol and review](#) section.

We applied a comprehensive search strategy to identify all potential studies and their reports. However, although we emailed the first author of two included studies to ask for clarification about methodological issues and to provide us with further information, neither of these authors responded ([DRCRNET 2007](#); [Laursen 2004](#)).

Agreements and disagreements with other studies or reviews

No systematic review has compared the results of retinal laser photocoagulation versus no intervention or sham, and between different techniques and types of lasers. However, there is one narrative review highlighting that subthreshold diode laser micropulse photocoagulation can be an effective and harmless phototherapy for DMO ([Luttrull 2012](#)). Another review on laser photocoagulation for DMO described qualitatively the developments in laser systems ([Park 2014](#)).

One more recent narrative review discussed the published literature of subthreshold micropulse laser treatment and concluded that it is an effective and safe option in terms of affordability compared to the cost-intensive anti-VEGF therapy ([Scholz 2017](#)).

One systematic review concluded that laser is a potentially destructive form of treatment which may be of greater benefit in combination with newer forms of treatment such as intravitreal steroid or intravitreal antiangiogenic agents ([O'Doherty 2008](#)).

One more recent systematic review also assessed the efficacy of subthreshold micropulse diode laser compared to standard macular photocoagulation finding a benefit in relation to visual acuity and a similar anatomical outcome ([Chen 2016a](#)). Furthermore, another systematic review concluded that subthreshold micropulse diode laser presented equally good effects on visual acuity, contrast sensitivity and reduction of DMO as compared with standard macular photocoagulation with less retinal damage ([Qiao 2016](#)). Finally, one Bayesian network meta-analysis found that "the efficacy of subthreshold diode micropulse photocoagulation is numerically, but non-significantly, superior to standard laser photocoagulation monotherapy (MD, -0.225; 95% credible interval, -0.501 to 0.058)" ([Wu 2018](#)). [Wu 2018](#) pooled nanopulse photocoagulation ([Casson 2012](#), included in this review) with the micropulse group. However, we believe that nanopulse

laser is similar in principle, but this laser technique is not yet sufficiently standardised; moreover, [Casson 2012](#) did not adopt a confluent, or high-density, spot pattern but left one spot between each 400 µm spot, as opposed to current recommendations on micropulse laser treatment of DMO ([Chen 2016a](#); [ISRCTN17742985](#); [Luttrull 2012](#)). Thus, our results overlap with those of [Chen 2016a](#) regarding the fact that micropulse laser may be similar or better than standard laser for treating DMO.

There are eight ongoing studies ([CTRI/2015/03/005628](#); [ISRCTN17742985](#); [ISRCTN66877546](#) [NCT01045239](#); [NCT01928654](#); [NCT02309476](#); [NCT03641144](#)) and the DIAMONDS study ([ISRCTN17742985](#)), a multicentre RCT evaluating the clinical and cost-effectiveness of diode subthreshold micropulse laser (DSML), when compared with standard threshold laser for the treatment of people with DMO with a follow-up of 24 months.

AUTHORS' CONCLUSIONS

Implications for practice

Macular grid or focal laser has been used for decades to prevent visual loss in people with diabetic macular oedema (DMO), and has been replaced by intravitreal injection of antiangiogenic drugs. The benefit achieved with macular laser is of moderate-certainty evidence mostly due to inadequate reporting in trials conducted many years ago.

There is moderate-certainty evidence that subthreshold photocoagulation is probably similar to standard photocoagulation, but any benefit is very imprecisely estimated. Moreover, a post-hoc subgroup analysis suggested that subthreshold photocoagulation is more effective when delivered using a micropulse laser.

Implications for research

Further research is ongoing to investigate whether subthreshold photocoagulation performed with a micropulse laser is more effective than standard laser treatment and can be used in addition, combination or as replacement of antiangiogenic therapy for specific people with DMO.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akduman 1997

Methods	<p>Study design: parallel RCT. If a participant had 1 eye eligible for randomisation, that eye was randomised to treatment either with argon green or diode laser. If a participant had both eyes eligible for randomisation, 1 eye was randomised to treatment with argon green and 1 with diode laser.</p> <p>Number of centres: not reported</p> <p>Setting: USA</p> <p>Period: April 1993 to October 1996</p> <p>Sample size calculation: not reported</p> <p>Follow-up: minimum of 12 months (median 15)</p>
Participants	<p>91 participants (171 eyes).</p> <p>Mean age: 64 (range 36–85) years</p> <p>Sex (M:F): 50:41</p> <p>Inclusion criteria: diagnosis of either type I or type II diabetes mellitus and DMO with or without CSMO documented by slit-lamp and contact lens examination and confirmed with intravenous FA.</p> <p>Exclusion criteria: renal failure requiring any type of dialysis, diastolic blood pressure > 100 mmHg or HbA1c > 10 mg/dL (referred for further medical treatment and asked to return in 4–6 months for re-evaluation), ≥ 2 DRS risk factors, previous laser photocoagulation for DMO, preretinal or vitreous haemorrhage, retinal detachment, significant media opacities, iris neovascularisation, previous retinal or intraocular surgery that was thought to possibly interfere with assessment of treatment results, cataract extraction or lens implantation within the past 12 months, history of glaucoma or any other ocular disease that was thought to interfere with assessment of the treatment results.</p> <p>Type of DMO: CSMO</p>
Interventions	Argon green (514 nm) 86 eyes versus diode laser (810 nm) 85 eyes. 80 participants were treated bilaterally and 11 participants were treated unilaterally.
Outcomes	Visual improvement, visual loss, reduction/elimination of macular oedema and number of supplemental treatments
Notes	<p>Funding: not reported</p> <p>Conflict of interest: reimbursement for travel expenses to Dr Olk (consultant to Iris Medical Instruments, Inc.) from Coherent Radiation, Inc.</p> <p>Trial registration: none reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	Unclear risk	Not reported

Akduman 1997 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the 12 months' follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	High risk	An author was a consultant of medical instruments and had also been reimbursed for travel expenses

Bandello 2005

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: not reported</p> <p>Setting: Europe</p> <p>Period: September 2001 to November 2002</p> <p>Sample size: not reported</p> <p>Follow-up: 12 months</p>
Participants	<p>24 participants (29 eyes)</p> <p>Mean age: 64 years in "classic" group and 63 years in "light" group</p> <p>Sex (M:F): 9:5 in "classic" group; 10:5 in "light" group</p> <p>Inclusion criteria: diagnosis of either type I or type II diabetes mellitus and NPDR with CSMO documented by slit lamp contact lens biomicroscopy, as defined by the ETDRS, and confirmed by OCT; if the FTH exceeded 2 SD the mean normal value (i.e. > 210 µm); HbA1c ≤ 10%; diastolic blood pressure < 90 mm Hg and VA ≥ 20/200 on ETDRS chart</p> <p>Exclusion criteria: previous laser treatment, PDR, history of retinal detachment, glaucoma or any other clinically relevant ocular disease, cataract extraction or lens implantation within the past 12 months or significant media opacities</p> <p>Type of DMO: CSMO</p>
Interventions	"Classic" Nd:Yag 532 nm laser treatment (14 eyes) versus "light" Nd:Yag 532 nm laser treatment (15 eyes)
Outcomes	Primary outcome: proportion of participants with significant decrease in FTH on OCT retina thickness maps. Secondary outcomes included: proportion of participants with reduction elimination of CSMO on biomicroscopy and fluorescein leakage on FA compared with baseline examination at 3, 6 and 12 months after study entry; proportion of eyes that experienced a visual gain or loss of ≥ 5 letters (approximately 1 line) on the ETDRS chart; mean changes in VA; contrast threshold; MD of the central 10°

Bandello 2005 (Continued)

sensitivity; and number of local losses > 5 dB at each test point of the central 10°, suggestive of post-treatment scotomata

Notes

Funding: not reported

Conflict of interest: not reported

Trial registration: not reported

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All visits and tests performed by the same masked examiners
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Blankenship 1979

Methods

Study design: within-person RCT. 1 eye randomly assigned to argon laser treatment, the other remained untreated

Number of centres: not reported

Setting: USA

Period: June 1973 to 1975

Sample size: not reported

Follow-up: 2 years

Participants

39 participants (78 eyes). 1 year after: 35 participants (70 eyes)

Mean age: 59.7 years

Sex (M:F): 23:16

Blankenship 1979 (Continued)

Inclusion criteria: aged ≤ 75 years, documentation of diabetes mellitus. Eyes had to have BCVAs of $\geq 20/100$, no more than 3 lines of difference between the 2 eyes, both eyes had to have clear enough means for fundus photography and laser photocoagulation, be phakic, and have macular oedema.

Exclusion criteria: neither eye could have previous photocoagulation or PDR.

Type of DMO: diffuse and cystoid

Interventions	Argon laser photocoagulation (39 eyes) versus no treatment (39 eyes)
Outcomes	Changes of VA
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed cards
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Optometrist unaware of the eye assignments
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss > 20%
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Casson 2012

Methods	Study design: parallel RCT Number of centres: 2 retinal clinics Setting: Australia Period: not reported Sample size: a sample size of 37 eyes was required. An increase in sample size of 15% in each group was added to allow for loss of follow-up or incomplete data.
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Casson 2012 (Continued)

Follow-up: 6 months

Participants	<p>38 participants (44 eyes)</p> <p>Mean age: laser: 63.8 years; control: 56.3 years</p> <p>Sex (M:F): 28:10</p> <p>Inclusion criteria: aged ≥ 18 years; types I or II diabetes mellitus, with 1 or both of their eyes meeting the following criteria: a best-corrected ETDRS VA score ≥ 19 letters; retinal thickness measured on Stratus 3.0 OCT (Carl Zeiss Meditec, Dublin, CA, USA) of ≥ 250 μm in central subfield, or ≥ 300 μm in ≥ 1 of the 4 inner subfields; and no prior laser treatment or other treatment for DMO.</p> <p>Exclusion criteria: retinal thickening from any other cause or had undergone any ocular surgery within the prior 6 months.</p> <p>Type of DMO: focal or diffuse macular oedema</p>
Interventions	<p>Nanopulse (2RT) laser treatment (24 eye) versus standard photocoagulation (20 eyes). 2RT treatment was performed using a Integre (Ellex Medical Lasers Ltd, Adelaide, Australia) providing variable length pulses at a wavelength of 532 nm. After the initial laser treatment, the participant was seen at a 3-month follow-up visit, and a further laser treatment was applied at the clinicians' discretion.</p>
Outcomes	<p>Changes of VA, CRT</p>
Notes	<p>Funding: RJ Casson received travel expenses from Ellex Medical Lasers (Ellex R&D Pty Ltd, 82 Gilbert Street, Adelaide, South Australia, 5000).</p> <p>Conflict of interest: none</p> <p>Trial registration ID: ACTRN12608000369325</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Trial co-ordinator performed the randomisation procedure and retained sequentially numbered opaque containers that were opened by the treating clinicians just prior to laser.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VA testing and OCT measurements were performed by masked observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Laser group: 1 person died (1 eye), 1 person withdrew (2 eyes); control: 1 person died (1 eye), 1 person withdrew (2 eyes)
Selective reporting (reporting bias)	Low risk	Protocol available and registered at the Australian New Zealand Clinical Trials Registry (ACTRN12608000369325): accessed 27 January 2018. Outcomes match those reported.

Casson 2012 (Continued)

Other Bias	High risk	An author received travel expenses from laser industry
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Casswell 1990

Methods	<p>Study design: parallel RCT. Participants eligible for treatment to both eyes received argon to 1 eye and krypton to the other. 27 participants had both eyes treated and 37 had 1 eye treated.</p> <p>Number of centres: 1</p> <p>Setting: Europe</p> <p>Period: not reported</p> <p>Sample size: not reported</p> <p>Follow-up: 2 years</p>
Participants	<p>64 participants (91 eyes)</p> <p>Mean age: 62 years overall; 63 in argon group; 61 years in krypton red group</p> <p>Sex (M:F): 22:26 in argon group; 20:23 in krypton red group</p> <p>Inclusion criteria: CSMO, presence of ≥ 1 areas of retinal thickening, ≥ 1 disc diameters across, any part of which encroached within 1 disc diameter of the centre of the macula. Participants presenting to Moorfields Eyes Hospital over a 2-year period were considered for inclusion into study.</p> <p>Exclusion criteria: uncontrolled hypertension, poorly controlled diabetes, clinical evidence of cardiac or renal dysfunction with fluid overload, VA worse than 6/60, significant opacities in the ocular media such as cataract or vitreous haemorrhage, glaucoma, rubeosis, areas of capillary non-perfusion disrupting the perifoveal capillary arcade, proliferative retinopathy, previous laser treatment and participants unable to attend the hospital regularly or to comprehend the informed consent</p> <p>Type of DMO: CSMO</p>
Interventions	Krypton red, 43 eyes (647 nm) versus argon blue/green, 48 eyes (488/514 nm)
Outcomes	VA and macular oedema
Notes	<p>Conflict of interest: not reported</p> <p>Trial registration: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Casswell 1990 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

DRCRNET 2007

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: 79</p> <p>Setting: USA</p> <p>Period: July 2003 to October 2004</p> <p>Sample size: assuming no more than a 10% loss to follow-up and a 2-sided alpha of 0.05, 90% power to detect a minimum difference between groups of 50 μm of CRT reduction, assuming that the common SD for the change of baseline was 100 μm.</p> <p>Follow-up: 12 months</p>
Participants	<p>323 eyes of 263 participants randomised; 285 eyes completed study at 12 months</p> <p>Mean age: 58 years (SD 11) in mETDRS group; 59 years (SD 11) in MMG group</p> <p>Sex (M:F): 101:61 in mETDRS group; 92:69 in MMG group</p> <p>Inclusion criteria: aged ≥ 18 years; had type I or II diabetes mellitus; no history of renal failure that required dialysis or renal transplant; 1 or both of their eyes meet the following criteria: best-corrected electronic ETDRS VA score ≥ 19 (approximately 20/400 or better); definite retinal thickening due to previously untreated DMO (and not primarily due to vitreoretinal interface disease as determined by investigator clinical examination) within 500 μm of the macular centre on clinical examination; retinal thickness measured on OCT ≥ 250 μm in the central subfield or ≥ 300 μm in ≥ 1 of the 4 inner subfields; no prior laser or other treatment for DMO</p> <p>Exclusion criteria: retinal thickening from epiretinal membranes or vitreomacular traction (as determined by the investigator), needed or received panretinal scatter photocoagulation within the prior 4 months, YAG capsulotomy within the prior 2 months, or major ocular surgery including cataract extraction within the prior 6 months. A person could have 2 study eyes in the trial only if both were eligible at the time of study entry.</p> <p>Type of DMO: CSMO</p>
Interventions	<p>mETDRS style focal laser photocoagulation (162 eyes) versus MMG laser photocoagulation (161 eyes). MMG burns were lighter and more diffuse in nature and were distributed throughout the macula in both areas of thickened and unthickened retina. Microaneurysms were not directly photocoagulated. In contrast, mETDRS direct/grid photocoagulation comprised of treating only areas of thickened retina (and areas of retinal non-perfusion) and leaking microaneurysms. Although microaneurysms were directly treated, treatment was modified from original ETDRS protocol to not require a treatment-induced change in microaneurysm colour. The other primary modification to the original ETDRS protocol was that the laser burns were less intense (grey) and smaller (50 μm).</p>

DRCRNET 2007 (Continued)

Outcomes	Primary outcome: change in retinal thickening in the central subfield on OCT. Secondary outcomes: change in VA and adverse events
Notes	Conflict of interest: not reported Trial registration ID: NCT00071773

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Obtained from the DRCR.net website
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported (participants) and not masked (personnel)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VA testers were masked to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12.3% in mETDRS group and 10.5% in MMG group
Selective reporting (reporting bias)	Low risk	No concern
Other Bias	Unclear risk	Not reported

ETDRS 1985

Methods	Study design: parallel RCT Number of centres: 23 Setting: Co-ordinating Center, Baltimore, MA Period: April 1980 to August 1985 Sample size: not reported Follow-up: minimum of 4 years
Participants	1122 participants (2244 eyes) Mean age: not reported Sex: not reported Inclusion criteria: people with diabetes with early proliferative retinopathy, moderate-to-severe non-proliferative retinopathy, DMO in each eye, or a combination of these.

ETDRS 1985 (Continued)

Exclusion criteria: right risk proliferative retinopathy (moderate or severe optic nerve neovascularisation or any neovascularisation with haemorrhage) and other ocular disease or VA < 20/200.

Excluded from this report were the results for the eyes with mild-to-moderate retinopathy and macular oedema that were randomly assigned to an initial treatment of PRP and follow-up focal photocoagulation if macular oedema persisted.

Type of DMO: CSMO

Interventions	Immediate photocoagulation (754 eyes) versus deferred argon laser (no intervention) (1490)
Outcomes	VA and occurrence of retinal thickening
Notes	Funding: not reported Conflict of interest: not reported

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary means of gauging treatment effects in this study was measured at each visit by an examiner who did not know the treatment assignment (masked) and who followed a detailed protocol using a specially developed VA chart.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 months had elapsed since the time of initial treatment for 80% of the enrolled participants, and 36 months had elapsed since initial treatment for 35% of these participants.
Selective reporting (reporting bias)	Low risk	No concern. Royle P, Mistry H, Auguste P, et al. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. Southampton (UK): NIHR Journals Library; 2015 Jul. (Health Technology Assessment, No. 19.51.) Chapter 2, The landmark trials: Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305100/
Other Bias	Unclear risk	Not reported

Figueira 2009

Methods	Study design: parallel RCT
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Figueira 2009 (Continued)

	<p>Number of centres: 2</p> <p>Setting: Europe</p> <p>Period: not reported</p> <p>Sample size: not reported</p> <p>Follow-up: 12 months</p>
Participants	<p>53 participants (84 eyes)</p> <p>Mean age: 60.5 years</p> <p>Sex (M:F): 32:21</p> <p>Inclusion criteria: aged < 80 years, type II diabetes and with both eyes fulfilling the ETDRS criteria for CSMO, based on stereo fundus photography and BCVA $\geq$ 55 letters on the modified ETDRS chart (equivalent to 20/80 or better).</p> <p>Exclusion criteria: any previous retinal laser treatment, PDR, rubeosis, FAZ disrupted by capillary closure in > 30% of the central circle on the FA, glaucoma (visual field alteration or intraocular pressure > 29 mmHg), significant cataract (which did not allow complete ocular examination and proposed measurements), pseudophakic eyes with surgery within 1 year before enrolment, other intraocular surgery other than cataract, dilation of pupil < 5 mm, other retinal vascular diseases, any condition that might have interfered with assessment of progression of macular oedema, brittle diabetes (people who reported decompensation in their glycaemic control, with recurrent ketoacidosis or hypoglycaemia), HbA1c > 11%, impaired renal function demonstrated by receiving dialysis, uncontrolled hypertension (diastolic blood pressure > 90 mmHg or systolic blood pressure > 165 mmHg) and participants who had received any investigational drug or device within 4 weeks prior to screening.</p> <p>Type of DMO: CSMO</p>
Interventions	MPDL (n = 44) versus standard argon green laser (n = 40)
Outcomes	Primary outcome: BCVA using the ETDRS letter scores. Secondary outcomes: change in the CMT, contrast vision sensitivity and presence of macular laser scars
Notes	<p>Funding: Ophthalmic Fund within the King's College Hospital NHS Trust (UK)</p> <p>Conflict of interest: no relevant financial relationships</p> <p>Trial registration ID: ISTRN 90646644</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised the eyes into 2 treatment groups according to a randomisation table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Figureira 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	ETDRS letter scores were recorded in a masked manner. A masked observer reviewed all the colour fundus images, without knowing the treatment performed in those eyes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	Low risk	No concern
Other Bias	Low risk	No concern

Freyler 1990

Methods	Study design: within-person RCT. 1 eye randomly assigned to argon laser treatment, the other remained untreated. Number of centres: 1 Setting: Europe Period: not reported Sample size: not reported Follow-up: 6–24 months	
Participants	100 eyes of 50 participants Mean age: not reported Sex: not reported Inclusion criteria: participants with preproliferative diabetic retinopathy, and biomicroscopic and angiographic documentation of diffuse macular oedema Exclusion criteria: not reported Type of DMO: diffuse	
Interventions	Dye red 630 nm laser (50 eyes) versus argon green 514 nm laser (50 eyes)	
Outcomes	VA and reduction/elimination of macular oedema evaluated by FA	
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported	

Risk of bias

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

Freyler 1990 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Karacorlu 1993

Methods	Study design: parallel RCT Number of centres: 1 Setting: Europe-Asian (Turkey) Period: 1998–1991 Sample size: not reported Follow-up: 1 year
Participants	85 eyes of 85 participants Mean age: 58.9 years Sex (M:F): 17:21 Inclusion criteria: people with diabetes with CSMO and moderate-to-severe NPDR Exclusion criteria: VA 20/200 or worse, PDR with ≥ 1 high-risk factors, areas of capillary arcade, previous laser treatment, previous retinal or intraocular surgery, glaucoma, or any other ocular disease that was thought to interfere with the assessment of the planned treatment results Type of DMO: CSMO
Interventions	Argon green grid (47 eyes) versus dye yellow grid (38 eyes)
Outcomes	Correction of VA and reduction of retinal thickening
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Karacorlu 1993 (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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Khairallah 1996

Methods	<p>Study design: parallel RCT. 74 participants were treated bilaterally: in 70 participants, 1 eye was treated with argon green and the other eye with Krypton red; 3 participants had both eyes treated with argon green and 1 participant had both eyes treated with Krypton red.</p> <p>Number of centres: not reported</p> <p>Setting: Africa</p> <p>Period: July 1992 to June 1994</p> <p>Sample size: not reported</p> <p>Follow-up: 1 year</p>
Participants	<p>151 eyes (78 participants)</p> <p>Mean age: 55.7 years</p> <p>Sex (M:F): 35:43</p> <p>Inclusion criteria: type I or type II diabetes mellitus, and diabetic exudative maculopathy in 1 or both eyes with a BCVA > 20/100</p> <p>Exclusion criteria: renal failure maintained or renal dialysis, PDR, previous laser photocoagulation, previous ocular surgery, significant media opacities or any other ocular disease that was thought to interfere with assessment of treatment results</p> <p>Type of DMO: focal with or without cystoid macular oedema</p>

Khairallah 1996 (Continued)

Interventions	Argon green (79 eyes) versus Krypton red (72 eyes). At 1-year follow-up evaluation: argon (73 eyes), krypton (68 eyes).
Outcomes	VA, resorption of hard exudates and resolution of focal retinal oedema
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Eyes were randomised, using a sealed envelope system, to receive either argon green or krypton red.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	141 eyes of 73 participants were available for evaluation after 1-year follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Ladas 1993

Methods	Study design: parallel RCT Number of centres: not reported Setting: Europe Period: not reported Sample size: not reported Follow-up: 3 years
Participants	50 eyes of 42 participants Mean age: 60 years Sex (M:F): 16:26

Ladas 1993 (Continued)

Inclusion criteria: background diabetic retinopathy; CSMO confirmed by biomicroscopy and diffuse macular oedema confirmed by FA as defined by the ETDRS; diastolic blood pressure ≤ 100 mmHg and HbA1c < 10.0 mg/dL.

Exclusion criteria: renal failure, eyes with BCVA ≤ 0.1 , previous history of PRP or photocoagulation to within 2 disc diameters of the foveola, iris neovascularisation, significant media opacities, retinal or other intraocular surgery and serious ocular disease that could affect the assessment of the treatment results and eyes treated with PRP during the follow-up time.

Type of DMO: CSMO

Interventions	Blue-green argon laser (27 eyes) versus control (23 eyes)
Outcomes	Change in VA defined as a difference of ≥ 2 lines on the standard Snellen's VA charts
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	BCVA was measured by an independent examiner.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% loss
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Laursen 2004

Methods	Study design: parallel RCT. If a participant had both eyes eligible for randomisation, both eyes were randomised independently. Number of centres: 1 Setting: Europe
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Laursen 2004 (Continued)

Period: not reported

Sample size: not reported

Follow-up: 1, 3 and 6 months after laser treatment

Participants	<p>23 eyes of 16 participants</p> <p>Mean age: 61 years</p> <p>Sex (M:F): 14:2</p> <p>Inclusion criteria: type I or type II diabetes mellitus, CSMO documented by biomicroscopy and confirmed by FA and OCT, HbA1c ≤ 10.0; systolic blood pressure ≤ 160 mmHg; diastolic blood pressure ≤ 100 mmHg</p> <p>Exclusion criteria: PDR, previous laser photocoagulation for diabetic retinopathy, preretinal or vitreous haemorrhage, retinal detachment, significant media opacities, iris neovascularisation, previous retinal or intraocular surgery, cataract extraction or lens implantation within the past 12 months and glaucoma or other ocular disease interfering with assessment of the treatment results.</p> <p>Type of DMO: CSMO</p>
Interventions	Subthreshold MPDL (12 eyes of 9 participants) versus conventional argon laser (11 eyes of 10 participants)
Outcomes	Visual improvement/loss by > 2 lines on ETDRS chart and reduction/elimination of macular oedema evaluated by OCT
Notes	<p>Funding: not reported</p> <p>Conflict of interest: not reported</p> <p>Trial registration: not reported</p>

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% loss
Selective reporting (reporting bias)	Unclear risk	No protocol available

Laursen 2004 (Continued)

Other Bias	Unclear risk	Not reported
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Lavinsky 2011

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: 1</p> <p>Setting: Brazil</p> <p>Period: not reported</p> <p>Sample size: 35 participants in each group (to detect change in VA) and 39 participants in each group (to detect change in CMT)</p> <p>Follow-up: 12 months after treatment</p>
Participants	<p>123 participants (123 eyes)</p> <p>Mean age: 61.9 years in high-density group; 62.0 years in normal-density group; 61.8 years in mETDRS group</p> <p>Sex (M:F): 18:24 in high-density group; 18:21 in normal-density group; 19:23 in mETDRS group</p> <p>Inclusion criteria: aged ≥ 18 years, with significant DMO, HbA1c $< 10\%$, BCVA $> 20/400$ and $< 20/40$ by the ETDRS protocol, retinal thickening within 500 μm of macular centre and CMT $\geq 250 \mu\text{m}$ measured by OCT</p> <p>Exclusion criteria: history of renal failure or uncontrolled hypertension, no prior laser or drug treatment for DMO, thickening of the epiretinal membrane or vitreomacular traction syndrome, treatment with PRP 4 months before, rubeosis iridis or severe glaucoma, poor dilation, other retinal vascular disease, any condition that could interfere with VA or OCT measurement (other than macular oedema), and increased FAZ on FA</p> <p>Type of DMO: CSMO</p>
Interventions	mETDRS focal/grid photocoagulation (42 eyes) versus normal-density SDM photocoagulation (39 eyes) versus high-density SDM photocoagulation (42 eyes)
Outcomes	Primary outcome: changes from baseline in ETDRS BCVA and in CMT assessed by OCT; secondary outcome: potential complications of laser photocoagulation, such as macular scarring, central scotoma or many other adverse collateral effect
Notes	<p>The authors also evaluated further 39 eyes that received normal-density SDM photocoagulation; however, we decided not to insert in to the meta-analysis, based on the reports effects on the VA and the interpretation of other studies as well as personal communication (Chen 2016a; Luttrull 2012; ISRCTN17742985).</p> <p>Funding: stated as none</p> <p>Conflict of interest: no evidence</p> <p>Trial registration: NCT00552435</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Lavinsky 2011 (Continued)

Random sequence generation (selection bias)	Low risk	A table of computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masked investigator performing the OCT and ophthalmic examinations, and participants not informed of which laser modality they would undergo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masked VA examiners
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.7% in high-density SDM group; 5.1% in normal-density SDM group; 4.7% in mETDRS group
Selective reporting (reporting bias)	Low risk	No concern
Other Bias	Low risk	No concern

Olk 1986

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: single</p> <p>Setting: USA</p> <p>Period: 1981–1984</p> <p>Sample size: not reported</p> <p>Follow-up: 24 months</p>
Participants	<p>160 eyes of 92 participants</p> <p>Mean age: 63 years; median: 64 years</p> <p>Sex (M:F): 31:61</p> <p>Inclusion criteria: HbA1c $\leq$ 10.0 mg/dL; diastolic blood pressure $<$ 100 mmHg and BCVA $<$ 20/32+2 and better than 20/200-3, as measured by an independent examiner using an ETDRS VA chart at 4 m</p> <p>Exclusion criteria: participants with $<$ 2 disc areas of retinal thickening or retinal thickening that did not involve the centre of the macula; participants in renal failure requiring any type of dialysis; $>$ 2 DRS "high risk" factors; previous laser photocoagulation to within 2 disc diameters of the centre of the FAZ; preretinal or vitreous haemorrhage; retinal detachment or schisis; significant media opacities; iris neovascularisation; previous retinal or intraocular surgery which was thought to interfere with assessment of treatment results; cataract extraction or lens implantation (or both) within the previous 12 months; history of glaucoma or any other ocular disease which was thought to interfere with assessment of treatment results</p> <p>Type of DMO: diffuse with or without cystoid macular oedema</p>

Olk 1986 (Continued)

Interventions	Grid with PRP (82 eyes) versus no treatment (78 eyes)
Outcomes	Improvement or worsening of visual acuity and reduction of macular oedema and/or cystoid macular oedema
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cards drawn from an envelope.
Allocation concealment (selection bias)	Unclear risk	An independent person carried out randomisation but no further details given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Follow-up examinations were performed every 4 months and included an independent examiner using the same ETDRS VA chart and the same examining lane
Incomplete outcome data (attrition bias) All outcomes	High risk	49.4% loss with balance and causes in each arm not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Olk 1990

Methods	Study design: parallel RCT. If a participant had 1 eye eligible for randomisation, that eye was randomised to treatment with either argon green or krypton red modified grid photocoagulation. If a participant had both eyes eligible for randomisation, 1 eye was randomised to treatment with argon green and the other eye treated with krypton red. Number of centres: 1 Setting: USA Period: 1984–1988 Sample size: 100 eyes in each treatment group Follow-up: 24 months
Participants	225 randomised eyes of 132 participants (205 analysed eyes after 1 year)

Olk 1990 (Continued)

Mean age: 61 years

Sex (M:F): 41:91

Inclusion criteria: HbA1c $\leq$ 10.0 mg/dL; diastolic blood pressure $<$ 100 mmHg and BCVA better than 20/200-3, as measured by an independent examiner using an ETDRS VA chart at 4 m.

Exclusion criteria: any participants with $<$ 2 disc areas of retinal thickening or retinal thickening that did not involve the centre of the FAZ; participants in renal failure requiring any type of dialysis; $>$ 2 DRS "high risk" factors; previous laser photocoagulation to within 2 disc diameters of the centre of the FAZ; preretinal or vitreous haemorrhage; retinal detachment or senile retinoschisis; significant media opacities; iris neovascularisation; previous retinal or intraocular surgery which was thought to possibly interfere with assessment of treatment results; cataract extraction or lens implantation within the previous 12 months; history of glaucoma or any other ocular disease that was thought to interfere with assessment of treatment results.

Type of DMO: not reported

Interventions	Argon green (116 eyes) versus krypton red (109 eyes). At 1-year follow-up evaluation: argon green (107 eyes), krypton red (98 eyes)
Outcomes	Reduction or elimination of macular oedema and cystoid macular oedema
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Baseline and follow-up examinations included a BCVA performed by an independent examiner.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss $>$ 20%
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Pei-Pei 2015

Methods	<p>Study design: within-person RCT. 1 eye randomly assigned to argon laser treatment, the other remained untreated.</p> <p>Number of centres: 1</p> <p>Setting: China</p> <p>Period: September 2011 to June 2013</p> <p>Sample size: not reported</p> <p>Follow-up: 6 months</p>
Participants	<p>46 randomised eyes of 23 participants (42 analysed eyes of 21 participants)</p> <p>Mean age: 61.61 years</p> <p>Sex (M:F): 11:12</p> <p>Inclusion criteria: aged > 18 years, with type II diabetes mellitus who meet the WHO or ADA criteria for diabetes; ETDRS VA > 19 letters (Snellen's equivalent of 20/400 or better); newly diagnosed severe NPDR; mean CRT > 300 µm as measured by OCT scans; adequate pupil dilation and clear media to perform laser photocoagulation and OCT</p> <p>Exclusion criteria: planned PRP within 6 months; previous intraocular surgical or laser treatment to study eye within 6 months; previous retinal treatment: laser, drug or surgery; previous laser photocoagulation or macular laser treatment to study eye; any previous ocular condition that may be associated with a risk of macular oedema; uncontrolled hypertension, renal failure and mental illness; planned insulin therapy within 6 months because of poor glycaemic control; planned intraocular surgery within 6 months</p> <p>Type of DMO: diffuse and cystoid</p>
Interventions	<p>532 nm subthreshold photocoagulation group (laser grid) (21 eyes) versus threshold photocoagulation group (21 eyes). 14 eyes with residual oedema (8 eyes of subthreshold group and 6 eyes of threshold group) accepted repeat treatments</p>
Outcomes	<p>Postlaser VA as determined by the ETDRS vision chart, mean CMT as determined by OCT, DMO area measurement, laser burn dosimetry and intensity of the laser spot reaction</p>
Notes	<p>Funding: supported by the Zhongshan Ophthalmic centre of Sun Yat-sen University and was funded by Sun Yat-Sen University Clinical Research 5010 Program.</p> <p>Conflict of interest: authors disclosed no relevant financial relationships</p> <p>Trial registration: NCT01759121</p>

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Monotherapy laser photocoagulation for diabetic macular oedema (Review)

Pei-Pei 2015 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 4 eyes from the initial study were lost to follow-up (< 10%), plus study had a paired design and losses are thus balanced in study arms.
Selective reporting (reporting bias)	Low risk	No concern
Other Bias	Low risk	No concern

Rutllan Civit 1994

Methods	Study design: parallel RCT Number of centres: 1 Setting: Europe Period: not reported Sample size: not reported Follow-up: mean 12 months
Participants	30 eyes of 19 participants Mean age: not reported Sex (M:F): 3:16 Inclusion criteria: diabetes mellitus but no other metabolic disease, biomicroscopic and angiographic documentation of diffuse macular oedema but no other macular disorders, and fluorescein leakage in the macular area extensive enough to necessitate a complete macular grid to be performed. Exclusion criteria: eyes which had received previous laser burns in the macular area and eyes which had previously been treated at other centres. Type of DMO: diffuse
Interventions	Dye-yellow (14 eyes) versus argon green (16 eyes)
Outcomes	Improvement/worsening of visual acuity
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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Rutllan Civit 1994 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss > 20% and no detail on balance and causes in study arms
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Striph 1988

Methods	Study design: parallel RCT Number of centres: not reported Setting: USA Period: not reported Sample size: not reported Follow-up: not reported
Participants	36 participants (64 eyes) Mean age: not reported Sex: not reported Inclusion criteria: diffuse DMO Exclusion criteria: not reported Type of DMO: diffuse
Interventions	Argon green (514 nm) (32 eyes) versus krypton red (647 nm) (32 eyes). 28 eyes received additional laser.
Outcomes	Changes in threshold sensitivity of the central visual field, VA
Notes	Funding: not reported Conflict of interest: not reported

Striph 1988 (Continued)

Trial registration: not reported

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A masked observed, aware of study results regarding the changes in threshold sensitivity but not in the treatment history associated with each visual field, compared pre- and post-treatment visual fields.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Tewari 1998

Methods	<p>Study design: within-person RCT. 1 eye randomly assigned to argon laser treatment, the other remained untreated.</p> <p>Number of centres: 1</p> <p>Setting: India</p> <p>Period: 1994–1996</p> <p>Sample size: not reported</p> <p>Follow-up: 1, 3 or 6 months</p>
Participants	<p>40 participants (80 eyes)</p> <p>Mean age: not reported</p> <p>Sex: not reported</p> <p>Inclusion criteria: bilateral clinically significant DMO on biomicroscopic examination as defined by the ETDRS and a BCVA of 6/60 or better in each eye</p> <p>Exclusion criteria: severe NPDR or PDR in either of the eyes, optic nerve disease or any other maculopathy that was thought to interfere with the assessment of treatment results, previous laser photocoagulation and eyes with significant media opacity</p>

Tewari 1998 (Continued)

Type of DMO: CSMO

Interventions	Diode laser (40 eyes; 20 focal and 20 grid) versus argon green (40 eyes; 20 focal and 20 grid). Areas of persistent retinal oedema received supplemental treatment at 3-month follow-up period.
Outcomes	Primary outcome: VA (considering a 2 line change of Snellen's). Secondary outcome: complications such as submacular haemorrhage
Notes	Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss for each eye
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ocular evaluation of all participants before and after treatment was carried out by an independent observer
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

Venkatesh 2011

Methods	Study design: parallel RCT Number of centres: 1 Setting: India Period: July 2006 to January 2008 Sample size: not reported Follow-up: 6 months
Participants	33 participants (46 eyes)

Venkatesh 2011 (Continued)

Mean age: not reported

Sex: not reported

Inclusion criteria: only participants with the non-proliferative stage of diabetic retinopathy

Exclusion criteria: proliferative retinopathy, significant media opacities precluding fundus evaluation and laser therapy, prior medical treatment (intravitreal/peribulbar steroids or antiangiogenic drugs), prior laser treatment, macular pathology other than diabetic maculopathy, ocular surgery within 6 months prior to screening, uncontrolled hypertension, and renal failure requiring dialysis

Type of DMO: focal and diffuse

Interventions	SDM laser (n = 23) versus double-frequency neodymium YAG (Nd:YAG) laser (n = 23)
Outcomes	Change in the Central Macular Thickness as measured by OCT and change in macular retinal sensitivity measured using multifocal electroretinography and change in BCVA and contrast sensitivity
Notes	<p>Funding: not reported</p> <p>Conflict of interest: the authors disclosed no relevant financial relationships</p> <p>Trial registration: not reported</p>

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Low risk	No concern

Vujosevic 2010

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: 1</p>
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Vujosevic 2010 (Continued)

Setting: Europe

Period: 2005–2007

Sample size: not reported

Follow-up: 12 months

Participants	<p>50 participants (62 eyes)</p> <p>Mean age: 63 (SD 10.1) years in MPDL (micropulse diode laser) group; 62 (SD 9.4) years in mETDRS group</p> <p>Sex: both, but not specified how many per group</p> <p>Inclusion criteria: type II diabetes mellitus and HbA1c $\leq$ 10%</p> <p>Exclusion criteria: any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intravitreal steroids, antiangiogenic drugs), any intraocular surgery at least 6 months before treatment, ischaemic maculopathy, tractional maculopathy and significant media opacities that precluded fundus examination or imaging</p> <p>Type of DMO: CSMO</p>
Interventions	MPDL (32 eyes) versus mETDRS with green laser (30 eyes)
Outcomes	Retinal sensitivity and FAF changes; OCT changes and BCVA.
Notes	<p>Funding: not reported</p> <p>Conflict of interest: authors disclosed no relevant financial relationships</p> <p>Trial registration: not reported</p>

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Low risk	No concern

Monotherapy laser photocoagulation for diabetic macular oedema (Review)

Vujosevic 2015

Methods	<p>Study design: parallel RCT</p> <p>Number of centres: 1</p> <p>Setting: Europe</p> <p>Period: not reported</p> <p>Sample size: 2-tailed Wilcoxon signed-rank test with significant level $\alpha = 0.05$</p> <p>Follow-up: 6 months</p>
Participants	<p>53 participants (53 eyes)</p> <p>Mean age: 61.7 (SD 9.3) in IR-MPL group; 63.3 (SD 11.7) in Y-MPL group</p> <p>Sex (M:F): 24:2 in IR-MPL group; 18:9 in Y-MPL group</p> <p>Inclusion criteria: type I or II diabetes mellitus, $HbA1c \leq 10\%$, previously untreated centre involving macular oedema with CRT up to $400 \mu m$ (mild centre involving DMO) confirmed with spectral domain OCT, BCVA ≥ 35 letters on the modified ETDRS chart (log-MAR 1.0, Snellen's 20/200)</p> <p>Exclusion criteria: any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intravitreal steroids, antiangiogenic drugs), any intraocular surgery at least 6 months before the treatment, ischaemic or tractional maculopathy, and significant media opacities that precluded fundus examination or imaging</p> <p>Type of DMO: CSMO</p>
Interventions	IR-MPL (27 eyes) versus Y-MPL (26 eyes)
Outcomes	BCVA, CRT, macular volume
Notes	<p>Funding: supported by the grant from the Seventh Framework Programme (EUROCONDOR: FP7-278040), and Ministry of Health and Fondazione Roma.</p> <p>Conflict of interest: authors disclosed no relevant financial relationships.</p> <p>Trial registration: not reported</p>

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Vujosevic 2015 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Low risk	No concern

Xie 2013

Methods	Study design: parallel RCT Number of centres: not reported Setting: China Period: not reported Sample size: not reported Follow-up: 6 months
Participants	84 participants (99 eyes) Mean age: not reported Sex: not reported Inclusion criteria: not reported Exclusion criteria: not reported Type of DMO: not reported
Interventions	Argon ion laser (49 eyes) versus SMD (50 eyes)
Outcomes	Change in BCVA; and baseline FA and OCT measurements
Notes	Funding: Fund of Urumqi Municipal Science and Technology (No. T101310005) Conflict of interest: not reported Trial registration: not reported

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
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Monotherapy laser photocoagulation for diabetic macular oedema (Review)

Xie 2013 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants (and eyes) completed study
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other Bias	Unclear risk	Not reported

ADA: American Diabetes Association; BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CSMO: clinically significant macular oedema; DMO: diabetic macular oedema; DRS: diabetic retinal study; ETDRS: Early Treatment of Diabetic Retinopathy Study; F: female; FA: fluorescein angiography/angiogram; FAF: fundus autofluorescence; FAZ: foveal avascular zone; FTH: foveal thickness; HbA1c: haemoglobin A1c; IR-MPL: infra-red micropulse laser; M: male; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; MD: mean difference; MMG: mild macular grid; MPDL: micropulse diode laser; n: number of participants; NPDR: non-proliferative diabetic retinopathy; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; RCT: randomised controlled trial; SD: standard deviation; SDM: subthreshold micropulse diode; VA: visual acuity; WHO: World Health Organization; Y-MPL: yellow micropulse laser.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akduman 1999	Case series
Arévalo 2013	Case series with a matched retrospective control group
Berger 2015	RCT, but evaluated ranibizumab with laser versus laser
Chen 2016b	RCT, but evaluated ranibizumab with laser versus laser
Dong 2001	Non-randomised controlled clinical trial
Dosso 1994	Non-randomised controlled clinical trial
Fang 2016	RCT, but evaluated bevacizumab with laser versus laser
Fernandez-Vigo 1989	Non-randomised controlled clinical trial
Gaudric 1984	Non-randomised controlled clinical trial
Huang 2016	RCT, but evaluated ranibizumab with laser versus laser
Inagaki 2015	Non-randomised controlled clinical trial
Ishibashi 2015	RCT, but evaluated ranibizumab with laser versus laser
Ivanisević 1992	Non-randomised controlled clinical trial
Lacava 1995	Retrospective study

Study	Reason for exclusion
Lai 1996	Case series
Lee 1981	Case series
Lee 2000	Case series
Lingyan 2001	Non-randomised controlled clinical trial
Marcus 1977	Non-randomised controlled clinical trial
Okuyama 1995	Non-randomised controlled clinical trial
Reeser 1981	Non-randomised controlled clinical trial
Sinclair 1999	Non-randomised controlled clinical trial
Taylor 1977	Non-randomised controlled clinical trial
Tomasetto 2007	Non-randomised controlled clinical trial
Yan 2016	RCT, but evaluated ranibizumab with laser versus laser

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Ludwig 1991](#)

Methods	Prospective clinical trial
Participants	15 eyes with diffuse diabetic maculopathy
Interventions	Grid laser photocoagulation
Outcomes	Visual acuity and visual fields
Notes	Awaiting translation

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

[CTRI/2015/03/005628](#)

Trial name or title	Micropulse laser versus standard laser in diabetic macular oedema
Methods	Randomised, parallel group. Multiple arm trial
Participants	Participants aged ≥ 18 years with type I or II diabetes and diabetic macular oedema (DMO) Decreased vision due to centre-involved clinically significant macular oedema (CSMO) and not to other causes BCVA better than 20/400 (≥ 21 ETDRS letter score) and worse than 20/40 (≤ 69 ETDRS letter score) Increased foveal thickening due to DMO and not explained by any other cause

CTRI/2015/03/005628 (Continued)

CMT $\geq$ 250 μ m (central subfield), measured with Zeiss Cirrus OCT

Interventions	mETDRS (focal/grid laser threshold photocoagulation (visible endpoint) performed with a 532 nm continuous wave green-laser system in accordance with the mETDRS guidelines versus subthreshold yellow micropulse
Outcomes	Change in BCVA on ETDRS chart Change in CMT on SD-OCT (Zeiss Cirrus) Percentage of participants gaining 5, 10 or 15 or more letters from baseline Percentage of participants losing 5, 10, or 15 or more letters from baseline Central 12° retinal sensitivity changes on microperimetry contrast sensitivity (change from baseline)
Starting date	11 March 2015
Contact information	narayanan@lvpei.org
Notes	

ISRCTN17742985

Trial name or title	Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser (DIAMONDS): a pragmatic, multicentre, allocation concealed, prospective, randomised, non-inferiority double-masked trial
Methods	Randomised controlled trial
Participants	DMO
Interventions	Diode subthreshold micropulse laser
Outcomes	Visual acuity, CMT
Starting date	17 August 2016
Contact information	Noemi Lois. E-mail: n.lois@qub.ac.uk
Notes	DIAMONDS

ISRCTN66877546

Trial name or title	A prospective, randomised, double-masked, controlled trial of the treatment of diabetic maculopathy using diode micropulsed laser versus standard argon laser
Methods	Randomised controlled trial
Participants	Adults with no other ocular pathology apart from diabetic maculopathy; all newly diagnosed
Interventions	Laser application in a grid/focal pattern to participants with macula oedema secondary to diabetic retinopathy

ISRCTN66877546 (Continued)

Outcomes	Visual acuity, reduction of oedema by angiographic methods and use of OCT
Starting date	30 September 2005
Contact information	dhmail@doh.gsi.org.uk
Notes	www.dh.gov.uk/Home/fs/en

NCT01045239

Trial name or title	Micropulse 577 nm laser photocoagulation versus conventional 532 nm laser photocoagulation for diabetic macular oedema (UMDMO)
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-masked (participant, investigator, outcomes assessor) Primary purpose: treatment
Participants	Aged ≥ 18 years; with type I or II diabetes mellitus. DMO in study eye associated to diabetic retinopathy. Diffuse macular oedema defined as macular thickening determined by biomicroscopy, OCT, fluorescein angiography, or a combination of these. BCVA between 34 (20/200) and 68 letters (20/50). Macular thickness $> 300 \mu\text{m}$ on OCT
Interventions	Device: micropulse 577 nm yellow diode laser Device: 532 nm green diode laser
Outcomes	BCVA by logMAR; macular thickness measured by OCT; photocoagulation scars on fundus photograph
Starting date	October 2009
Contact information	lindaong@hotmail.com
Notes	

NCT01928654

Trial name or title	Comparison between treatment with yellow micropulse laser and green conventional laser in diabetic macular edema
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open label

NCT01928654 (Continued)

	Primary purpose: treatment
Participants	Men or women aged ≥ 18 years with diagnosis of type I or II diabetes and clinically significant macular oedema. Visual impairment due to clinically significant DMO. BCVA included between 21 and 74 ETDRS letters. Central retinal thickness $> 320 \mu\text{m}$.
Interventions	Device: micropulse laser treatment Device: laser-modified ETDRS
Outcomes	Mean change in visual acuity (ETDRS letters); mean change in central retinal thickness; central retinal thickness corresponds to the mean retinal thickness within the 1-mm central subfield centred on the fovea; percentage of participants gaining ETDRS lines; percentage of participants who gained 1, 2 or 3 ETDRS lines of visual acuity; percentage of participants losing ETDRS lines; percentage of participants that lose 1, 2 or 3 ETDRS lines of visual acuity
Starting date	July 2013
Contact information	andrea.giani@unimi.it
Notes	

NCT02309476

Trial name or title	Subthreshold photocoagulation of diabetic macular oedema (MEM)
Methods	Allocation: randomised Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Men or women aged ≥ 18 years with type I or II diabetes mellitus. ETDRS visual acuity equivalent to ≥ 35 letters (Snellen's equivalent 20/200 or better). Participant must have non-proliferative diabetic retinopathy with diffuse macular oedema. Mean central retinal thickness $\geq 300 \mu\text{m}$ as measured by deep range imaging OCT scans
Interventions	Device: PASCAL laser, green laser 0.75 Device: PASCAL laser, green laser 1 Device: PASCAL laser, 70% yellow laser 0.75 Device: PASCAL laser, 70% yellow laser 1 Device: PASCAL laser, 40% yellow laser 0.75 Device: PASCAL laser, 40% yellow laser 1
Outcomes	Reduction of DMO (central retinal thickness) within the 6 arms of study. To compare Green PASCAL laser and Yellow PASCAL laser using EM among 6 groups of participants using PASCAL laser with an application of full grid 112 burns in a single session
Starting date	October 2012
Contact information	Danielle.ridyard@cmft.nhs.uk
Notes	

NCT03519581

Trial name or title	Micropulse for suppression of diabetic macular edema (PULSE)
Methods	Allocation: randomised Intervention model: parallel assignment Masking: double (participant, outcomes assessor) Primary purpose: treatment
Participants	Aged ≥ 18 years with type I or type II diabetes mellitus. Clinical evidence of centre-involved diabetic macular oedema confirmed on OCT. BCVA 20/32 or better on ETDRS testing
Interventions	Subthreshold micropulse laser (Iridex IQ577 laser unit with TxCell scanning laser delivery system) versus sham laser treatment
Outcomes	Percentage of participants with vision loss to 20/40 or worse (time frame: 12 and 24 month). Mean change in visual acuity (3, 6, 9, 12, 15, 18, 21 and 24 months)
Starting date	20 April 2018
Contact information	clwallace@ucdavis.edu
Notes	

NCT03641144

Trial name or title	Navigation Laser Versus Traditional Laser Photocoagulation for Mild Diabetic Macular Edema
Methods	Allocation: randomised Intervention model: parallel assignment Masking: double (participant, outcomes assessor) Primary purpose: treatment
Participants	<ul style="list-style-type: none"> Aged ≥ 18 years Diagnosed as diabetic retinopathy with Mild macular edema BCVA ≥ 0.5 No macular laser coagulation or surgery or medicine therapy of macular edema within the last 6 months
Interventions	Navigation laser photocoagulation treatment versus Traditional laser photocoagulation treatment
Outcomes	Primary: Best corrected visual acuity Secondary: Central Retinal Thickness, 10° retinal sensitivity, treatment time, participants pain intensity, number of laser spots within macular fovea.
Starting date	June 1, 2018
Contact information	gongyay@126.com
Notes	

Monotherapy laser photocoagulation for diabetic macular oedema (Review)

BCVA: best-corrected visual acuity; CMT: central macular thickness; DMO: diabetic macular oedema; ETDRS: Early Treatment of Diabetic Retinopathy Study; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; OCT: optical coherence tomography; SD-OCT: spectral domain optical coherence tomography.

DATA AND ANALYSES

Comparison 1. Laser versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months	4	3703	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.90]
2 Worsening of best-corrected visual acuity (≥ 15 letters) at 24 months	3	3421	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.53, 0.74]
3 Worsening of best-corrected visual acuity (≥ 15 letters) at 36 months	2	3194	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.79]
4 Anatomic measures: partial to complete resolution of the macular oedema at 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Clinically significant macular oedema	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Not clinically significant macular oedema	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Laser versus no intervention, Outcome 1 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.

Analysis 1.2. Comparison 1 Laser versus no intervention, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 24 months.

Analysis 1.3. Comparison 1 Laser versus no intervention, Outcome 3 Worsening of best-corrected visual acuity (≥ 15 letters) at 36 months.

Analysis 1.4. Comparison 1 Laser versus no intervention, Outcome 4 Anatomic measures: partial to complete resolution of the macular oedema at 36 months.

Comparison 2. Subthreshold versus standard macular photocoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Continuous best-corrected visual acuity (logMAR) at 12 months	7	385	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.07, 0.03]
3.1 Non-visible conventional	2	71	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.11]
3.2 Micropulse	4	276	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.16, -0.00]
3.3 Nanopulse	1	38	Mean Difference (IV, Random, 95% CI)	0.0 [-0.06, 0.06]
4 Contrast sensitivity (log unit)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Anatomic measures: partial to complete resolution of macular oedema at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Central macular thickness (μm) at 12 months	7	385	Mean Difference (IV, Random, 95% CI)	-9.09 [-26.20, 8.02]
6.1 Micropulse	4	276	Mean Difference (IV, Random, 95% CI)	-10.71 [-30.47, 9.06]
6.2 Non-visible conventional	2	71	Mean Difference (IV, Random, 95% CI)	-0.02 [-89.76, 89.72]
6.3 Nanopulse	1	38	Mean Difference (IV, Random, 95% CI)	5.90 [-42.84, 54.64]

Analysis 2.1. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months.

Study or subgroup	Subthreshold n/N	Standard n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bandello 2005	0/15	1/14		0%	0.31[0.01,7.09]

Analysis 2.2. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.

Study or subgroup	Subthreshold n/N	Standard n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bandello 2005	2/15	2/14		0%	0.93[0.15,5.76]
Favours subthreshold				Favours standard	

Analysis 2.3. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 3 Continuous best-corrected visual acuity (logMAR) at 12 months.

Analysis 2.4. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 4 Contrast sensitivity (log unit).

Study or subgroup	Subthreshold		Standard		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Figueira 2009	44	1.4 (0.1)	40	1.4 (0.2)		0%	0.01[-0.05,0.07]
Venkatesh 2011	23	1.4 (0.3)	23	1.5 (0.2)		0%	-0.12[-0.27,0.03]
Favours subthreshold						Favours standard	

Analysis 2.5. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 5 Anatomic measures: partial to complete resolution of macular oedema at 12 months.

Analysis 2.6. Comparison 2 Subthreshold versus standard macular photocoagulation, Outcome 6 Central macular thickness (µm) at 12 months.

Comparison 3. Type of laser devices: argon versus others

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of best-corrected visual acuity (≥ 15 letters) within 12 months	6	773	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.62, 1.22]
1.1 Diode	2	251	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.48, 1.64]
1.2 Dye	1	85	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.33, 1.61]
1.3 Krypton	3	437	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.51, 1.92]
2 Worsening of best-corrected visual acuity (≥ 15 letters) within 12 months	6	773	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.21]
2.1 Diode	2	251	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.26, 1.21]
2.2 Dye	1	85	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.45, 4.48]
2.3 Krypton	3	437	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.41]
3 Anatomic measures: partial to complete resolution of macular oedema within 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Anatomic measures: partial to complete resolution of macular oedema within 12 months	6	773	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.05]
4.1 Diode (focal vs grid)	2	251	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.98, 1.20]
4.2 Dye (grid)	1	85	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.16]
4.3 Krypton	3	437	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.04]

Analysis 3.1. Comparison 3 Type of laser devices: argon versus others, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) within 12 months.

Study or subgroup	Argon n/N	Others n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Diode

Analysis 3.2. Comparison 3 Type of laser devices: argon versus others, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) within 12 months.

Analysis 3.3. Comparison 3 Type of laser devices: argon versus others, Outcome 3 Anatomic measures: partial to complete resolution of macular oedema within 6 months.

Analysis 3.4. Comparison 3 Type of laser devices: argon versus others, Outcome 4 Anatomic measures: partial to complete resolution of macular oedema within 12 months.

Comparison 4. Type of laser techniques: mild macular grid versus modified ETDRS grid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Continuous best-corrected visual acuity (logMAR) at 12 months (change)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Central macular thickness (μm) at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 1 Improvement of best-corrected visual acuity (≥ 15 letters) at 12 months.

Analysis 4.2. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 2 Worsening of best-corrected visual acuity (≥ 15 letters) at 12 months.

Analysis 4.3. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 3 Continuous best-corrected visual acuity (logMAR) at 12 months (change).

Analysis 4.4. Comparison 4 Type of laser techniques: mild macular grid versus modified ETDRS grid, Outcome 4 Central macular thickness (µm) at 12 months.

Comparison 5. Yellow versus infrared micropulse laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous best-corrected visual acuity (logMAR) at 12 months	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Contrast sensitivity (log unit)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Central macular thickness (µm) at 12 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5 Yellow versus infrared micropulse laser, Outcome 1 Continuous best-corrected visual acuity (logMAR) at 12 months.

Analysis 5.2. Comparison 5 Yellow versus infrared micropulse laser, Outcome 2 Contrast sensitivity (log unit).

Analysis 5.3. Comparison 5 Yellow versus infrared micropulse laser, Outcome 3 Central macular thickness (µm) at 12 months.

Study or subgroup	Yellow		Infrared		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Vujosevic 2015	26	339.9 (55.7)	27	335.3 (54.5)		0%	4.6[-25.08,34.28]
					Favours yellow -100 -50 0 50 100 Favours infrared		

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Edema explode all trees
#2 MeSH descriptor Macula Lutea
#3 macula* near/3 oedema
#4 macula* near/3 edema
#5 maculopath*
#6 CME or CSME or CMO or CSMO
#7 DMO or DME
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Diabetes Mellitus explode all trees
#10 MeSH descriptor Diabetic Retinopathy explode all trees
#11 MeSH descriptor Diabetes Complications explode all trees
#12 diabet*
#13 retinopath*
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 MeSH descriptor Light Coagulation explode all trees
#16 photocoagulat*
#17 photo near/1 coagulat*
#18 (focal or grid) near/3 laser*
#19 coagulat* or argon or diode or micropulse
#20 (#15 OR #16 OR #17 OR #18 OR #19)
#21 (#8 AND #14 AND #20)

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. exp macular edema/
14. macula lutea/
15. (macula\$ adj3 oedema).tw.
16. (macula\$ adj3 edema).tw.
17. maculopath\$.tw.
18. (CME or CSME or CMO or CSMO).tw.
19. (DMO or DME).tw.
20. or/13-19

21. exp diabetes mellitus/
22. diabetic retinopathy/
23. diabetes complications/
24. diabet\$.tw.
25. retinopath\$.tw.
26. or/21-25
27. exp light coagulation/
28. photocoagulat\$.tw.
29. (photo adj1 coagulat\$).tw.
30. ((focal or grid) adj3 laser\$).tw.
31. (coagulat\$ or argon or diode or micropulse).tw.
32. or/27-31
33. 20 and 26 and 32
34. 12 and 33

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by [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
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. exp retina maculopathy/
34. (macula\$ adj3 oedema).tw.
35. (macula\$ adj3 edema).tw.
36. maculopath\$.tw.
37. (CME or CSME or CMO or CSMO).tw.
38. (DMO or DME).tw.
39. or/33-38
40. exp diabetes mellitus/
41. diabetic retinopathy/
42. diabet\$.tw.
43. retinopath\$.tw.

44. or/40-43
45. exp laser coagulation/
46. argon laser/
47. photocoagulat\$.tw.
48. (photo adj1 coagulat\$).tw.
49. ((focal or grid) adj3 laser\$).tw.
50. (coagulat\$ or argon or diode or micropulse).tw.
51. or/45-50
52. 39 and 44 and 51
53. 32 and 52

Appendix 4. LILACS search strategy

maculopathy or oedema or edema or CME or CSME or CMO or CSMO or DMO or DME and diabet\$ or retinopath\$ and laser\$ or photocoagulat\$ or focal or grid or coagulat\$ or argon or diode or micropulse

Appendix 5. ISRCTN search strategy

(diabetic macular edema OR diabetic macular oedema) AND (laser OR photocoagulation OR argon OR diode OR micropulse)

Appendix 6. ClinicalTrials.gov search strategy

(diabetic macular edema OR diabetic macular oedema) AND (laser OR photocoagulation OR argon OR diode OR micropulse)

Appendix 7. WHO ICTRP search strategy

(diabetic macular edema OR diabetic macular Oedema) = CONDITION AND (laser OR photocoagulation OR argon OR diode OR micropulse) = Intervention

CONTRIBUTIONS OF AUTHORS

ECJ and ENJ: conceived the review.

RED and GV: co-ordinated the review.

ECJ, ENJ, RED and GV: wrote the review.

MSB: responsible for the organisation of studies; manual searches and entering data into Review Manager 5.

ECJ and RED: responsible for the selection of titles, data extraction and risk of bias assessment.

JGF: responsible for writing the discussion and assisted on writing the final review.

DECLARATIONS OF INTEREST

ECJ: none known.

ENJ: none known.

MSB: none known.

JGF: none known.

GV: none known.

RED: none known.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Amendments to protocol

- Scope of the review: we redefined the scope of the review changing the title to "monotherapy laser photocoagulation for diabetic macular oedema"
- [Types of interventions](#): we excluded laser as adjuvant therapy and laser compared with combination of pharmacological treatments considering that this comparison is not of interest. We excluded studies of xenon laser as this type of laser is no longer used in clinical settings.
- [Types of outcome measures](#): we clarified the conversion of ETDRS letters scores to logMAR. We changed "presence of macular oedema" to "partial to complete resolution of macular oedema," which better reflects the aim of treatment. We had planned to extract 'change of EDRS best-corrected visual acuity' but used both 'final' and 'change' as available.
- [Unit of analysis issues](#): we planned to report on participants as the unit of analysis, but we accepted reporting on eyes because most studies included only one eye of a participant in analyses.
- [Subgroup analysis and investigation of heterogeneity](#): the following planned subgroup analyses were no longer indicated due to the change in scope: different types of antiangiogenic drugs associated with laser; different types of steroids associated with laser.
- [Dealing with missing data](#): we clarified that we used complete case as our primary analysis; that is, we excluded participants with missing data.
- [Data synthesis](#): we planned to use random-effects models in cases where there were two or more studies, but we used fixed-effect models if there were two studies and random-effects models if there were three or more studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetic Retinopathy [*complications]; Laser Coagulation [*methods] [statistics & numerical data]; Lasers, Gas [therapeutic use]; Macular Edema [etiology] [*surgery]; Randomized Controlled Trials as Topic; Treatment Outcome; Visual Acuity

MeSH check words

Humans