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Henein C, Steel DHW

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[Intervention Protocol]

Photobiomodulation for non-exudative age-related macular degeneration

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of photobiomodulation for people with non-exudative AMD.

BACKGROUND

Description of the condition

Age-related macular degeneration (AMD) is an irreversible, degenerative eye condition involving the central retina. AMD is the leading cause of irreversible blindness in people aged 50 years or older in the UK. It accounts for 50% of blind and partially sighted registrations (Macular Society 2017).

Clinically, AMD occurs in two forms: dry-AMD where cellular debris, clinically identifiable as round deposits called drusen accumulate between the choroid and the retina. This is followed by gradual retinal cell death, which can be further complicated by the 'wet' form where blood vessels grow from the choroid underneath the retina. Wet-AMD is more rapidly advancing, and always has some degree of dry-AMD present. The exact cause of the underlying disease process is unknown but the major aetiological factors are oxidative stress, abnormalities in autophagy and heterophagy and innate immune activation exacerbated by genetic predispositions. Dry-AMD has early, intermediate and advanced forms; people with intermediate AMD develop advanced AMD, with profound central visual loss in over 15% of cases (Klein 2007). Treatments are evolving for wet-AMD, but there are no licensed treatments for dry-AMD.

Description of the intervention

Photobiomodulation (PBM) is the process by which low level light technology affects cellular function. Visible to near-infrared (NIR) light wavelength can be delivered by low-level lasers or light-emitting diodes to have beneficial clinical effects.

How the intervention might work

Exposing people with AMD to light ranging from low-intensity visible to NIR (500 nm to 1000 nm), PBM therapy allows for high tissue penetration and offers a non-invasive approach for the treatment of AMD. Mitochondrial cytochrome C oxidase acts as a photoacceptor for NIR irradiation, resulting in the oxidation

reduction state of the enzyme. NIR enhances the activity of mitochondrial cytochrome C oxidase and production of adenosine triphosphate (ATP) in the retina leading to a reduction of free radical production and oxidative damage (Sivapathasuntharam 2017). PBM reduces gene expression of retinal stress and inflammatory markers in the outer retina (Begum 2013; Kokkinopoulos 2013). Animal studies have shown PBM reduces complement propagation, increases phagocytosis and improves aged retinal function (Fuma 2015; Rutar 2012). A review concluded by Fitzgerald et al shows there is a growing body of preclinical evidence to support PBM has a disease modifying potential (Fitzgerald 2013). This has prompted many investigators to conduct clinical trials to assess the efficacy of PBM therapy in improving visual function and reducing disease progression in people with AMD.

Why it is important to do this review

Consultation with patients and eye care professionals prioritised the need for a treatment to stop non-exudative AMD progression (James Lind Alliance 2013). Each year in the UK 70,000 people are diagnosed with advanced AMD, a figure which is expected to rise to 1.3 million by 2050 (Macular Society 2017). Associated healthcare costs of £16.4 billion are forecasted by 2020 (RNIB 2009). Over 15% of people with AMD develop advanced AMD, with profound central visual loss/blindness (Macular Society 2017). In the UK 600,000 people have already progressed to advanced AMD (Owsley 2007).

AMD limits day-to-day activities due to vision-related impairment (Berdeaux 2005; Owsley 2006; Scilley 2002). There is currently no available treatment. An effective and cost-effective intervention would be of considerable benefit to those globally with this untreatable and debilitating condition. PBM offers the possibility of a safe and non-invasive therapy for AMD. Currently there is wide heterogeneity of PBM treatment regimens and uncertainty exists regarding its efficacy. It is important to do this review to obtain an overall estimate of the effectiveness of PBM treatment in non-exudative AMD and to assess any harmful effects.

OBJECTIVES

To assess the effects of photobiomodulation for people with non-exudative AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only in the review.

Types of participants

We will include studies where participants are aged 50 years or older and have non-exudative AMD early, intermediate or late as defined by the Age Related Eye Disease Study (AREDS 2001). Late stages can feature geographic atrophy; a well-demarcated area of retinal pigmented epithelium atrophy with or without central foveal involvement.

Types of interventions

We will include trials where PBM is compared to standard care with or without sham treatment. We will include studies using visible to NIR light (500 nm to 1000 nm) delivered by low-level lasers or light-emitting diodes. Trials that have adequately described the PBM therapy parameters in terms of wavelength(s), dose, frequency, duration and coverage will be included.

Standard care consists of modifying risk factors; smoking cessation, nutritional advice and supportive measures; referral to low-vision services and visual rehabilitation.

Types of outcome measures

Primary outcomes

- Mean best-corrected visual acuity (BCVA) using a logMAR chart at 12 months follow-up.

Secondary outcomes

- Mean best-corrected visual acuity (BCVA) using LogMar chart at three months after treatment (range one to three months).
- Mean contrast sensitivity measured using a Pelli Robson chart at short- (one to three months) and long-term (12 months) follow-up.
- Mean near vision between at short- (one to three months) and long-term (12 months) follow-up.
- Mean low luminance deficit (LLD) score (the difference between low luminance visual acuity and BCVA) measured in logMAR chart units at short- (one to three months) and long-term (12 months) follow-up.
- Mean reading speed at short- (one to three months) and long-term (12 months) follow-up.
- Mean vision-related quality of life score at short (one to three months) and long-term (12 months) follow-up measured using a validated questionnaire.

If these outcomes are measured using alternative techniques, for example other visual acuity or contrast sensitivity charts, we will collect the data and include it in the analysis where possible, e.g. by converting scales. We will report any cost benefit data reported in included studies.

Adverse events

The main complication of PBM is visual loss, especially due to choroidal neovascularisation. We will collect all adverse events such as:

- The proportion of participants with worse vision following PBM therapy. Worse vision is defined by a loss of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters.
- The proportion of participants who developed new geographic atrophy or progression of geographic atrophy.
- The proportion of participants who developed neovascular macular degeneration.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1);
- MEDLINE Ovid (1946 to present) (Appendix 2);
- Embase Ovid (1980 to present) (Appendix 3);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch (Appendix 4);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 5);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 6).

Searching other resources

We will review the reference lists of included trial reports and related systematic reviews to identify additional potentially relevant trials. We will contact medical device companies conducting studies on PBM for information about any ongoing or completed but not published clinical trials. We will search abstracts from the annual meetings of the European VitreoRetinal Society, the Macula Society, the Retina Society, subspecialty meetings from the American Academy of Ophthalmology, and the American Society of Retinal Surgeons for ongoing trials.

Data collection and analysis

Selection of studies

Two review authors will screen independently the titles and abstracts resulting from the searches using web-based software (Covidence 2015). We will obtain full-text copies of potentially relevant trials and contact trial investigators for further information if required. Discrepancies between authors as to whether or not studies meet inclusion criteria will be resolved by discussion. We will document the excluded studies and reasons for exclusion. For potentially eligible studies identified on trials registers we will do the following.

- If the study has a completion date more than two years previously, we will look for publications of this trial and contact the investigators if necessary to obtain published or unpublished data from the trial. If eligible, we will include the study in the review irrespective of whether we can identify a publication.
- If the study has a completion date within two years, or in the future, we will document the study in the ongoing studies section.

Data extraction and management

Two review authors will extract data independently using an online form developed by Cochrane Eyes and Vision and using Covidence. We will pre-pilot the data extraction template. We will resolve discrepancies by discussion. Two attempts will be made to contact trial investigators for missing data. Data will be directly imported into Review Manager 5 (RevMan 5) (Review Manager 2014); and the accuracy of the data import will be checked by one author.

Study characteristics

We will collect the following information on study characteristics (Appendix 7).

- Study design: parallel group RCT/within-person RCT/one or both eyes reported
- Participants: country, total number of participants, age, sex, inclusion and exclusion criteria
- Intervention and comparator details: including number of people (eyes) randomised to each group
- Intervention details in terms of wavelength, dose, fluence, intensity, coverage, treatment time, frequency, intervals, total number of sessions and route of administration
- Primary and secondary outcomes as measured and reported in the trials
- Adverse events
- Length of follow-up
- Date study conducted
- Sample size and study power

- Funding and conflicts of interest
- Trial registration, if available

Outcome data

We will extract the following data from each included study for intervention and comparator groups separately.

- Mean, standard deviation and number of participants on which outcome measured for continuous variables (visual acuity, contrast sensitivity, reading speed, LLD score).
- Number of events and number of participants on which outcome data collected for dichotomous variables (adverse events).

For multi-arm studies we will use data relevant to our intervention and comparator groups. If two groups contain relevant data we will combine groups using the calculator within RevMan 5.
If standard deviation is not available we will use information from confidence intervals and P values, where possible, to estimate it, using the RevMan 5 calculator.

Assessment of risk of bias in included studies

Two review authors will assess independently the risk of bias using Cochrane's 'Risk of bias' tool for assessing risk of bias in each included study (Higgins 2011). We will resolve disagreements by discussion. We will specifically consider and report on the following sources of bias.

- Selection bias (random sequence generation, allocation concealment): was the sequence of allocation generated using a random procedure and was the allocation concealed to people recruiting/enrolling participants and to participants?
- Performance bias (masking of participants and researchers): were the recipients of care unaware of their assigned intervention? Were persons providing care unaware of the assigned intervention?
- Detection bias (masking of outcome assessors). Were persons evaluating outcomes unaware of the assigned intervention?
- Attrition bias: were the rates of follow-up and compliance similar in the groups? Was the analysis by intention to treat and were there any post-randomisation exclusions?
- Selective outcome reporting bias: is there any evidence that the outcomes that were measured have not been reported?

We will grade each domain as low risk of bias, high risk of bias or unclear (lack of information or uncertainty of potential for bias). We will contact trial investigators for clarification of parameters graded as 'unclear'.

Measures of treatment effect

We will calculate the mean difference for the following continuous outcomes: visual acuity, contrast sensitivity, reading speed and LLD score. Where possible, we will check for the skewness of continuous data (Altman 1996).
We will calculate the risk ratio for adverse events.

Unit of analysis issues

PBM can be applied unilaterally or bilaterally. Usually it is applied to the affected eye(s). A pilot interventional study showed bilateral drusen size reduction when an ultra low energy nanosecond laser was applied unilaterally in AMD-affected eyes (Guymer 2014; Jobling 2015). Application to only one eye may have an effect in the fellow eye, although the evidence is unclear and beyond the scope of this review.

Eyes and people

Trials may randomise one or both eyes to the intervention or comparator. If people are randomly allocated to treatment but only one eye per person is included in the trial then there will not be a 'unit of analysis' issue. In these cases, we will document how the eye was selected. If people are randomly allocated to treatment but both eyes are included and reported, we will analyse as 'clustered data' i.e. adjust for within-person correlation. If the study is a within-person study, i.e. one eye is randomly allocated to intervention and the other eye receives the comparator, then we will analyse as paired data. We may have to contact the trial investigators for further information to do this.

Cross-over trials

Cross-over trials are feasible; however, the wash out period of the PBM therapy is undetermined which would make designing a cross-over trial difficult. Where cross-over trials are available only relevant outcomes of the first phase will be collected.

Dealing with missing data

If possible, we will conduct an intention-to-treat (ITT) analysis. We will use imputed data if computed by the trial investigators using an appropriate method, but will not impute missing data ourselves. If ITT data are not available, we will do an available case analysis. This assumes that data are missing at random. We will assess whether this assumption is reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up and reasons for loss to follow-up by treatment group, if reported.

Assessment of heterogeneity

We will examine the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess the extent to which the studies are similar enough to make pooling

study results sensible. We will look at the forest plots of study results to see how consistent the results of the studies are, in particular looking at the size and direction of effects. We will calculate I^2 which is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins 2002). We will consider I^2 values over 50% to indicate substantial inconsistency but will also consider Chi^2 P value. As this may have low power when the number of studies are few we will consider $P < 0.1$ to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We will use the 'Risk of bias' assessment tool to look for selective or incomplete reporting. See Assessment of risk of bias in included studies.

If there are 10 trials or more included in a meta-analysis, we will construct funnel plots and consider tests for asymmetry for assessment of publication bias, according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We will pool data using a random-effects model in RevMan 5. If there are fewer than three trials in a comparison we will use a fixed-effect model.

If there is inconsistency between individual study results such that a pooled result may not be a good summary of the individual trial results - for example, the effects are in different directions or $I^2 > 50\%$ and $P < 0.1$ - we will not pool the data but will describe the pattern of the individual study results.

If there is statistical heterogeneity we may pool the data if all the effect estimates are in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results.

Subgroup analysis and investigation of heterogeneity

If there are sufficient trials we will compare the effect of treatment in the following subgroups.

- early, intermediate and late dry-AMD.

Sensitivity analysis

We will examine the impact of excluding studies at high risk of bias in one or more domains.

Summary of findings

We will prepare a 'Summary of findings' table presenting relative and absolute risks for the following outcomes at 12 months:

- Mean best-corrected visual acuity (BCVA)
- Mean contrast sensitivity
- Mean near vision
- Mean LLD score
- Mean reading speed
- Mean vision-related quality of life score
- Adverse events

Two authors will grade independently the overall certainty of the evidence for each outcome using the GRADE classification (GRADEpro 2015).

ACKNOWLEDGEMENTS

Cochrane Eyes and Vision (CEV) created and will execute the electronic search strategies. We thank Ms Anupa Shah, the CEV UK editorial base and Tim Jackson (peer review) for their assistance with this protocol.

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Sivapathasuntharam 2017
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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Macular Degeneration] explode all trees
#2 MeSH descriptor: [Retinal Degeneration] explode all trees
#3 MeSH descriptor: [Retinal Neovascularization] explode all trees
#4 MeSH descriptor: [Choroidal Neovascularization] explode all trees
#5 MeSH descriptor: [Macula Lutea] explode all trees
#6 macula* near lutea*
#7 (macula* or retina* or choroid*) near/4 degenerat*
#8 (macula* or retina* or choroid*) near/4 neovascul*
#9 AMD or ARMD or maculopath*
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Low-Level Light Therapy] this term only
#12 (low near/2 level near/2 light)
#13 (low near/2 level near/2 laser*)
#14 (low near/2 power near/2 laser*)
#15 (low near/2 energy near/2 laser*)
#16 (low near/2 intensity near/2 laser*)
#17 (light near/2 based near/2 technolog*)
#18 light emitting diode*
#19 (LLLT or LLL or LED-T)
#20 (photobiomodulat* or PBM or photomodulat*)
#21 (Gentlewaves or LT-300)
#22 laser* near/2 (irradiat* or phototherap* or biostimulat*)
#23 (phototherap* near/2 infrared)
#24#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25#10 and #24

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 retinal degeneration/
14. retinal neovascularization/
15. choroidal neovascularization/
16. exp macula lutea/
17. (macula$ adj2 lutea).tw.
18. ((macul$ or retina$ or choroid$) adj4 degener$).tw.
19. ((macul$ or retina$ or choroid$) adj4 neovasc$).tw.
20. (AMD or ARMD or CNV).tw.

21. maculopath$.tw.
22. or/13-21
23. Low-Level Light Therapy/
24. (low adj2 level adj2 light).tw.
25. (low adj2 level adj2 laser$).tw.
26. (low adj2 power adj2 laser$).tw.
27. (low adj2 energy adj2 laser$).tw.
28. (low adj2 intensity adj2 laser$).tw.
29. (light adj2 based adj2 technolog$).tw.
30. light emitting diode$.tw.
31. (LLLT or LLL or LED-T).tw.
32. (photobiomodulat$ or PBM or photomodulat$).tw.
33. (Gentlewaves or LT-300).tw.
34. (laser$ adj2 (irradiat$ or phototherap$ or biostimulat$)).tw.
35. (phototherap$ adj2 infrared).tw.
36. or/23-35
37. 22 and 36
38. 12 and 37

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 macula degeneration/
34. exp retina degeneration/
35. exp retina neovascularization/
36. exp subretinal neovascularization/
37. (AMD or ARMD or CNV).tw.
38. ((macul$ or retina$ or choroid$) adj4 degener$).tw.
39. ((macul$ or retina$ or choroid$) adj4 neovasc$).tw.
40. exp retina macula lutea/
41. (macula$ adj2 lutea$).tw.
42. maculopath$.tw.
43. or/33-42
44. low level laser therapy/
45. light emitting diode/
46. (low adj2 level adj2 light).tw.
47. (low adj2 level adj2 laser$).tw.
48. (low adj2 power adj2 laser$).tw.
49. (low adj2 energy adj2 laser$).tw.
50. (low adj2 intensity adj2 laser$).tw.
51. (light adj2 based adj2 technolog$).tw.
52. light emitting diode$.tw.
53. (LLLT or LLL or LED-T).tw.
54. (photobiomodulat$ or PBM or photomodulat$).tw.
55. (Gentlewaves or LT-300).tw.
56. (laser$ adj2 (irradiat$ or phototherap$ or biostimulat$)).tw.
57. (phototherap$ adj2 infrared).tw.
58. or/44-57
59. 43 and 58
60. 32 and 59

Appendix 4. ISRCTN search strategy

(Condition: Macular Degeneration OR AMD OR ARMD OR CNV AND Interventions: photobiomodulation OR low level light OR low level laser)

Appendix 5. ClinicalTrials.gov search strategy

Interventional Studies | Macular Degeneration OR AMD OR ARMD OR CNV | photobiomodulation OR low light OR low laser

Appendix 6. WHO ICTRP search strategy

Condition = Macular Degeneration OR AMD OR ARMD OR CNV AND Interventions = photobiomodulation OR low level light OR low level laser

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	· **Parallel group RCT** *i.e. people randomised to treatment* · **Within-person RCT** *i.e. eyes randomised to treatment* · **Cluster RCT** *i.e. communities randomised to treatment* · **Cross-over RCT** · Other, specify	Exclusions after randomisation Losses to follow up Number randomised/analysed How were missing data handled? *e.g., available case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Eyes *or* Unit of randomisation/ unit of analysis	· **One eye included in study**, *specify how eye selected* · **Two eyes included in study, both eyes received same treatment**, *briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country		Setting Ethnic group Participation rate
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.*	
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =) ***See MECIR 65 and 70***	· Number of people randomised to each group · Wavelength of photobiomodulation therapy · Dose, fluence, intensity, coverage, treatment time	

(*Continued*)

	· Frequency, intervals and total number of sessions · Route of administration · Specify whether another intervention was performed at same time as intervention	
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	· Best corrected visual acuity at 12 months · Contrast sensitivity · Near visual acuity · Reading speed · Low luminance deficit score · Quality of life score · Cost benefit data (if available) · The proportion of participants with worse vision following photobiomodulation therapy. Worse vision is defined by a loss of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters · The proportion of participants who developed new geographic atrophy or progression of geographic atrophy · The proportion of participants who developed neovascular macular degeneration	Planned/actual length of follow up · Length of follow up · Loss to follow up · Intervals at which outcomes assessed
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Reported subgroup analyses (Y/N) Were trial investigators contacted? Trial Registration Number: (*if applicable)*
Sources of funding		
Declaration of interest ***See MECIR 69***		

CONTRIBUTIONS OF AUTHORS

CH prepared the protocol draft and DS reviewed and edited the draft.

DECLARATIONS OF INTEREST

CH: no conflicts of interest to declare

DS: no conflicts of interest to declare

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